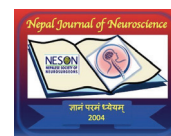


Disease Modifying Therapies in Multiple Sclerosis: A Review

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Abstract

Multiple Sclerosis is an autoimmune demyelinating disease of the nervous system. This review paper evaluates disease modifying therapies for multiple sclerosis, a chronic autoimmune disease of the central nervous system. Over 20 Disease Modifying Therapies are available, categorized into injectables, oral agents, and infusions. The review covers their efficacy, safety, and tolerability. Established injectable Disease Modifying Therapies include interferon beta and glatiramer acetate, while newer oral agents like fingolimod offer convenience with more adverse effects. Infusions like natalizumab have higher efficacy but greater risks of adverse events. The paper also discusses newer Disease Modifying Therapies like cladribine. Treatment should be individualized based on patient characteristics, risk factors, and treatment goals. Overall, this review provides a comprehensive summary to aid clinicians in selecting appropriate Disease Modifying Therapies for Multiple Sclerosis.

Key words: Multiple Sclerosis, Disease Modifying Therapies, Immunomodulators.

Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system that affects millions of people worldwide. The disease causes inflammation, demyelination, and neurodegeneration, leading to a wide range of neurological symptoms and disability. While the etiology of MS is not fully understood, it is believed to involve a complex interplay between genetic and environmental factors, resulting in an aberrant immune response against myelin and other components of the nervous system. The introduction of disease-modifying therapies (DMTs) for MS in the 1990s revolutionized the

management of the disease. These therapies have been shown to reduce relapse rates, slow disease progression, and improve quality of life for MS patients. DMTs have traditionally been categorized into injectable, oral, and intravenous therapies. Established injectable DMTs include interferon beta and glatiramer acetate, which have been widely used for over two decades. However, newer oral agents like fingolimod offer more convenient dosing regimens, although they have been associated with higher rates of adverse events.

More recently, monoclonal antibodies targeting specific immune cells or molecules have been developed, offering a higher efficacy but a greater risk of serious adverse events. Natalizumab, which targets alpha-4 integrin, has shown significant efficacy in reducing relapse rates and disease progression, although they require close monitoring for potential adverse events such as progressive multifocal leukoencephalopathy (PML). There has also been growing interest in repurposing existing medications for the treatment of MS. One such medication is rituximab, a monoclonal antibody that targets B cells, which has been used off-label for the treatment of MS for over a decade. Recently, the phase III Ocrelizumab in Multiple Sclerosis trial demonstrated the efficacy and safety of a similar medication, ocrelizumab, in the treatment of primary progressive MS, leading to its approval by the US Food and Drug Administration (FDA) in 2017.

In this review paper, I will provide a comprehensive overview of the latest therapies for MS, including established and newer DMTs, as well as emerging and repurposed therapies. I will also summarize the latest

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evidence-based guidelines and recommendations for their use in clinical practice. This review will serve as a practical guide for clinicians, helping them to provide optimal care for MS patients based on the latest evidence and guidelines.^{1,2}

Therapeutic Role of Disease Modifying Therapies:

Multiple sclerosis (MS) is a chronic autoimmune disorder that causes inflammation, demyelination, and axonal damage in the central nervous system. Disease modifying therapies (DMTs) are a class of drugs that can reduce the frequency and severity of MS relapses, slow the progression of disability, and improve the quality of life for MS patients. The therapeutic goals of using DMTs in MS are to decrease the number and severity of relapses, delay the onset of disability, and improve patients' physical and cognitive function.

DMTs work by modulating the immune system through various mechanisms, such as inhibiting the production of pro-inflammatory cytokines, reducing the number of immune cells that cross the blood-brain barrier, and promoting the activity of regulatory T-cells that suppress the immune response. By controlling inflammation and protecting the nervous system from damage, DMTs can slow down the progression of MS and delay the onset of disability. In choosing the appropriate DMT, healthcare professionals need to consider several factors, such as the drug's efficacy, safety, tolerability, and adherence to treatment. Achieving the therapeutic goals of DMTs requires balancing these factors to provide the best outcomes for individual MS patients.³

“Classical” Injectable DMTs:

Glatiramer Acetate:

Glatiramer acetate has been extensively studied for its efficacy, safety, tolerability, side effects, and adherence to treatment in multiple sclerosis (MS). Multiple clinical trials have demonstrated the efficacy of glatiramer acetate in reducing relapse rates and improving disability in patients with relapsing-remitting MS.^{4,5} Furthermore, a long-term study of over 15 years showed the sustained efficacy and safety of glatiramer acetate.⁶ Glatiramer acetate was found to be well-tolerated and associated with minimal side effects such as injection site reactions.⁷ High adherence rates to glatiramer acetate treatment were reported in several studies.⁸⁻¹⁰ However, some studies have shown that adherence rates may decline over time, particularly in patients with more severe forms of MS. In summary, glatiramer acetate is an effective and safe treatment option for MS with minimal side effects and high adherence rates.

Interferon Beta:

Interferon beta (IFN-β) is one of the disease-modifying therapies (DMTs) used for the treatment of multiple sclerosis (MS). Multiple studies have reported the efficacy of IFN-β in reducing relapse rates and disease progression in MS patients. IFN-β-1a reduced the risk of disability progression by 37% compared to placebo.¹¹ Similarly, IFN-β-1b reduced the relapse rate in relapsing-remitting MS patients by 34% compared to placebo.¹² Another long-term follow-up study showed that IFN-β treatment was associated with sustained efficacy and safety over 15 years.¹³

However, IFN-β treatment is also associated with several side effects such as flu-like symptoms, injection site reactions, depression, and liver function abnormalities. A systematic review by reported that the most common side effects associated with IFN-β treatment were injection site reactions, flu-like symptoms, and depression.¹⁴ Despite these side effects, many patients tolerate IFN-β treatment well, and adherence to treatment is critical for its effectiveness. A multicenter observational study reported that the adherence rate to IFN-β treatment was , with higher adherence associated with a lower relapse rate.¹⁵

In conclusion, IFN-β is an effective DMT for MS treatment, with proven efficacy in reducing relapse rates and disease progression. However, it is also associated with several side effects, which can affect patient adherence to treatment. The benefits and risks of IFN-β treatment should be carefully weighed before initiating treatment, and patients should be closely monitored for side effects.¹⁶

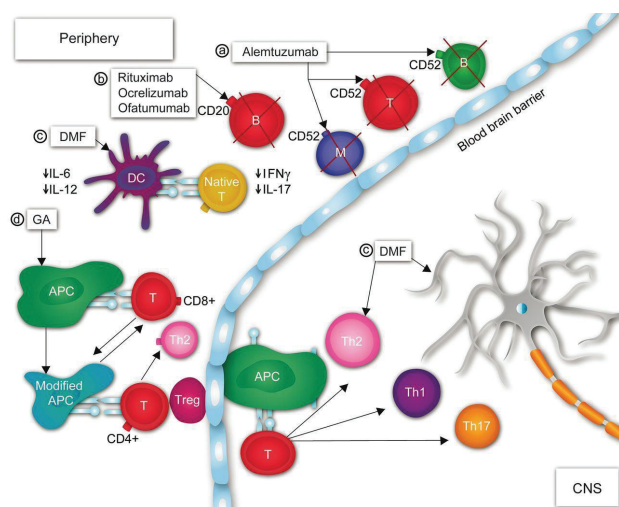


Figure 1: Figure showing the main therapeutic role of DMTs across the Blood Brain Barrier(BBB)

Oral DMTs:

Fingolimod:

Fingolimod is an oral sphingosine-1-phosphate receptor modulator that has been shown to be effective in reducing the frequency of relapses and delaying disability progression in patients with relapsing-remitting multiple sclerosis (RRMS).¹⁷⁻²⁰ It works by sequestering lymphocytes in lymph nodes, thereby reducing their migration to the central nervous system.²¹ Fingolimod has a favorable safety profile and is generally well-tolerated by patients. However, common side effects of fingolimod treatment include bradycardia, macular edema, and liver function abnormalities.²²⁻²⁵ In clinical trials, serious adverse events such as infections, malignancies, and cardiovascular events were rare.²⁶ Adherence to fingolimod treatment is high, with a study reporting a persistence rate of 80% at 2 years.²⁷

Dimethyl Fumarate:

Dimethyl fumarate (DMF) is an oral medication that has been approved for the treatment of relapsing-remitting multiple sclerosis (RRMS). Several clinical trials have demonstrated its efficacy in reducing the relapse rate and slowing disease progression.^{28,29} However, it is associated with certain side effects such as gastrointestinal symptoms, flushing, and lymphopenia.³⁰ Gastrointestinal symptoms were the most commonly reported side effects, and were usually mild to moderate in severity.³¹ The incidence of flushing was higher in the DMF group than in the placebo group, but it generally resolved within a few weeks of starting treatment. Lymphopenia is another potential side effect of DMF, and its severity can vary from mild to severe. However, the incidence of severe lymphopenia is rare and is usually reversible upon discontinuation of the drug. In terms of tolerability, DMF has been shown to be well-tolerated in most patients, with low rates of discontinuation due to adverse events. Overall, DMF is an effective and safe treatment option for RRMS, with a favorable benefit-risk profile.

Cladribine:

Cladribine, an oral purine nucleoside analogue, has been approved for the treatment of relapsing-remitting multiple sclerosis (RRMS). Cladribine is efficacious in reducing the annualized relapse rate and the risk of disability progression in patients with RRMS.³²⁻³⁴ However, its use has been associated with several side effects, including lymphopenia, infections, and malignancies.^{35,36} Despite this, the long-term safety profile of cladribine has been found to be acceptable, with no new safety concerns identified over the course of 10 years of follow-up.³⁷ Moreover, cladribine has been found to be well-tolerated by patients, with few discontinuations due

to adverse events. Adherence to cladribine treatment has been reported to be high, with a one-year persistence rate of 82.5% in a real-world study. In conclusion, cladribine is an effective and well-tolerated treatment option for RRMS, although the risk of side effects should be carefully considered before initiating therapy.

Traditional agents vs Oral DMTs:

Several studies have compared the efficacy and safety of traditional injectable therapies, including interferon beta and glatiramer acetate, with newer oral agents such as dimethyl fumarate, fingolimod, and cladribine, for the treatment of multiple sclerosis. In terms of efficacy, the newer oral agents appear to have greater efficacy in terms of reducing the risk of relapse and slowing disease progression. Specifically, fingolimod and cladribine have demonstrated greater efficacy compared to traditional injectable therapies and have been approved for use in the treatment of multiple sclerosis.^{38,39} However, the oral agents also have a higher risk of adverse events, including infections and lymphopenia, which require monitoring and management.⁴⁰ On the other hand, traditional injectable therapies are generally well-tolerated but may be less effective in reducing relapse rates and disease progression compared to oral agents. Overall, treatment decisions should be based on individual patient factors, including disease severity, comorbidities, and patient preference.⁴¹

New oral agents under trial:

Bruton kinase inhibitor (BKI) is a newer agent that has shown promising results in the treatment of multiple sclerosis (MS). BKI evobrutinib demonstrated significant reductions in brain lesions and relapse rates in patients with relapsing-remitting MS (RRMS).⁴² Additionally, it was found that evobrutinib was well-tolerated and had a low incidence of adverse events. Common side effects included upper respiratory tract infections and headache. Another BKI, fenebrutinib, also showed significant reductions in brain lesions and relapse rates in patients with RRMS.⁴³ Fenebrutinib was also well-tolerated with a low incidence of adverse events, and the most common side effects were mild to moderate in severity and included headache, nasopharyngitis, and fatigue. Overall, BKIs have shown promising efficacy and tolerability in the treatment of MS and represent a potential new class of drugs for this condition.

Highly efficacious and injectable forms of DMTs:

Natalizumab:

Natalizumab is a monoclonal antibody used in the treatment of multiple sclerosis (MS). Several studies have shown that natalizumab reduces relapse rates and slows the progression of disability in patients with relapsing-

remitting MS (RRMS).⁴⁴ However, its use is associated with potential side effects such as progressive multifocal leukoencephalopathy (PML), which is a rare but serious brain infection that can be fatal.⁴⁵ Studies have also reported other adverse events such as headache, fatigue, allergic reactions, and increased risk of herpes simplex virus infections.⁴⁶ In terms of tolerability and adherence, it was reported that patients on natalizumab are more likely to adhere to treatment than those on other disease-modifying therapies (DMTs).⁴⁷ Overall, natalizumab is an effective treatment option for RRMS, but its potential for serious side effects should be carefully considered when prescribing it to patients.

Rituximab:

Rituximab, a monoclonal antibody, has been evaluated for the treatment of multiple sclerosis (MS) in a few clinical trials. Rituximab reduced the annualized relapse rate by 47% and delayed disability progression compared to placebo in primary progressive MS (PPMS) patients.⁴⁸ Additionally, in a phase II study involving relapsing-remitting MS (RRMS) patients, rituximab significantly reduced gadolinium-enhancing lesions and the number of relapses.⁴⁹ However, adverse events associated with rituximab treatment included infusion-related reactions, infections, and hypogammaglobulinemia, which was more common in patients treated with rituximab than placebo. Although rituximab has shown promising efficacy in MS, further studies are needed to determine its long-term safety profile and optimal dosing regimen.

Mitoxantrone:

Mitoxantrone is an immunosuppressive drug that has been used for the treatment of multiple sclerosis (MS). Mitoxantrone reduced the annualized relapse rate by 67% compared to placebo and slowed the progression of disability in patients with secondary progressive MS (SPMS).⁵⁰ It was also reported a reduction in relapse rate and disability progression in patients with relapsing-remitting MS (RRMS).⁵¹ However, mitoxantrone is associated with several serious adverse effects, including cardiotoxicity, myelosuppression, and an increased risk of secondary acute myeloid leukemia (AML). Therefore, the use of mitoxantrone is limited to patients with aggressive MS who have failed other therapies and who have undergone a careful risk-benefit assessment. Additionally, the lifetime cumulative dose of mitoxantrone should not exceed 140 mg/m² to minimize the risk of cardiotoxicity and leukemia.

Ocrelizumab:

Ocrelizumab is a monoclonal antibody that targets CD20-positive B cells and has been approved for the treatment of multiple sclerosis (MS). Ocrelizumab has

shown significant efficacy in reducing the annualized relapse rate and disability progression in patients with relapsing-remitting MS and primary progressive MS. Ocrelizumab has a good safety profile with no unexpected adverse events reported in either study. However, infusion-related reactions, including hypersensitivity reactions, have been observed in a small percentage of patients. Ocrelizumab is generally well-tolerated and has a high adherence rate due to its convenient dosing schedule of two infusions given every six months.^{52,53}

Ofatumumab:

Ofatumumab is a fully human monoclonal antibody that targets CD20-positive B cells and has been studied for the treatment of multiple sclerosis (MS). Ofatumumab has shown efficacy in reducing the annualized relapse rate and MRI lesions in patients with relapsing-remitting MS. Ofatumumab has a generally good safety profile, with infusion reactions being the most commonly reported adverse event. Serious infections were reported in a small percentage of patients. In terms of tolerability, ofatumumab was found to be well-tolerated in both studies, with a low discontinuation rate due to adverse events. Ofatumumab has a convenient dosing schedule of two subcutaneous injections given every four weeks, which has been shown to improve adherence to treatment.^{54,55}

Autologous haemtopoietic stem cell transplantation:

Autologous hematopoietic stem cell transplantation (AHSCT) has shown promising results as a treatment option for multiple sclerosis (MS). Patients with highly active relapsing-remitting MS were treated with AHSCT. At a median follow-up of 6 years, 73% of patients remained free of disease progression and 86% were free of relapses. Additionally, the study reported an improvement in neurological disability and quality of life.⁵⁶ Similarly, patients with severe MS with AHSCT and reported a progression-free survival rate of 87.8% at 2 years and 79.1% at 5 years. It was also reported that an improvement in neurological function and quality of life is seen.

Although AHSCT has shown promising results, it is not without risks. The procedure carries a risk of infection, bleeding, and organ damage. The most serious adverse event associated with AHSCT is treatment-related mortality, which has been reported to range from zero to four percent in different studies. Other common side effects include hair loss, nausea, and fatigue. Tolerability to the procedure is highly variable and depends on the individual patient's response. Adherence to treatment can also be challenging, as the procedure is invasive and requires a significant time commitment.

Strategies for Neuroprotection and Remyelination:

Remyelination is a critical regenerative process in the CNS, which can restore the lost myelin and promote neuronal survival. Remyelination is a complex process that involves the proliferation and differentiation of oligodendrocyte precursor cells (OPCs) into mature oligodendrocytes that produce new myelin sheaths.^{57,58} However, in chronic MS lesions, remyelination is often incomplete due to the failure of OPC differentiation and the inhibitory effects of the MS environment. Therefore, developing neuroprotective strategies that can promote remyelination and prevent axonal damage is a promising therapeutic approach for MS. The neuroprotective effects of exercise in MS patients may be due to its ability to promote remyelination.⁵⁹ These findings suggest that promoting remyelination and neuroprotection may be a potential therapeutic strategy for MS.

Conclusion

Over the past 30 years, there has been a significant expansion in the available treatments for Multiple Sclerosis (MS) and an increase in the efficacy of newer agents against relapses. However, effective treatments for progressive disease remain scarce. Although newer disease-modifying therapies (DMTs) are more effective in reducing the relapse rate and MRI disease activity, they may also carry higher side effect profiles due to increased levels of immunosuppression. The challenge in managing MS lies in its heterogeneous nature, which is influenced by environmental and genetic factors, as well as the naturally adaptive and evolving nature of the immune system that changes with time and age.

There are promising developments in the field of neuroprotective and remyelinating therapies that aim to support mitochondrial function, and cell-based therapies targeting chronic inflammation culprits. Harnessing immunoprotective mechanisms such as supporting regulatory T-cell function and reparative microglial function are also potential therapeutic approaches. Further studies are necessary to identify early risk factors for an increased inflammatory state, early neurodegeneration, or a combination of both. Early therapeutic interventions for both the neuroinflammatory and neurodegenerative aspects of the disease, used in tandem, will likely be crucial to further therapeutic advances and the ultimate goal of true remission of the disease.

In conclusion, despite significant progress in the treatment of MS, there is still a need for more effective therapies to address the underlying progressive disease. Promising therapeutic approaches include neuroprotective and remyelinating therapies, harnessing immunoprotective

mechanisms, and early therapeutic interventions for both neuroinflammatory and neurodegenerative aspects of the disease. Further research is needed to improve our understanding of MS pathogenesis and identify new treatment targets.

Conflict of Interest: None

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