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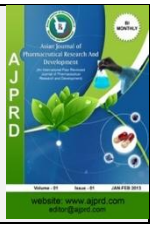

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Review Article

A Review on Current Treatment of Multiple Sclerosis Disease

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A B S T R A C T

Multiple sclerosis is a chronic inflammatory disease of the CNS characterized by the demyelination and axonal loss. The incidence of the MS is increasing worldwide. The underlying cause of MS and mechanisms behind this increase remain opaque, although complex gene, environmental interactions almost certainly play a significant role. The epidemiology of MS indicates the low serum level serum level of vitamin D, smoking and childhood obesity are likely to play a role in disease development. Diagnostic criteria have been adapted to facilitate earlier diagnosis with increased sensitivity and specificity.

Key words: Multiple Sclerosis, Relapses, Lesions, diagnosis,

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INTRODUCTION

Multiple Sclerosis is an immune mediated inflammatory demyelinating disease. It is a disease of human central nervous system (Brain, Spinal cord and optic nerves). Its name is derived from the scarring caused by the attacks at multiple sites in the CNS. MS is a disease that "short circuits" nerves. It attacks the myelinated axons in the CNS. It is the non-traumatic disease which affect the young adults, mostly in women, twice as often as men(2:1) with peak incidence between20 and 30 years of age. Multiple sclerosis is a complex, neurologic condition of white matter lesions separated by time (acute and past symptoms) and space (different parts of the CNS affected), marked by unpredictable relapses with long asymptomatic remissions[1].

Multiple sclerosis is an auto immune demyelination of oligodendrocytes in the CNS, histologically characterized by sharply defined area of myelin loss with relative preservation of axons. Low Vitamin D and smoking are the possible risks factor for developing Multiple sclerosis. In Multiple sclerosis, Inflammation causes tissue damage, called lesions in the brain, spinal cord and optic nerves and damaged myelin sheaths affect nerve signals. Most attacks are mild however some can be severe and quite debilitating.

Neurologists stated that, patients may be grouped into four major categories based on the course of the disease,

1. **Relapsing-remitting MS:** Almost 85% of the patients are affected by this form of MS. This is the most common form of MS. It is marked by relapses of symptoms followed by periods of remission, when symptoms improve or disappear.

2. **Secondary progressive MS:** The disease course continues to worsen with or without periods of remission or leveling off of symptom severity
3. **Primary progressive MS:**Primary progressive MS affects approximately 10% of patients. There are no relapses or remissions, but there may be occasional symptom severity. Symptoms continue to worsen gradually from the beginning.
4. **Progressive-relapsing MS:** This is a very rare form of MS, affecting fewer than 5% of patients. It is progressive from the start with intermittent flare-ups of worsening symptoms along the way. There are no periods of remission.

Epidemiology and etiology:

Etiology is unknown but genetic factors and environmental factors are thought to contribute. The cause of MS is not known, but this is quite incorrect. EBV,UVB, smoking and vitamin D, when combined with an individual's genetic background, and also the place of birth and latitude residence, play vital role in the causal pathway which results with MS development. Adult migrants from risk countries are at less risk of developing MS but children of migrants in Europe are at high risk. The study of migration indicates that environment trumps genetics and argue strongly for prevention for studies targeting known environmental risk factors.

EBV negative protects development of MS while symptomatic EBV infection (infectious mononucleosis)doubles the chances of developing MS. Increasingly, Multiple sclerosis is a global disease.Its prevalence increases as the latitude increases[2].However, this gradient is decreasing in Norwayand the USA. The latitudinal gradient in MS prevalence is strongly corrected with UVB exposure, which stimulate vitamin D production. Low vitamin D levels,decrease intake of vitamin D, less outdoor activities increase MS susceptibility associated with genetic polymorphisms, causing low vitamin D levels have implicated the vitamin D in the casual pathway of MS

Multiple sclerosis affects more than 2 million people worldwide and is currentlyincurable[3] . Multiples sclerosis is more common in females but this has not always been the case from the early 1900s. The sex ratio was almost equal.Since then,In most developed countries,the sex ratio hasconstantly increasing and it is now closed to 3:1 (F:M). Smoking increases MS risk upto 55% can explain upto 45% of the increased incidence of MS in women. After second World war few women smoked but the number of women smoking rapidly increased in the post war,mirroring the increasing incidence of MS in women, the observation that organic solvents and smoked tobacco, but not oral tobacco and snuff, are associated withs MS has led to the hypothesis that these agents cause post-translational modification through antigen presentation that occurs in the lungs. MS risks modification occurs throughout the life, starting in utero. On MS susceptibility, there is influence of genetics. In a family history of MS about two in ten patients have MS[4]. According to genome wide association studies, it has been identified that more than 150 single nucleotide polymorphisms are associated with MS susceptibility. The studies of mendelian randomization provided a proof for a role of vitamin D and obesity as a risk factors causing disease.

Recently, some work has uncovered genetic differences between relapsing-remitting MS and Primary progressive MS. Genetic variations which are associated with other progressive MS. When all the MS associated alleles are taken into an account, it indicates the additional risk for progressive disease superimposed on underlying genetic susceptibility[5]. Evidence of differential gene transcriptionbetween RRMS and PPMS again hints at individual differences on a background of shared genetic risk.

Signs and Symptoms:

Patients having MS tend to have their first symptoms between the ages of 20 to 40. Usually the symptoms get better, but then they come back. Some come and go, while others linger.

No two people have exactly the same symptoms. You may have a single symptom, and then go months or years without any others. A problem can also happen just one time, go away, and never return. For some people, the symptoms get worse within weeks or months.

Early Signs of MS:

For many people, the first brush with what's later diagnosed as MS is what doctors call Clinically Isolated Syndrome (CIS). The episode of neurological symptoms usually lasts 24 hours. It happens when your immune system mistakenly tells your body to attack myelin, the protective sheath over nerve cells in your brain and spine[6]. You may hear your doctor call this demyelination. It causes scars, or lesions, that make it harder for signals to travel between your brain and your body.

These are two types of CIS:

- Mono focal episode: You have one symptom.
- Multiple episode: You have more than one symptom.

The most common symptoms in CIS are:

Optic neuritis: This condition damages the nerve that connects your eye to your brain. It usually affects just one eye, but in rare condition, it involves both. You might notice:

Blurry vision and pain in your eye

Numbness and Tingling: This condition affects your legs. You might feel:

An electric shock-feel like feeling when you move your head or neck. It may travel down your spine or into your arms or legs.

Not everyone who has will get MS. The odds are higher if you have lesions in your brain from loss of myelin. If you have another CIS or other MS symptoms later, Doctor will do a test called MRI that takes a picture of brain to look for them.

Primary Symptoms of MS

These are come from ongoing damage to your myelin. They aren't pleasant but your MS treatment team can help you keep most of them under control with medications, rehabilitation, and other tactics. The most common symptoms are:

Emotional changes and depression, the disease damages nerve fibers in your brain, and that can affect your emotions.

Fatigue: You may feel very tired. It often comes on in the afternoon and causes weak muscles, slowed thinking, or sleepiness.

Secondary Symptoms of MS

These problems created by your primary MS symptoms, not by damaged myelin.

- Not being able to empty your bladder can lead to a bladder infection.
- If you have trouble in walking and are often fatigued, you're likely to become less active. That can make a toll on your muscle tone, make your breathing shallow, and even affect your bone density.

Tertiary Symptoms of MS

These are the social, psychological, and job-related problems of life with MS.

If MS makes it hard for you to walk or drive, you may not able to do your job well.

- Because it's tough to get around and hard to talk to people about what life with chronic disease is like, you may not be as social as you once were.

As MS varies so much, it's best not to compare yourself with other patients of MS. Your experience is likely to be different. Most people learn to manage their symptoms and can keep leading full, active lives[7].

Pathophysiology and Immunology:

Multiple sclerosis is the chronic inflammatory disease of the CNS. Lymphocytes cross the blood brain barrier and myelin antigens in the central nervo system.Demyelination is the primary pathological feature. Axonal loss is an important pathological finding correlates with disease progression and disability. In Charcot's descriptions of the Pathology which is associated with 'sclerosed plaques' which affects the periventricular area of pons and spinal cord.The pathological hallmark of MS is perivenular inflammatory lesions, which leads to demyelinating plaques the inflammatory infiltrates contain T-lymphocytes which is dominated by MHC class I CD8+ T-cells. B-cells and plasma cells are also present which is in much lower numbers. As a result, oligodendrocyte damage and demyelination occur[8] .In the early stages of disease axons are relatively preserved, as it progresses axonal damage which is not reversible. The 'classical active lesion', with profound inflammation of lymphocytes, predominates in RRMS which is seen less commonly in progressive diseases, where lesions tend to have a lesion which is inactive surrounded by an arrow rem of microglia and macrophages which is activated.

Despite a clinical distinction between progressive MS and RRMS, the inflammatory changes are seen in both progressive MS an RRMS.Pathologically, albeit to a greater degree in relapsing-remitting disease. The inflammatory infiltratecomposition in relapsing–remitting and progressive MS is same, but in progressive MS the proportion of B-cells and plasma cells is higher[9].The cytokine profile of activation stage of B-cells and T-cells differ between clinical disease types remains unclear.

Remyelination is most commonly seen in progressive MS. As it is seen in every stages of disease. Higher level of demyelination is seen in patients with secondary progressive MS and also a reduction axonaldensity in the normal appearing white matter in the cervical spinal cord in PPMS. There is no single characteristics histological difference between MS subtypes. But instead a difference in the proportion of areas showing particular features[10]. Thus, three clinical forms of MS have been defined, the pathological changes form of continuumwhich fits with gradual clinical disease evolution in patients, form RRMS two secondary progressive MS over a period of years.

Clinical Features:

▪ Abrupt hearing loss

▪ Encephalopathy

▪ Prominent fever, headache, impairment of consciousness

Optic neuritis:

▪ Inflammation of the uvea

▪ Severe optic disc edema

▪ Very severe visual loss without recovery

Transverse myelitis:

▪ Radicular pain

▪ Hyperacute non-progressive onset

▪ Anterior spinal artery distribution

Diagnosis:

- Find evidence of damage, in at least two separate areas of the CNS, which includes the brain, spinal cord and optic nerves.
- Then determine that damaged areas developed at least one month apart.
- Exclude all other possible diagnoses.
- Observe all the symptoms that lasts for more than 24 hours.
- perform MRI (The most sensitive imaging test foe MS)
- perform a spinal tap and examination for oligoclonal bands

Drugs used in the treatment of Multiple Sclerosis:

Up until twenty years ago, for the treatment of Multiple sclerosis (MS), only steroids were available. Recently,

several new compounds have been developed. The evaluation of the effectiveness of treatments for MS is complex, and identifying the most appropriate treatment for an individual patient may be difficult. The following drugs are used in the treatment of MS.

Drugs	Brand (Manufacturer)	Dose	Dosing frequency	Route	Adverse effects
Interferon beta-1a	Avonex (Biogen Idec)	30 mcg	Once weekly	IM	Local reaction at injection site Leukopenia Mood disorders Liver and thyroid dysfunction
Interferon beta-1a	Rebif (Pfizer)	22 or 44 mcg	Three times weekly	SQ	Same as interferon beta -1a
Interferon beta-1b	Betaseron (Bayer)	0.25 mg	Every other day	SQ	Same as interferon beta -1a
Interferon beta-1b	Extavia (Novartis)	0.25 mg	Every other day	SQ	Flu-like syndrome after injection Mood disorders
Glatiramer acetate	Copaxone (Teva)	20 mg	Once daily	SQ	Local reaction at injection site Systemic reaction after injection Allergic reaction
Natalizumab	Tysabri (Biogen Idec)	300 mg	1-hour infusion every 4-weeks	IV	Liver dysfunction Allergic reaction
Fingolimod	Gilenya(Novartis)	0.5 mg	Once daily	PO	Liver dysfunction, Macularedema Leukopenia and lymphopenia
Mitoxantrone	Novatrone	5-12 mg/m^2	Short infusion every three months	IV	Nausea, vomiting, infection and leukopenia
Dimethyl fumarate	BG-12	240 mg	Twice daily	PO	Flushing, nausea, Lymphopenia
Teriflunomide	Aubagio	7 mg or 14 mg	Once daily	PO	Headache, liver problems and influenza
Laquinimod	Teva	0.6 mg	Once daily	PO	Back pain, increased liver enzyme levels

Beta-Interferons (Avonex, Rebif, Betaseron, Extavia): Beta interferons have two forms of interferons, Interferon beta-1a (Avonex, Rebif) and Interferon beta-1b (betaseron,Extavia). This are approved by the FDA for the treatment of Multiple sclerosis. This are naturally occurring cytokines secreted by immune cells. Viral replication is inhibited by these agents through a variety of immunomodulating and antiviral activities. Although, the mechanisms of action of interferons beta-1a and beta-1b in MS is unknown. The regulatory functions in the immune system are performed by the cytokines.

Patients who are treated with any of the beta interferon agent have high risks for the liver function abnormalities, leukopenia, thyroid disease and depression. It is compulsory to monitor liver enzymes (alanine amino transferase and aspartate amino transferase) and the White blood cell (WBC) count with differential upon the initiation of treatment and periodically thereafter[11].The most common adverse effects of beta-interferons are flu like symptoms (e.g., fever, chills, muscle aches and fatigue) which occurs in approximately 60% of patients. Other common AEs associated with beta interferons include injection site reactions and worsening of pre-existing spasticity. Treatment of any other of the beta-interferons can result in development of neutralizing antibodies. Peripheral neuropathy was reported as a side effect of treatment with interferon-alpha but not with interferon-beta. The neuropathy dissipated after discontinuation of interferon-alpha.

Glatiramer Acetate (Copaxone): Glatiramer Acetate was originally designed to mimic and compete with myelin basic protein. Glatiramer acetate is a synthesized copolymer polypeptide mixture consisting of L-glutamic acid, L-lysine,L-alanine,L- tyrosine. Glatiramer acid reduced the rate of attacks in patients with relapsing-remitting MS. The mechanism of action of this drug is different from that of the beta-interferons. Therefore, patients may respond to this agent differently. This medication is recommended as a first-line treatment in patients with relapsing-remitting MS and in patients who cannot tolerate beta-interferons. In MRI evaluations of patients with relapsing-remitting MS, glatiramer acetate reduced inflammatory activity by one-third. Although, the precise mechanism of action of glatiramer acetate is unknown, but in-vitro observations suggest that upon administration glatiramer acetate-specific suppressor of T cells are induced and activated in the periphery. Unlike the beta interferons, Glatiramer acetate does not cause liver function abnormalities, leukopenia or thyroid disease, and it is not associated with depression or a flu-like reaction.

Natalizumab (Tysabri): Natalizumab is the first monoclonal antibody, approved for the treatment of MS. It is a recombinant humanized immunoglobulin (IG4). Like the beta-interferons and glatiramer acetate the precise mechanism of action of Natalizumab in patients with MS

has not been fully defined. Natalizumab binds to the alpha 4-subunit of alpha 4-beta1 and alpha 4-beta7 integrins expressed on the surface of leukocytes (except neutrophils) and it inhibits the alpha 4-mediated adhesion of leukocytes to their counterreceptors. Natalizumab decreases the number of contrast-enhancing and new MRI lesions. It also decreases the proportion of new MRI lesions that become persistent black holes, which suggests an inhibition of mechanisms leading to axonal damage. The main complication of Natalizumab treatment is the risk of progressive multifocal leukoencephalopathy, a severe potentially life threatening central nervous system infection caused by the reactivation of JC virus. JC virus is the widespread in the population and usually remains in the kidneys[12]. The clinical onset of progressive multifocal leukoencephalopathy may resemble a relapse of MS and therefore requires a careful diagnostic workup and proper treatment. Clinicians should consider the risk factors for progressive multifocal leukoencephalopathy as a combination of three conditions: treatment with Natalizumab lasting longer than two years, prior use of immunosuppressants and the presence of anti-JC virus antibodies. In patients without anti-JC virus antibodies, the estimated risk of progressive multifocal leukoencephalopathy is less than 0.1 per 1000 patients, whereas in patients with all three conditions, the risk is 11.1 per 1000 patients.

Fingolimod (Gilenya): Fingolimod is the first oral treatment for MS. This drug is approved by the FDA to reduce relapses and to delay the progression of disability in patients with relapsing forms of MS. Fingolimod acts by internalizing the sphingosine-1 receptors, which are expressed on lymphocyte surfaces, thus preventing T-cell migration from secondary lymphoid organs to circulating blood. Sphingosine-1 receptors are also present in cardiac tissue, their block may lead to bradycardia and delayed atrioventricular conduction. Therefore, after the first administration of fingolimod, cardiovascular monitoring is needed for six hours. Moreover, the use of this drug is associated with leukopenia, increased risk of infections (mainly related to varicella-zoster virus), macular edema, increased risk of skin cancer and liver dysfunction.

Mitoxantrone (Novantrone): Mitoxantrone interferes with RNA synthesis and inhibits DNA repair, this medication is a potent inhibitor of topoisomerase II, an enzyme responsible for repairing damaged DNA. Prior to its approval for use in MS treatment, Mitoxantrone was used to treat certain forms of cancer. Mitoxantrone suppresses the activity of T-cells, B-cell and macrophages that are thought to lead the attack on the myelin sheath. Mitoxantrone treatment when combined with steroids reduced the proportion of patients with new contrast-enhancing MRI lesions after 6 months compared with steroids alone. Adverse effects are nausea and vomiting, alopecia, urinary tract infection and infertility. Cyclophosphamide and azathioprine have been considered as potential therapies for MS with immunosuppressive effects but azathioprine is not FDA approved specifically for MS. Cyclophosphamide is an alkylating agent of DNA, and azathioprine is a purine antagonist that affects DNA replication. As confirmed by MRI studies, their actions seem to reduce inflammatory activity in the central nervous system.However, their safety profiles are characterized by several adverse effects, such as leukopenia with increased risk of infection [13].

Dimethyl fumarate: Dimethyl fumarate is an orally administered drug. Dimethyl fumarate acts by inhibiting proinflammatory cytokines and activating an antioxidant pathway in response to the cytotoxic effects of oxidative stress. Dimethyl fumarate treatment reduced MRI activity and the relapse rate. Reported adverse effects include flushing, nausea, liver dysfunction and lymphopenia.

Teriflunomide: Teriflunomide is an oral agent that inhibits the synthesis of DNA pyrimidine bases in rapidly dividing cells such as T and B cells and macrophages, and may thereby reduce inflammation and likely produce immune suppression. It reversibly inhibits dihydro-orotate dehydrogenase(DHODH), DHODH is a mitochondrial membrane protein which is essential for pyrimidine synthesis. There is some evidence from in vitro studies suggesting that teriflunomide induces Th2-mediated anti-inflammatory cytokine activation. A phase II study examined the efficacy of teriflunomide daily doses of 7 and 14 mg compared with placebo over 13 weeks in patients with RRMS and SPMS. Teriflunomide efficacy was measured by the number of new lesions as observed on MRI scans. Active treatment resulted in 61% reduction in MRI activity compared with placebo. Teriflunomide was generally well tolerated and occurrence of adverse events was similar between the two treatment groups. Serious adverse events included elevated liver enzyme levels, hepatic dysfunction, neutropenia and trigeminal neuralgia.

Laquinimod: Laquinimod is a derivate of linomide, it is am immunomodulatory agent which is used as a once-daily oral drug for the treatment of MS. It is an experimental drug in phase III trials for relapsing MS, and phase II trials for PPMS. It may prevent immune cells from reaching the brain. Laquinimod has both anti-inflammatory and neuroprotective actions, and it may affect the levels of certain cytokines, which are substances secreted by immune cells, as well as diminish the immune cells that gain to the brain and the spinal cord. Phase III studies have shown that, there is a 23% of reduction in annual relapse rate compared with placebo, a 33% decrease in disability progression and 44% reduction in brain volume loss.

CONCLUSION:

MS is a progressive disease with no cure so far. Although, the treatments are available to manage the disease. The FDA has approved the medications for the treatment of relapsing-remitting MS. All have been shown to reduce the number of relapses or attacks and the number of new lesions or plaques on MRI brain scans. Five injectables-four beta-interferons (Avonex, Rebif, Betaseron, Extavia) and Glatiramer acetate are generally viewed as first-line treatments of MS. Most experts recommend that, treatment begin with one of these drugs as soon as the diagnosis of relapsing-remitting MS has been confirmed. Natalizumab and Mitoxantrone are included in second line therapies of MS. Patients with relapsing-remitting MS, which is the most common form of MS experience attacks of worsening

neurological functioning which is followed by periods of remission, characterized by partial or complete recovery.

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