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Review Article

Recent advances in the management of multiple sclerosis

Reka Deva[1]*, Priyadharsini Rajendran[2]

[1]Department of Pharmacology, MGMCRI, Puducherry, India
[2]Department of Pharmacology, JIPMER, Puducherry, India

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***Correspondence:**
Dr. Reka Deva,
Email: meter.reka478@gmail.com

ABSTRACT

Every 5 minutes, someone somewhere in the world is diagnosed with an inflammatory, demyelinating, neurodegenerative disorder known as multiple sclerosis (MS). MS was historically known as "La sclèrose en plaques" which involves the central nervous system (the brain and the spinal cord). It is always considered to be a disease of adulthood but nowadays pediatric MS is also gaining popularity. It is the most common non-traumatic chronic disabling disease of adults. MS is said to have etiology of multifactorial origin. of the myelin structure thereby producing a dysregulated immune system. MS is an ongoing disease with episodes of relapses and remissions whereas the basic pathophysiology remains increasing over time. Since the pathophysiology of MS is very complex, it makes the pharmacotherapy part bit difficult. MS therapy is disease subtype-specific. The drugs which were previously approved for MS lacks efficacy and sometimes possess serious adverse effects and thereby creating lacunae in treating MS patients include the need for a drug with better efficacy especially it should be evidence-based. There are several new drugs approved for the treatment of MS in recent times especially over the past 5-8 years and 'n' number of new molecules being tried in clinical trials. In this review, an effort was made to discuss MS epidemiology, potential etiological factors, pathophysiology, clinical aspects of MS before moving on to pharmacotherapy and other non-pharmacological management of MS. A special elaborative note on recently approved drugs and drugs under pipeline has been discussed in this review.

Keywords: Multiple sclerosis, Drugs promoting remyelination, Non-pharmacological measures, Pharmacotherapy of MS, Recent advances

INTRODUCTION

MS is the commonest non-traumatic disease that causes permanent disability in young adults.[1] March month is considered as MS awareness month and 30 May is being celebrated as World MS day every year. The diagnosis of MS is made after a thorough review of events in a patient's life, findings observed on neurological examination, data acquired from diagnostic tests and after the exclusion of other diseases that could account for the clinical and paraclinical findings.[2] MS is postulated to have an etiology of multifactorial origin as shown in Figure 1. The inflammation and neurodegeneration of MS are attributed to the dysregulated arms (innate and adaptive) of the immune system.[3] Demyelinated lesions are disseminated throughout the central nervous system (CNS), involving both white and grey matter. The hallmark of MS is the characteristic pathological lesion affecting the periventricular area, brain stem, basal ganglia and spinal cord.[1] The pathophysiology of MS is very complex and has distinct subtypes which make the pharmacotherapy part difficult. The drugs which were previously approved for MS lacks efficacy and sometimes possess serious adverse effects and thereby creating lacunae in treating MS patients include the need for the drug with better efficacy especially it should be evidence-based hence MS has been the target

of intensive preclinical and clinical research as well as drug development over the past two decades. As the understanding of the pathophysiology of MS improves with the emergence of new technology and computational tools, more specific treatments with new molecules have evolved over the past few years. Here is an effort to review the agents which are recently approved for MS and under pipeline agents in the development of MS.

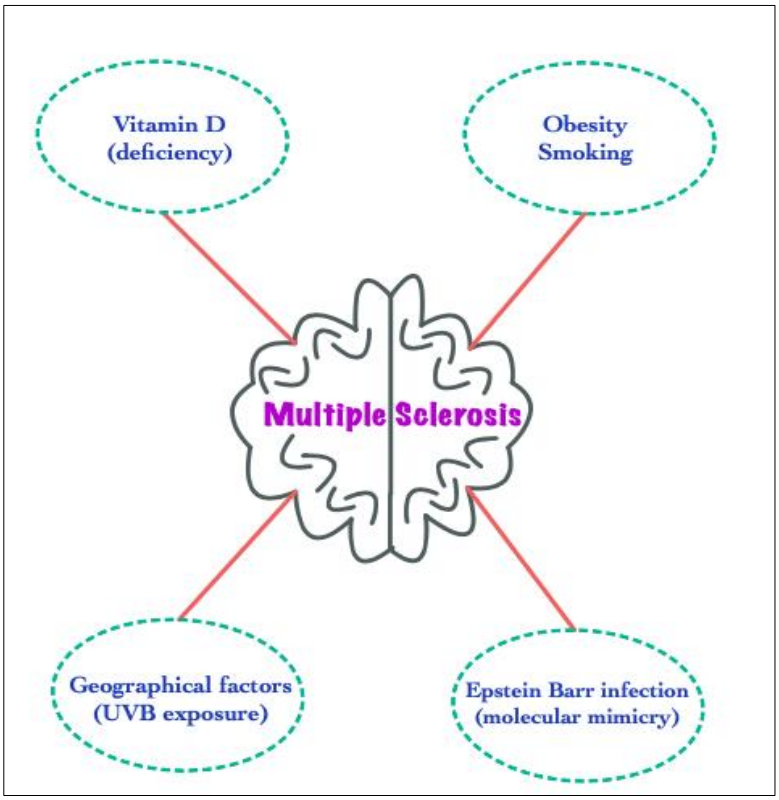

Figure 1: Etiological factors for MS.

Pathophysiology of MS

MS is a T-cell mediated autoimmune disease characterized by chronic inflammation and demyelination of the CNS. Both genetic and environmental factors play a crucial role. In the pathogenesis of MS. Myelin basic protein (MBP) is a candidate autoantigen in MS because it can induce MS-like disease, experimental autoimmune encephalomyelitis, in rodents and primates with susceptible genetic backgrounds.[1,2,4]

Inflammation

Blood-brain barrier (BBB): It is found that autoreactive, myelin-specific lymphocytes are activated outside the CNS, cross the BBB and form new inflammatory demyelinating lesions.

T lymphocyte: Lymphocytic inflammation is associated with profound macrophagic infiltration and microglial activation particularly in lesions with active demyelination or tissue injury.

B lymphocyte: B cells are sparse in the parenchyma of MS lesions as compared to T cells. CD20+ B cells and plasma cells are found in the perivascular and meningeal inflammatory areas in patients with pronounced inflammatory pathology.

Microglia and macrophages: The quantity of macrophages in an MS lesion always depends on the stage of activity of the disease. The actively demyelinating disease has a high number of macrophages throughout the lesion whereas chronically active plaques are demarcated by a rim of macrophages and microglia and the centre of the lesion is devoid of macrophages similarly, on the other hand, chronically inactive plaques contain no macrophages.[5,6]

Demyelination

Demyelination is the common final phase in the pathology of MS and comprises the stripping of myelin lamellae and removal of myelin fragments by phagocytes. There is evidence that demyelination occurs due to various mechanisms involving both immune systems (adaptive and innate). One such mechanism which proves to be important is damage to myelin and oligodendrocyte mainly by nitric oxide, nitrogen species, diffusible oxygen and other reactive oxygen species secreted by activated macrophages and microglial cells. Antibodies against anti-myelin

oligodendrocyte glycoprotein (MOG), astrocytic water channel aquaporins (AQP4). Another mechanism leading to demyelination is oxidative stress causing oligodendrogliopathy that starts in the distal processes of oligodendrocytes with preferential loss of oligodendrocytes by apoptosis.[7]

Remyelination

Remyelination of demyelinated lesions occurs spontaneously but usually, it is incomplete both structurally and functionally. Remyelination is produced by oligodendrocyte precursor cells (OPC) which are activated and migrated to the site of the lesion to get differentiated to myelin-generating cells. Remyelinated fibres are very thin and can be found only in the border zone of the lesion when it can fully remyelinate a lesion it is termed as shadow plaque. Usually, remyelination occurs in the early phase of the disease where the inflammatory phase is dominant. The remyelinated fibres can undergo new demyelination either within or overlapping the previously remyelinated areas. The lack of remyelination has been attributed to a failure of OPC to get differentiated at the site of the lesion due to hormonal and age-related factors.[7,8]

Neurodegeneration

At any stage of MS, usually, there will always be damage to axons, neurons, and synapses which is collectively called neurodegeneration. The axonal damage which causes axonal loss is postulated to be the substrate for permanent motor disability in MS. The axonal loss can be due to direct oxidative stress on axons and also may be due to loss of myelin which contributes to the loss of trophic factors needed for axons.[7]

Types of MS[9,10]

Multiple sclerosis is of several types. They are radiologically isolated syndrome; clinically isolated syndrome; relapsing-remitting MS; secondary progressive MS; primary progressive MS.

clinical features of MS

MS is a journey from being at risk, through the asymptomatic, prodromal and symptomatic phases of the disease. The most commonly seen presentations are optic neuritis, brainstem and spinal cord syndromes. During the initial phase of MS recovery from relapses often appears completely but it may leave behind some damage, e.g. following acute optic neuritis may cause abnormalities with colour vision, contrast sensitivity and depth perception persist. Few asymptomatic lesions will be found in an MRI following each attack. MS typically develops over 10-15 years, cognitive impairment and progressive brain atrophy in MRI may be seen at that phase. The progressive disability may set in and presents with spastic paraparesis, weakness, fatigue, sensory ataxia, vertigo, diplopia, cerebellar ataxia and visual failure may happen. Other less common features are bladder dysfunction, constipation, cognitive dysfunction, pain, dementia, facial palsy, impotence and epilepsy.[1,2,7,11-13]

Pharmacotherapy of MS[12-15]

The treatment for MS can be broadly classified into several categories such as: therapy of acute attacks; therapy with disease-modifying agents to reduce the biologic activity of MS; symptomatic therapy; therapies that promote remyelination.

Therapy of acute attacks

The acute attacks in a patient with MS are defined as episodes of focal neurologic disturbance lasting longer than 24 hours with a preceding period of clinical stability of at least 30 days and without an alternate explanation.[12] It happens when there is acute deterioration due to the initial demyelinating process. The treating physician should always have to distinguish between whether the exacerbation is due to disease activity or any form of pseudo exacerbation arising cause of fever or an infection. In cases of true exacerbation/new disease activity, the treatments are as follows.

Glucocorticoid therapy

This is the mainstay and first-line treatment in cases of either first attacks in exacerbations.

Intravenous methylprednisolone: High dose of methylprednisolone at a range of 500-1000 mg/day for 3-7 days.

Oral prednisolone: 625-1250 mg daily for 3-7 days with or without taper.

According to COPOUSEP trial, both oral and intravenous route has the same efficacy in terms of acute attacks. It shows that it will shorten the duration of relapse.[16] There is no evidence of long term benefit. The steroid helps in acute relapses by reducing white matter edema. No evidence suggesting immunological factors concerning the course of treatment.[17,18] The preferred regimen is intravenous methylprednisolone 1000mg daily for 5 days without an oral taper.[19] Few side effects like mental status changes, increased susceptibility to infection and gastric disturbances may happen.

Corticotropin

Corticotropin acts as an alternative to high dose corticosteroids. It is given at a dose of 80 units daily for one week followed by a tapering schedule over a second week. However, it is more expensive than steroids.[20]

Table 1: First line injectables for MS.[1,14,15,18,22-24]

Agent with FDA approval year	Drugs	Mechanism of action (MOA)	Route of administration (ROA)	Dose	Adverse effects	Trials
Interferon (INF)-beta (1993)	Type 1a (Avonex and Rebif); type 1b (Betaseron)	It decreases the production of metalloproteases by the vascular endothelium that constituents the blood-brain barrier	Intramuscular (or) subcutaneous	INF-beat 1a: 44 mcg subcutaneously thrice a week INF-beta 1b: 250 mcg subcutaneously on alternate day	Injection site reactions; flu-like symptoms; depression; neutropenia; elevated liver enzymes.	CHAMPS ETOMS BENEFIT PRISMS INCOMIN EVIDENCE BEYOND.
Pegylated INF-beta (2014)	Type 1a (Pledgridy)	Same as INF MOA. But with a long-circulating half-life	Subcutaneous	Prefilled syringe 125 mcg twice weekly	Same as above but with less incidence.	ADVANCE ATTAIN
Glatiramer acetate (1996)	Copaxone (a mixture of random polymers of 4 amino acids)	Induces type 2 T helper suppressor cells and suppresses their migration to the brain. Also, express anti-inflammatory cytokines	Subcutaneous	20 mg daily (or) 40 mg thrice weekly.	Injection site reactions, transient ischemic post-injection reactions, hepato-toxicity, Crohn's disease	REGARD BEYOND CONFIRM GLANCE GLACIER

Table 2: Other immunosuppressant injectables used in MS.[1,14,15,18,25-29]

Agent with FDA approval year	Description	MOA	Dose	Adverse effects	Trials
Natalizumab (more effective than any other DMTs) (2004)	Monoclonal antibody against the alpha 4 subunit of integrin molecule	It blocks integrin association with vascular receptors; there will be a prolonged decrease in lymphocyte count in CSF	300 mg intravenously every 4 weeks	Infusion related symptoms; progressive multifocal leuco-encephalopathy due to activation of JCV; fatigue; infection; arthralgia;	AFFIRM SENTINEL
Ocrelizumab (2017)	Recombinant human anti-CD20 monoclonal antibody	It depletes B-cell and enhances immune-suppression	600 mg every 24 weeks intravenously	Infusion reactions; skin infections; Hepatitis B reactivation.	OPERA I OPERA II ORATORIO
Rituximab	Monoclonal antibody against CD20 antigen on B cells	Thereby depletes B cell similar to ocrelizumab	1 g IV spaced two weeks for every 6 months (premedication with 100 mg steroid)	Infusion reactions; hypo-gammaglobulinemia; reactivation of Hep.B; neutropenia.	RIDOSE-MS

Continued.

Agent with FDA approval year	Description	MOA	Dose	Adverse effects	Trials
Alemtuzumab (2000)	Humanized monoclonal antibody against CD52.	It targets CD52 targeting T, B, natural killer cells and monocytes	12 mg daily for 5 days initially and 12 mg daily for 3 days after 12 months intravenously	Infusion reactions; autoimmune disorders; acute acalculous cholecystitis; neutropenia	CARE-MS I CARE-MS II
Ofatumumab (2009)	Monoclonal antibody against CD20	It causes selective B cell depletion	20 mg subcutaneously at weeks 0, 1 and 2 then 20 mg every month from 4th week	Headache, infusion related reactions; risk of opportunistic infections	ASCLEPIOS I and II

Table 3: Old immunosuppressants used in MS patients.[13-15,18]

Agents	MOA	ROA	Dose	Adverse effects
Azathioprine	It inhibits purine synthesis thereby decreasing T-cell production and causing immunosuppression	Oral	100-150 mg per day	Gastrointestinal symptoms; leucopoenia; alopecia; hepatotoxicity
Cyclophosphamide	Binds to DNA and interferes with mitosis and cell replication	Intravenous (pulse therapy)	50 mg/kg daily for 4 days followed by granulocyte colony stimulating factor	Haemorrhagic cystitis; alopecia; gonadal suppression
Methotrexate	It inhibits dihydrofolate reductase thereby acts as an antimetabolite	Subcutaneous (or) oral	7.5-20 mg per week.	Alopecia; leucopoenia; nausea and vomiting; hepatotoxicity; bone marrow suppression

Table 4: Newer immunosuppressants in treatment of MS patients.[1,13,30,31]

Agent with FDA approval year	MOA	Dose	Adverse effects	Trials
Fingolimod (2010)	Sphingosine analogue thereby modulates the receptor and inhibits lymphocyte migration	0.5 mg once daily orally	Bradycardia; headache; elevated liver enzymes; macular oedema; lymphopenia; opportunistic infections	FREEDOM TRANSFORMS
Siponimod (2019)	Similar to fingolimod but more selective	0.25 mg once daily orally	Headache; hypertension; elevated liver enzymes; Mobitz type I heart block	BOLD EXPAND
Ozanimod (2020)	Similar to fingolimod	Days 1-4: 0.23 mg once daily Days 5-7: 0.46 mg once daily On day 8 and thereafter: 0.92 mg once daily	Upper respiratory tract infections; orthostatic hypotension; urinary tract infection; bradyarrhythmia; liver injury; hypertension; macular oedema	SUNBEAM RADIANCE

Table 5: Oral immunomodulatory agents used in MS.[1,13-15,18,32]

Agent with FDA approval year	Drugs	MOA	Dose	Adverse effects	Trials
Fumarates (2013)	Dimethyl-fumarate; diroximel-fumarate; (Tecfidera)	It activates nuclear factor (erythroid-derived 2) Nrf2 pathway; (monomethyl-fumarate=active metabolite)	Initially 120mg twice daily, then increase after 7 days to 240 mg twice daily	Flushing; gastrointestinal effects; lymphopenia; abnormal LFTs progressive multifocal leukoencephalopathy	CONFIRM DEFINE
Teriflunomide (1998)	Active metabolite of leflunomide (Aubagio)	Inhibits pyrimidine synthesis and disrupts the interactions of T cells with antigen presenting cells	7 or 14 mg daily	Alopecia; gastrointestinal effects; abnormal LFTs; leukopenia; interstitial lung disease	TEMSO TOWER
Cladribine (1993)	Deoxy-adenosine analogue	It inhibits adenosine deaminase that targets B and T cells	3.5 mg/kg over two years. Two courses in a year divided into 2 cycles of 4-5 days separated by 4 weeks	Upper respiratory tract infections; headache; lymphocytopenia	CLARITY

Table 6: Agents used for symptomatic therapy in MS.[1,2,12-15,18,33,34]

Organ dysfunction	Mechanism	Symptoms	Treatment	Adverse effects of therapy
Urinary bladder	Detrusor overactivity; detrusor sphincter dyssynergia; inefficient bladder contractility; bladder hypoactivity	Urinary frequency, urgency, nocturia; urinary tract infections (UTI); incontinence	1. Anticholinergics: Oxybutynin: 5-15 mg twice daily orally; then add tolterodine (2-4 mg/day)/ propantheline (10-15 mg/day)/solifenacin (5-10 mg/day) propiverine/festerodine/as adjunctive therapy 2. Botulinum toxin: Injection onabotulinum- toxin A 200/300 IU into detrusor muscle 3. Oral/intranasal desmopressin for nocturia. 4. Phenoxybenzamine (10-20 mg/d)/terazosin (1-20 mg/d)/bethanechol (30-150 mg/day) for sphincter dyssynergia. 5. Cranberry juice/vitamin C and appropriate antibiotics for UTI	Confusion most common and other anticholinergic side effects Muscle pain; dry mouth; blurred vision Stuffy nose; sore throat Dizziness; sexual dysfunction
Bowel	Neurogenic bowel dysfunction; decreased physical activity and mobility; adverse effects of medications given for MS	Constipation; poor evacuation; incontinence	1.Laxatives: psyllium; methylcellulose; calcium polycarbophil; wheat dextrin; wheat bran; 2.Osmotic agents: magnesium sulphate, citrate, lactulose; sorbitol; glycerin; 3. Docusate sodium 100 mg twice daily;	Tolerance; dependence; muscle cramps; borborygmi Dehydration; hypernatremia.

Continued.

Organ dysfunction	Mechanism	Symptoms	Treatment	Adverse effects of therapy
			4. Prokinetics: lubiprostone; linaclotide can be used	Abdominal cramps Insomnia; respiratory difficulty may happen
Cognitive impairment	Due to direct CNS damage; differing phases of de and remyelination.	Abnormalities in attention; executive functioning; word recall; short term memory	1. Disease modifying agents of MS; 2. Cholinesterase inhibitors: donepezil; 3. Lisdexamfetamine: 40 mg/day orally	Side effects of DMTs mentioned above. Anticholinergic side effects for donepezil
Depression	Due to chronic pain; other dysfunctions arising due to disease; anxiety about the disease; medications for the disease	Low mood; helplessness; worthlessness	1.Duloxetine: for patients with concomitant pain; 2. Escitalopram/fluoxetine (20-80 mg/d) for patients with concomitant anxiety	Headache; dry mouth; blurred vision Gastrointestinal side effects; diarrhoea; insomnia
Fatigue	Characteristic finding in MS. Due to physical exhaustion.	Fatigue unrelated to amount of activity	1. Modafinil: 100-400 mg once daily orally; 2. Armodafinil: 150-250 mg once daily orally; 3.Dextroamphetamine: 5-40 mg once daily orally; 4. Methylphenidate: 5-25 mg/day orally; 4. Amantadine: 100 mg twice daily	Headache; nausea; insomnia; rhinitis Nausea; hallucinations; melanoma; neuroleptic malignant syndrome
Gait impairment	Due to weakness; fatigue; spasticity; sensory & visual loss; vestibular dysfunction	Ataxia; ambulatory imbalance; foot drop	1. Dalfampridine: 10 mg twice daily orally (potassium channel blocker)	Anxiety; focal seizure
Heat intolerance	Heat can further damage the demyelinated nerve fibres.	Heat increases or worsens the symptoms of MS. (Uhthoff phenomenon)	Dalfampridine: reduces sensitivity to visual impairment after exercise.	Same as above
Pain	Common feature in MS patients. Usually arises out of muscle weakness; spasticity and imbalance.	Trigeminal neuralgia; Lhermitte sign; Anaconda sign; persistent neuropathic pain.	1. Gabapentin (300- 3600 mg/d)/pregabalin (50-300 mg/d)/carbamazepine (100-1000 mg/d) can be used for Lhermitte sign and neuralgia; 2. Amitriptyline (25- 150 mg/d)/baclofen/tizanidine were used for MS hug	Tremors; fever; suicidal thoughts; increased creatinine. Headache; fatigue; constipation
Seizures	Most common in MS patients due to presence of lesions in frontal lobe and	Generalized tonic clonic seizure-most common	Antiepileptic drugs appropriate to the type of MS	-

Continued.

Organ dysfunction	Mechanism	Symptoms	Treatment	Adverse effects of therapy
	subcortical white matter	followed by simple/complex partial seizures.		
Sexual dysfunction	Due to drugs for depressants like SSRI; due to neurogenic cause; due to spasticity; fatigue	Decreased libido & arousal; anorgasmia; increased ejaculation latency; vaginal pain and dryness	1. Bupropion; 2. Phosphodiesterase inhibitors: sildenafil (50-100 mg)/tadalafil (5-20 mg)/vardenafil (5-20 mg) taken 1-2 hr before sex; 3.For vaginal dryness: belladonna and opium suppositories/12% gabapentin crème can be used as lubricant and analgesic	Headache; flushing; nasal congestion
Spasticity	Imbalance in the nerve impulse conduction makes the muscle contract and make tense	Exacerbating fatigue; impairing ambulation; interfering with activities of daily living	Baclofen (20-120 mg/d)/diazepam (2-40 mg/d)/tizanidine (8-32 mg/d)/dantrolene (25-400 mg/d)/dantrolene (25-400 mg/d)	Drowsiness; hypotonicity; confusion; sedation; coma
Sleep	Due to nocturia; pain; depression; effect of medication	Insomnia; restless leg syndrome; sleep related breathing disorders	Modafinil (100-400 mg/d); for insomnia usual sedative hypnotics can be given. (e.g. Z group of drugs; benzodiazepines)	Sedation; tolerance; hangover effects; dependence
Paroxysmal motor and sensory symptoms	Presence of MS lesions over brainstem may cause these effects.	Paroxysmal diplopia; akinesia; trigeminal neuralgia; ataxia; dysarthria	Acetazolamide (200-600 mg/d)/carbamazepine (50-400 mg/d)/phenytoin (50-300 mg/d) may help relieving the symptoms	Dry mouth; drowsiness; diplopia; diarrhoea
Tremor	Happens due to functional disability of cerebellum	Severe intention tremor; ataxia	Clonazepam (1.5-20 mg/d)/primidone (50-250 mg/d)/propranolol (40-200 mg/d)/ondansetron (8-16 mg/d) may help	Drowsiness; increased salivation; fatigue
Visual disturbances	Due to involvement of optic nerve; oculomotor nerve in cases of demyelination	Oscillopsia; ophthalmoplegia; nystagmus	Gabapentin/ memantine/clonazepam/ levetiracetam/baclofen; dalfampridine for nystagmus	-

Intravenous immunoglobulin

In patients who do not show improvement with glucocorticoids, intravenous immunoglobulin G (IVIG) may be safe and effective in reducing the frequency of attacks. IVIG is given as a loading dose of 0.4 g/kg/day for 5 consecutive days followed by a single booster dose of 0.4 g/kg body weight once every 2 months for 2 years.[15]

Plasma exchange

It is proposed as a supportive therapy. It enhances recovery of relapse related neurological deficits in patients with no/poor response to high dose corticosteroids.[24] It is used when is unresponsive to steroids or mostly when the relapse is rapidly progressive or severe. 5-7 exchanges: 40-60 ml/kg/exchange, every other day for 14 days may benefit the patient. Patients may experience serious complications like anaphylaxis.[21]

DMT (disease-modifying therapy)

Studies suggest that the use of DMT is associated with a lower long-term risk of MS disease progression particularly with the early use of the high-efficacy monoclonal antibody DMTs.[13]

Therapies such as physiotherapy and dietary modifications like a low-salt, potassium-rich diet are advisable to counteract the short-term adverse effects of glucocorticoids.

Therapy with disease-modifying agents to reduce the biologic activity of MS

These are the agents that target the inflammatory component which can be manifested in all phases of MS and mostly used in cases of RRMS. They can be of various categories targeting inflammatory component.[14,15,18] They are immunomodulatory agents; immunosuppressants and immune reconstitution therapies.

First-line injectables

These are the agents used to treat MS for a long period and so they are called platform drugs for MS. Based on the evidence of pathophysiology of MS which is a T-cell mediated autoimmune disease. The immunosuppressives are being tried for this condition since 1960s. Usually, they are used as a combination therapy along with other immunomodulatory drugs but rarely used as monotherapy where the other group of drugs has failed to control the disease activity. The agents are given in Table 1 and 2.

Older immunosuppressants (off-label use)

They are rarely used in the clinical practice of MS these days, due to its toxicity and availability of better drugs and is depicted in Table 3.

Newer immunosuppressants

There are few immunosuppressants which are specifically designed for use in MS. They are sphingosine-1- phosphate receptor modulators. Table 4 shows the newer immunosuppressants.

Oral immunomodulatory therapy

They decrease the relapses, the progression of disability and MRI measures of disease activity. The oral agents are given in Table 5.

Mitoxantrone

It is an anti-neoplastic compound acts by inhibiting the enzyme topoisomerase IV thereby reduces lymphocyte proliferation. By producing immune suppression, it is being used for the severe cases of RRMS and mostly it is used as a reserved agent where the other DMTs failed to produce remissions.

It is given via intravenous route at a dose of 12 mg/m^2 every 3 months. The serious adverse effects associated with mitoxantrone are cardiotoxicity and therapy relate acute leukaemia (TRAIL) due to which it is reserved for severe cases alone.[7,12-15]

Symptomatic therapy for MS

Pharmacological management of symptoms of MS that arising as a result of CNS damage. The group of drugs used under this category are not MS specific. They are as follows in Table 6.

Non-pharmacological measures for symptomatic management[1,2,13,33,34]

Bladder dysfunction

Usually, initial therapy for bladder problems is restriction of fluid intake <2 l/day; electrical stimulation of the S3 nerve root and peripheral nerve stimulation of the dorsal penile/clitoris nerves and posterior tibial nerve for detrusor overactivity; clean intermittent catheterization may be beneficial.

Bowel dysfunction

High intake of dietary fibres may reduce constipation; promote moderate amount of physical activity; avoid triggering foods/activities known to cause faecal incontinence; behavioural feedback and knowledge about perianal skin hygiene should be provided; colostomy/ileostomy in severe cases.

Cognitive impairment

Support and improvement of coping strategies; cognitive rehabilitation techniques; use of personal organizers; cognitive training for memory span; working memory and immediate visual memory are the cognitive impairment measures.

Depression

Psychotherapy; counselling; anaerobic exercises; aquatic therapy and resistance training may help the patients to overcome depression are for depression management.

Fatigue

Cognitive behavioural therapy; patient education; self-management programs are for fatigue management.

Gait impairment

Patients may require a cane/wheelchair; use of mobility aids like ankle foot orthosis; forearm crutches; walkers; scooters; electrical stimulation devices for peroneal nerve at the fibular head.

Sexual dysfunction

Effective vibrator stimulation involves high intensity, high frequency, wall powered devices that are applied just above the clitoris in women and to the ventral aspect of the penile corona in men. Energy conserving positions are recommended.

Spasticity

Physiotherapy; structured exercise programmes; transcranial magnetic stimulation; electromagnetic therapy; transcutaneous electrical nerve stimulation; whole body vibration are for spasticity management.

Speech, swallow and respiratory function

Cough assist device; respiratory muscle training; chest physiotherapy and non-invasive ventilation will ameliorate the symptoms.

Table 7: Drugs under pipeline that promote remyelination.[36,37]

Molecule	Proposed mechanism of action
Quercetin	Inhibits Notch signalling by producing gamma secretase
Olexosime	Increases number of mature oligodendrocytes in rodent animal model
Clemastine	Acts as an enhancer of OPC differentiation
BIIB033	Neutralization of leucine-rich repeat and Ig domain-containing Nogo receptor-interacting protein (LINGO-1) thereby enhances myelin sheath formation.
GNbAC1	Targets envelope protein of MS-associated retrovirus to promote OPC differentiation by reducing nitrosative stress
rHigM22	Recombinant antibody binds to vitronectin receptor and promotes synthesis of new myelin
IRX4204	Activated retinoic acid receptor gamma and enhances OPCs differentiation
GSK239512	H3 receptor antagonist enhances remyelination
VX15/2503	Humanized IgG4 anti-semaphorin 4D antibody interfering with Plexin B1 interactions thereby ameliorates OPCs differentiation and restores blood brain barrier breakdown.
Mangafodipir	Phase I

Vertigo and tremor

Vestibular rehabilitation for vertigo and deep brain stimulation of the ventral intermediate nucleus of the thalamus for tremor.

Therapies that promote remyelination[7,13,35,36]

The one of the current approaches to treat MS is by promoting remyelination which basically depends on the number of oligodendrocyte precursor cells (OPCs). The agents that can stimulate OPCs and helps in its differentiation pathway to produce proteolipid positive cells which in turn gives rise to mature remyelinating oligodendrocytes may be beneficial for repairing demyelinating lesions.

Under this category, there is no FDA approved drug for this purposes. The physicians and researchers around the world started using many drugs which has been approved for some other conditions (off-label). They are as follows:

DMT: DMT that promote remyelination: fingolimod.

Anticholinergic drug: Benztropine (it stimulates OPCs differentiation by blocking Notch signalling pathway).

Antipsychotic drug: Quetiapine fumarate (it stimulates proliferation and maturation of oligodendrocytes and increases antioxidant defences).

Other molecules being tried for promoting remyelination and not yet approved are given in Table 7.

Apart from the strategies and drugs mentioned above for the treatment of MS. There are few other several drugs tried for the treatment of MS. They are as follows.

Table 8: Drugs under pipeline for MS.[36,37]

Drugs	Phase of trial
Evobrutinib	Phase III
Ponesimod	Phase III (completed)
MD1003	Phase III
ALKS 8700	Phase III
HuL001	Phase III
Ublituximab	Phase II (completed)
Nersipirdine	Phase II
Imatinib mesylate	Phase II
Memantine	Phase II (terminated)
ONO-4641	Phase II
Temelimab	Phase II
Elezanumab	Phase II
Nanocurcumin	Phase II
ATX-MS-1467	Phase II
CNTO 1275	Phase II
NBT-NM108	Phase II
Lipoic acid	Phase II
RNS60	Phase II (withdrawn)
NeuroVax	Phase I
ANK-700	Phase I
ELND002	Phase I (terminated)
ABT-555	Phase I (terminated)
Cellular therapy with autologous EBV-specific Cytotoxic T lymphocytes	Phase I
Idebenone	Phase I
CS-0777	Phase I
Guanabenz	Phase I (terminated)
Liothyronine	Phase I

Tried and failed drugs[13-15,18,36]

Daclizumab; laquinimod; dirucotide; ciclosporin; riluzole; amiloride; masitinib; atorvastatin; firategrast; lithium bicarbonate; hydroxychloroquine; dantrolene; aspirin; acetaminophen; N-acetylcysteine; anakinra are the tried and failed drugs. Other drugs are listed in Table 8.

Since there is no definite cure for MS and being a chronic disabling disease it needs multi-modality approach with few non-pharmacological measures like diet, physiotherapy, exercise and aquatic therapy.

Autologous haematopoietic stem cell transplantation therapy (AHSCT)

Due to the immune pathology of MS, ablating the MS and followed by AHSCT is being explored for the past 2 decades. It has a high efficacy for the suppression of inflammatory activity of MS. AHSCT reported leads to neurological improvement in patients with RRMS. It is an one-off treatment to eradicate/induce long-term suppression of MS. It is considered as a rescue therapy after an escalation sequence where two or more drugs has failed. It is indicated only in severe cases of disability and disease progression.

AHSCT works by a characteristic mechanism termed as immune resetting where broad spectrum of lymphoid and myeloid cells is completely eliminated and subsequently a new immune system is gradually developed. The adverse effects of AHSCT are immune suppression, sepsis, viral infections, transient alopecia and amenorrhoea.

Mesenchymal stem cells and neural cell lines also being tried for MS and showed immunomodulatory effects in animal models.[12,38,39]

CONCLUSION

MS is a chronic inflammatory, demyelination, neurodegenerative, non-traumatic, disabling disease of the adulthood. The prevalence is increasing over the past few decades due to multitude of the etiological factors involved in the causation of the disease. The pathophysiology remains progressing and complex in nature, there are several modality of treatment strategies required to combat all the symptoms and lesions associated with MS. Even though there are 'n' number of molecules approved, used off-label, being tried in clinical trials and under pipeline there is no definitive cure of MS. The pharmacotherapy has to be personalized for each patient. There exists wide range of non-pharmacological measures for treating MS but the efficacy is still lacking. Adjunct use of other modalities like physio, exercise and aquatic therapies may impose a greater economic burden. Some of the patients with MS are completely dependent on a care taker who may fails to provide adequate management all around the clock which results in mortality and morbidity among pwMS. For developing the drug for the management of MS has many issues, few of them are non-availability of refined animal models and invitro assays; non-availability of routine investigational markers for neurodegeneration component; personalization of therapy for each patient have to be make up with the use of pharmacogenetic and proteomics tool.

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