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A comprehensive review on multiple sclerosis: It's etiology, symptoms, epidemiology and current therapeutic approaches

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Abstract

Multiple sclerosis is a chronic autoimmune, inflammatory neurological disease affecting the nervous system. It targets the myelin sheath of the axons and inflicts axonal degeneration. High susceptibility is seen in people of age group 20-40 years. The incidence rate is three times more in females compared to males. There are 4 types of multiple sclerosis, namely relapsing/remitting multiple sclerosis, secondary progressive multiple sclerosis, primary progressive multiple sclerosis, progressive relapsing multiple sclerosis with relapsing-remitting being the predominant type and makes up 85% of the cases. The pathogenesis of multiple sclerosis includes destruction of myelin sheath followed by formation of lesions and inflammation. Environmental factors and genetic variables play major role in development of the disease. Exposure to viral and bacterial agents can also lead to multiple sclerosis. Disease-modifying therapies (DMTs) are the most commonly employed management strategies for treating patients with multiple sclerosis. Conventional drugs like IFN-β-1a and glatiramer acetate are now being replaced by highly effective DMTs and autologous hematopoietic stem cell transplantation. Recently, there has been drastic developments in the management of multiple sclerosis, owing to the discovery of more tailored and individualized treatment protocols catering specifically to patient needs.

Keywords: Multiple sclerosis; Nervous system disease; Inflammation; Disease-modifying therapies; Glatiramer acetate

1. Introduction

The central nervous system (CNS) is affected by the chronic autoimmune, inflammatory neurological illness known as multiple sclerosis (MS) [1,2]. MS targets the CNS's myelinated axons, inflicting various degrees of myelin and axon degeneration [3]. The progression of MS is incredibly unpredictable and irregular. In the majority of patients, the condition is first characterized by transient neurological deficiency episodes, which are frequently followed by gradual neurological decline over time. MS can strike at any age, but is typically identified between the ages of 20 and 40 and is primarily documented in females (the incidence rate is 3 times more in females than in males) [4]. MS affects over 2.5 million people globally. The exact cause is unknown, but it seems to be a result of a genetic predisposition and a non-genetic trigger, such as a virus, a malfunction in the body's metabolism, or environmental factors. This combination causes a self-sustaining autoimmune disorder that results in recurrent immune attacks on the CNS.

2. Types of multiple sclerosis

The US National MS Society identified four MS types, and these types rely on the progression of the disease's symptoms in the future[5]; however, the International MS Panel added two more in 2013:

Clinically isolated syndrome and radiologically isolated syndrome, respectively.

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However, the following four categories continue to be the fundamental basic types[6]: relapsing-remitting MS, primary progressive MS, secondary progressive MS, and progressive relapsing MS.

Table 1 Disease course of the various types of multiple sclerosis

Type	Disease Course
Relapsing/Remitting Multiple Sclerosis (RRMS)	Makes up 85% of MS cases. It is characterized by preliminary isolated attacks developing over a period of days to weeks. And recovery over a period of weeks to months. No decline in neurological function is experienced by the patient in between episodes.
Secondary Progressive Multiple Sclerosis (SPMS)	Primarily characterized by initial relapses followed by progressive declination of neurological function totally unrelated to acute attacks.
Primary Progressive Multiple Sclerosis (PPMS)	It is characterized by loss of neurological function gradually at the onset of disease. Relapse is not seen.
Progressive Relapsing Multiple Sclerosis (PRMS)	It is characterized by continuous decrease in the neurological function since the onset of the disease and also by later superimposed acute attacks. As long as the relapses happen it is impossible to differentiate PPMS and PRMS.

3. Pathogenesis

Pathogenesis of MS occurs in two main steps:

3.1. Destruction of myelin sheath followed by lesions formation in the central nervous system (brain and spinal cord),

MS primarily involves lesions in the white matter of the visual neuron, basal ganglia, brain stem, and spinal cord. The white matter tracts extremely close to the lateral ventricles may include the lesions[7]. While no lesions form in the peripheral nervous system, white matter cells carry neural signals from the grey matter region where information is gathered throughout the entire body. In MS[7], oligodendrocytes (the cells that build and maintain the myelin coating of the neuron that transmits neural signals) are damaged, and as a result, the myelin sheath's deterioration has ultimately resulted in the breakage of the nerve axon. No electrical signals could be sent because the myelin sheath was destroyed.

3.2. Inflammation

T cells play a significant role in both inflammation and the demyelination process[7,8]. However, T cells can directly enter the brain through a breach in the blood-brain barrier, where they perceive the myelin sheath as a foreign object and start attacking it. The demyelination of the neuron sheath increases the activation of inflammatory processes, and as a result, immune cells start to release more cytokines and antibodies, further damaging the blood-brain barrier and triggering the activation of macrophages, cytokines, and other detrimental proteins.

Inflammatory processes reduce the flow of information in the central nervous system by

- Neurotransmitters produced by targeted assault neurons are stopped by antibodies and cytokines,
- The production of cytokines and antibodies increases the breakdown of the myelin sheath,
- The body's increased production of cytokines and antibodies causes complete axon destruction.

Together, the two processes work synergistically to damage the neuronal tissue and cause MS. On the other hand, MS is an immunological disorder that develops as a result of a person's inherited traits as well as environmental variables. Neuron tissues are destroyed as a result of immune system attacks on the individual.

4. Modalities of diagnosis

There is no single diagnostic test for MS. To potentially reduce the handicap and maintain the patient's health condition, early identification and treatments are crucial [9].

In order to make the initial diagnosis of MS the doctor must,

- detect proof of damage in at least 2 entirely different regions of the central nervous system, which comprises of the brain, optic nerves and spinal cord.
- note that the symptoms occur in independent episodes separated by one month or more and last for more than 24 hours.
- conduct an MRI [10]. (The MAGNIMS network has suggested a standardized MRI methodology to help with multiple sclerosis diagnosis) [11]
- conduct a spinal tap and oligoclonal band testing.

The best way to identify oligoclonal bands, which are present in up to 90% of individuals with multiple sclerosis, is through qualitative analysis of IgG utilizing isoelectric focusing and immunofixation.[12]

A clinically silent lesion in the central nervous system (CNS) that indicates spatial spread can be found by doing neurophysiological testing of evoked potentials in visual, sensory, or auditory pathways. On evoked potential testing, a long delay and well-preserved waveform are suggestive but not definitive of demyelination. [13]

The symptoms, MRI, and laboratory findings of the patient all play a role in the diagnosis of MS, which can only be made in the late stages. The McDonald criteria, which integrate laboratory, clinical, and radiological reports of lesions at various times in various body locations, is the most well-known approach for diagnosing MS. The McDonald 2010 criteria are simple to implement in a clinical environment and enable an earlier multiple sclerosis diagnosis. [14]

Furthermore, the earliest known criteria were those proposed by Schumacher[15] and Poser[16]. The most popular diagnostic techniques include MRI, patient physical characteristics, and cerebrospinal fluid investigation.

5. Clinical manifestations

5.1. Primary symptoms:[17]

5.1.1. Common symptoms:

- Sensory disturbances (numbness, tingling, itching, burning)
- Walking difficulties (due to fatigue, weakness, spasticity, loss of balance and tremor)
- Vision problems (diplopia, blurred, and pain on eye movement)
- Intestinal and urinary system dysfunction (constipation and bladder dysfunction)
- Cognitive and emotional impairment (inability to learn and depression)
- Dizziness and vertigo
- Sexual problems

5.1.2. Less common symptoms

Swallowing problems (dysphagia), Breathing problems, Hearing loss, Seizures, Speech problems (dysarthria), Headache.

5.2. Secondary symptoms

Urinary tract infections, Inactivity, Immobility.

5.3. Tertiary symptoms

Social complications, Vocational complications, Psychological complications, Depression.

6. Etiology

There is no known cause of MS. The prevalence of MS is unevenly distributed around the world, and epidemiological statistics suggest that both environmental and genetic variables are important in its development.

6.1. Environmental factors:[18]

The development of MS is influenced by environmental variables such as smoking, vitamin insufficiency, nutrition, and exposure to UV radiation, as well as exposure to bacterial and viral agents such as Epstein Barr virus (EBV), human herpes virus type 6, and mycoplasma pneumonia.

Nuclear antigens produced by the foreign agents may share structural similarities with proteins found in myelin sheet components such proteolipid protein, myelin basic protein, and myelin-associated glycoprotein.

Myelin sheath lesions are consequently created when these pathogens cause the immune system to become active.

Vitamin deficiency (especially vitamins D and B_{12}) are considered risk factors for MS. Vitamin D comprises a group of fat-soluble secosteroids that include vitamin D_3 (cholecalciferol) and vitamin D_2 (ergocalciferol).

6.2. Smoking

There is evidence that smoking contributes significantly to MS because it produces nitric oxide (NO) and carbon monoxide (CO). NO is a harmful soluble gas that, at pathological levels, can harm oligodendrocytes and neurons. Oligodendrocytes can undergo apoptosis, axonal degeneration, and demyelination as a result of lipid peroxidation and mitochondrial damage brought on by NO.

6.3. Genetic susceptibility

There may be a hereditary component to MS. According to studies, a patient's family members' risk of developing MS relies on how much genetic information they share. In monozygotic twins with 100% genetic resemblance, the risk rate is therefore around 25%. This risk is 2-5% for all persons with 50% genetic similarity, including dizygotic twins and first-degree relatives. Additionally, third degree cousins with 12.5% genetic similarity had a risk of less than 1%, compared to second degree relatives with 25% genetic similarity.[19]

6.4. Microbial infection

Multiple sclerosis, a demyelinating illness, has been linked to microbial infections that both start and exacerbate the severity of autoimmune diseases (MS). Although there is no indication of autoimmune consequences, the frequency of both acute and chronic viral infections shows that this process is under control. [20]

Ruminants, both wild and domestic, are the major targets of the contagious disease paratuberculosis. This condition, caused by the bacterium Mycobacterium avium paratuberculosis (MAP), is linked to an increased risk of MS. A study found that 56.57% and 66.60% of the cheese samples tested positive for MAP, which can raise the risk of MS in humans.[21]

7. Epidemiology

The prevalence of MS is low in childhood and rises after the age of 18, peaking between the ages of 20 and 40 (mean age of 30) with women being afflicted about 2 to 5 years earlier than men.[22] After then, the incidence decreases and eventually disappears at ages beyond 50. The prevalence rate of MS in India is approximately 1 in 9500 people, and the incidence is approximately 6500 new cases per year.[23] The prevalence of MS is higher in women than in men, and through time, the female: male ratio has gradually increased.

Accordingly, women have a 2.5% lifetime risk compared to men's 1.4%.[24] Longitudinal studies have shown an overall increase in prevalence, but this is not owing to a higher risk of the disease per se; rather, it is a result of MS patients living longer and the advancements in MS diagnosis. MS patients' life expectancy is decreased by 7–10 years. The standardized mortality ratio is tripled, but things have gotten better over the years. [25]

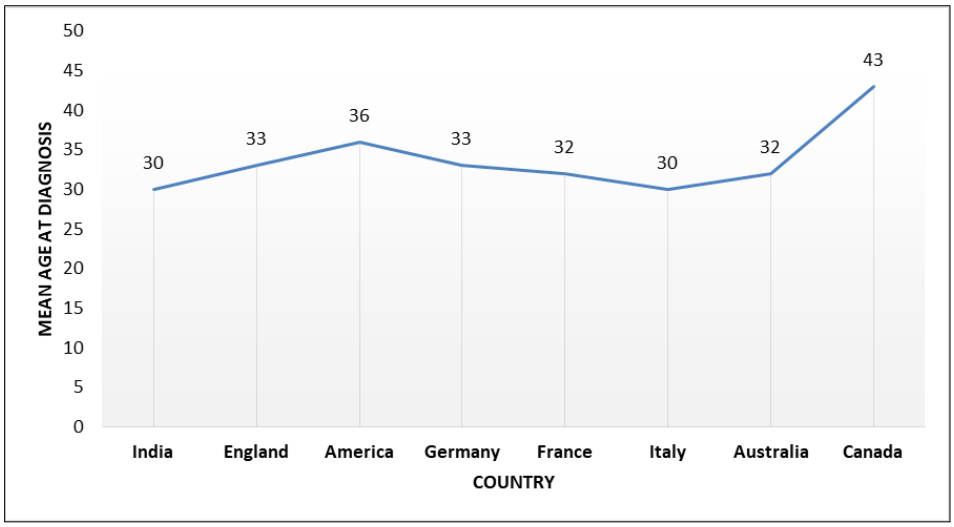

Figure 1 Country-wise mean age of diagnosis

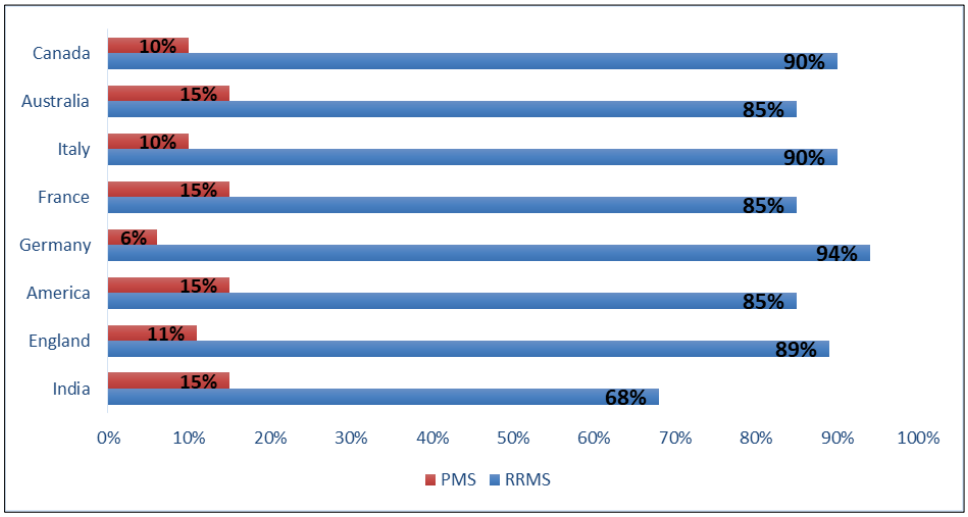

Figure 2 Presentation at initial diagnosis

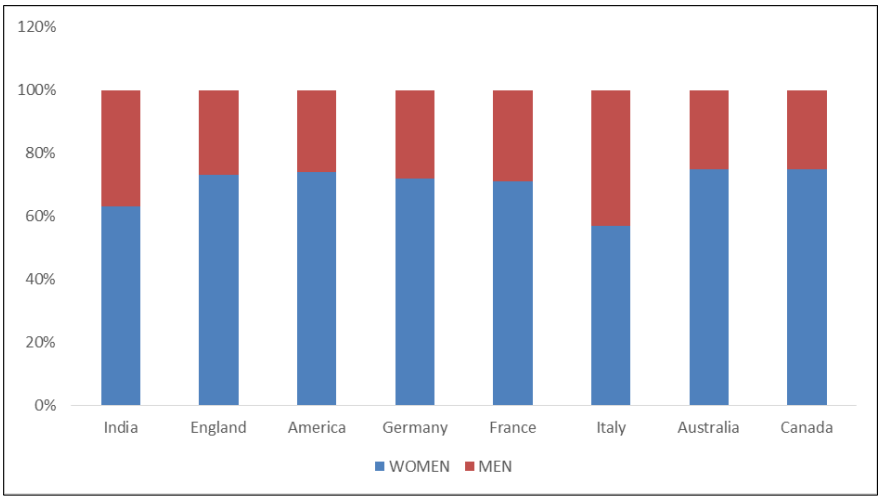

Figure 3 Gender distribution of multiple sclerosis

8. Treatment regimens currently employed

Disease-modifying therapies (DMTs) are the most commonly employed management strategies for aiding patients with multiple sclerosis. It is primarily focused on treating acute attacks and ameliorating the symptoms of MS.

The development of more successful treatments for RMS, as well as partially effective treatments for PPMS and SPMS, constitutes a significant success that has greatly increased the likelihood that people with RMS can lead active, independent lives.

Relapses are significantly diminished or prevented with highly effective therapy. Although attacks and remissions in RMS have previously covered up a relapse-independent "silent" development, management of RMS has revealed it[26,27]. In order to effectively control both relapses and progression, this awareness has also resulted in an increase in the use of very effective medicines early in the course of MS.

8.1. DMTs frequently employed for treating RMS

8.1.1. Ocrelizumab

The drug was approved in 2017. It is a humanized monoclonal antibody, that is being used exclusively to target the CD20 proteins found on the surface of mature B cells [28]. Ocrelizumab has proven to slowdown the growth of new white matter lesions that are shown on the MRI. Successfully used to prevent relapses and silent progression of disease in patients with RMS.

8.1.2. Rituximab

It is a chimeric anti-CD20 monoclonal antibody commonly used, even though no clearance has been gained from regulatory agencies for the treatment of MS. It is equally effective for treating RMS and PPMS in preliminary studies and clinical practice.

8.1.3. Ofatumumab

B cells primarily contribute to the development and progression of the disease multiple sclerosis. Ofatumumab [29] is a monoclonal antibody that effectively reduce the level of B cells. The drug has been approved to treat adult patients with relapsing forms of MS. Ofatumumab is given subcutaneously once a month and the advantage is that patients can administer the injection by themselves without the need of assistance. The drug has shown good tolerability profile.

8.1.4. Natalizumab

Natalizumab is a monoclonal antibody that inhibits the adhesion protein α4β1 integrin produced on lymphocytes' surface. The protein is also implicated in transmigration into the central nervous system through the endothelia[30]. Natalizumab has proven to be more effective in reducing relapses and slows down the disease progression in RMS patients, upon comparing with placebo or interferon beta (IFN-β)-1a [31]. Prolonged long-term usage of the drug can pose the risk of progressive multifocal leukoencephalopathy[32] (rare brain infection commonly caused by John Cunningham virus) and has been shown to affect 0.4% of patients receiving Natalizumab.

8.1.5. Fingolimod

Fingolimod was the first drug to be approved for orally treating RMS. Fingolimod is an active S1P inhibitor that acts by blocking the infiltration of autoreactive lymphocytes into central nervous system, by prohibiting the venting out of lymphocytes from the secondary lymphoid organs. Despite modest anomalies on regular laboratory findings (such as elevated liver function tests or lymphopenia),fingolimod is found to be well tolerated [33-36]. An initial 6 hour observation period is a prerequisite for all patients receiving the drug for the first time. ECG monitoring is done during the observation period as heart block and bradycardia might develop during the administration of the drug[37].

8.1.6. Ozanimod

Ozanimod is a recently authorized selective S1P receptor modulator. It is found to have meritorious effect in treating RMS patients and exemplary safety and tolerability[38,39].

8.1.7. Dimethyl fumarate

Dimethyl fumarate activates the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway and Nrf2-independent pathway which exerts properties such as anti-inflammatory and cytoprotective[40,41]. The drug is well tolerated in many cases however there is minor possibility of developing progressive multifocal leukoencephalopathy in rare cases[42]. It is important that lymphopenia be checked every 6-12 months as it is found to be present in majority of cases. Diroximel fumarate is a recently approved drug that gets converted to mono-methyl fumarate, similar to dimethyl fumarate [43].

8.1.8. Teriflunomide

Teriflunomide[44] inhibits dihydroorotate dehydrogenase, an enzyme primarily responsible for producing pyrimidines. The active metabolite of leflunomide (an immune suppressant drug used in the treatment of Rheumatoid arthritis) is teriflunomide. Teriflunomide inhibits the proliferation of activated lymphocytes. The most common adverse reactions involves teratogenesis and the risk of hepatotoxicity. Less frequent ADRs include nausea, diarrhoea, headache and a rise in hepatic alanine transferase.

8.1.9. IFN-β

IFN-β belongs to class I interferon, it acts by downregulating expression of major histocompatibility complex components on antigen presenting cells, simultaneously raising anti-inflammatory and lowering proinflammatory cytokines, slows down T cell proliferation and prevents the infiltration of inflammatory cells to the central nervous system. IFN-β likely delays the progression of disability, lowers the recurrence rate and enhance the disease activity measurements using MRI [45-49]. Adverse events frequently seen involves abnormalities during routine laboratory testing, flu-like symptoms and infection on injection sites with subcutaneous administration.

8.1.10. Glatiramer acetate

Four amino acid random polypeptides combine together to form the drug Glatiramer acetate. It acts by increasing the regulatory to pro inflammatory cytokines ratio [50-52].

Glatiramer acetate is an effective substitute for IFN-β in the treatment of RMS, as it reduce the recurrence rates and the severity of the disease [50,51,53]. Common adverse effects includes reactions on the injection site, chest tightness, dyspnea, anxiety, flushing and palpitations. Less common adverse effects include lipoatrophy, which leads to cessation of the treatment [50,51].

8.2. DMTs less frequently employed for treating RMS

These include mitoxantrone[54], alemtuzumab[55-57] and cladribine[58]. All have been shown to be beneficial in RMS, but their usage is constrained by severe treatment-related side effects.

Autologous hematopoietic stem cell transplantation is a new treatment approach for MS patients. However, recent research suggests that RMS patients often suffers from a durable remission following the treatment. The treatment is now only employed for treating patients with RMS who have not been successful with other treatments. This treatment is not currently advised for patients with progressive MS as current data implicates that progression usually continues after the treatment[59].

8.3. Treatment employed for treating Progressive MS

8.3.1. SPMS

Siponimod [60] is a highly selective S1P receptor modulator currently authorized for treating relapsing types of MS, which includes SPMS patients having evidence of new or expanding lesions found in MRI or experienced clinical relapses of the disease. Diroximel fumarate, ocrelizumab and cladribine are currently employed in the treatment of patients with active SPMS.

8.3.2. PPMS

The only licensed disease-modifying medicine for the treatment of PPMS is ocrelizumab. The dosage is the same as used for the treatment of RMS. Ocrelizumab has shown to slow down the development of clinical impairment by 25%[61]. The drug also improves the clinical and MRI indicators of inflammation and neurodegenerative disease.

8.4. Choice of drug therapy

Conventionally high-dose IFN-β-1a and glatiramer acetate were the first-line drugs for MS treatment. This is based on the "treat to target" approach, where a moderate efficacy drug is used first and is switched to a more effective drug only when breakthrough disease occurs. Recent studies suggested better long-term outcomes, when treatment was started with high efficacy drugs, following which DMTs were advocated as the first-line drugs for patients with active MS.

Anti-CD20 treatments are a desirable alternative, given their high degree of effectiveness, few infusions or injections, excellent safety profile, and lesser rebound phenomenon following withdrawal. Ocrelizumab therapy should be considered in patients with PPMS who have developing or growing MRI lesions. Suboptimal response, several relapses with active MRI scans during the previous year of treatment, safety concerns, such as the development of persistent high-titer neutralizing antibodies in IFN-β-treated patients, may all necessitate switching medications.

In situations of major adverse effects that may be drug-related, or in women who get pregnant while on treatment, disease-modifying therapies must be stopped. Glatiramer acetate is an exception since it may be used throughout pregnancy.

Table 2 Overview of the characteristics and pivotal data associated with approved agents, stratified according to frequency of use and perceived level of efficacy

Drug Name	**Mechanism of action**	**Indication**	**Pivotal Efficacy Data**	**Route of and frequency of administration**
Highly effective				
Ocrelizumab[61,62]	Anti-CD20 mAb	RMS and PPMS (first line)	RMS: Relative reduction in ARR compared with IFN-β 1a: 47% PPMS: Relative reduction in 12-week CDP compared with placebo: 24%	IV infusion, every 6 months
Ofatumumab[63]	Anti-CD20 mAb	RMS (first line)	Relative reduction in ARR compared with teriflunomide: 54%	SC injection, every 4 weeks
Natalizumab[64]	a4b1 integrin inhibitor	RMS (second line)	Relative reduction in ARR compared with placebo: 68% Relative reduction in sustained disease progression compared with placebo: 42%	IV infusion, every 4 weeks
Alemtuzumab [55-57]	Anti-CD52 mAb	RMS (first line)	Relative reduction in ARR compared with placebo: 49%-69%	IV infusion, once daily
Mitoxantrone[54]	DNA intercalator	RMS, SPMS (second or third line)	Relative reduction in relapses compared with placebo: 61%	IV infusion, every month or 3 months
Moderately effective				
Fingolimod[33,34]	Sphingosine-1-phosphate inhibitor	RMS (second line)	Relative reduction in ARR compared with placebo: 48%-60%	Oral, once daily
Siponimod[60]	Sphingosine1-phosphate receptor modulator	CIS, RMS, active SPMS (first Line)	Relative reduction in 12-week CDP compared with placebo: 21%	Oral, once daily
Ozanimod[38,39]	Sphingosine 1-phosphate receptor modulator	CIS, RMS, active SPMS	Relative reduction in ARR compared with placebo: 48%	Oral, once daily
Dimethyl fumarate and diroximel fumarate[65,66]	Nuclear factor (erythroid derived	RMS (first line)	Relative reduction in ARR compared with placebo: 48%-53%	Oral, twice daily

	2)–like 2 pathway inhibitor			
Cladribine[58]	Not fully known	RMS (second or third line)	Relative reduction in ARR compared with placebo: 55%-58%	Oral, 4-5 days over 2-week treatment courses
Modestly effective				
Teriflunomide[44]	Dihydroorotate dehydrogenase inhibitor	RMS (first line)	Relative reduction in ARR compared with placebo: 32%-36%	Oral, once daily
Glatiramer Acetate[50]	Not fully known	RMS (first line)	Relative reduction in ARR compared with placebo: 29%	SC injection, once daily or 3 times weekly
IFN-β-1a (Rebif)[67]	Not fully known	CIS and RMS (first line)	Relative reduction in ARR compared with placebo: 33%	SC injection, 3 times weekly
IFN-β-1a (Avonex)[46]	Not fully known	CIS and RMS (first line)	Relative reduction in 24-week CDP compared with placebo: 37%	IM injection, once weekly
Peg IFN-β-1a (Plegridy)[68,69]	Not fully known	CIS and RMS (first line)	Relative reduction in ARR compared with placebo: 39%	SC injection, every 2 weeks
IFN-β-1b (Betaseron)[45]	Not fully known	CIS and RMS (first line)	Relative reduction in ARR compared with placebo: 31%	SC injection, every other day

ARR = annualized relapse rate; CDP = confirmed disability progression; CIS = clinically isolated syndrome; IFN-β-1a = interferon beta 1a; IM = intramuscular; IV = intravenous; mAb = monoclonal antibody; PPMS = primary progressive multiple sclerosis; RMS = relapsing forms of multiple sclerosis; SC = subcutaneous; SPMS = secondary progressive multiple sclerosis.

9. Conclusion

The last few decades have witnessed drastic improvements in the treatment of MS which resulted due to the discovery of newer drugs with better efficacy and better understanding of the pathogenesis and clinical course of the disease. The introduction of DMTs as first line drugs in the treatment protocol of MS have favored patients to a greater extent. Though there have been milestone achievements in drug therapy for MS, therapies for delaying or halting the disease in progressive forms and therapies for regenerating or repairing the diseased neurons still remains challenging. Further studies are needed to address these lacunas, as we are marching towards an era of more tailored and individualized approach for MS treatment and management.

Compliance with ethical standards

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Disclosure of conflict of interest

There is no conflict of interest.

Author Contribution

Francis Kevin Raj S had principal responsibility for conception and design of the study and drafting of the manuscript. Dr. P. Muralidaran was responsible for revision of the manuscript for important intellectual content. Govindhan E, Pavithra J, Yuvaraj K contributed towards reviewing of the literature. All authors agreed on the final version of the manuscript.

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