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Review Article

A REVIEW ON ADVANCEMENTS IN MULTIPLE SCLEROSIS AND ITS TREATMENT

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ABSTRACT

Multiple sclerosis is a chronic autoimmune demylination disorder of central nervous system. Although the etiology and pathophysiology of multiple sclerosis remains still unclear but the present study shows that the cause of multiple sclerosis is multifactorial and also includes several environmental factors like Vitamin D deficiency, infectious agents, smoking etc. Advancement of disabilities can be prevented by early diagnosis and treatment. Current search in neuropathology, neuroimmunology, neurobiology, neuroimaging together with clinical neurology provide information that multiple sclerosis is a spectrum not a single disease. There are many number of multiple sclerosis treatments available today which show a decrease in the frequency of relapses and disease progression. Conventional treatment for multiple sclerosis depends on the use of immunomodulatory and anti-inflammatory drugs, and improves neuronal function and stop the disease progression. Clinical studies have shown that when compared to the known side effects of injectables such as glatiramer acetate and beta interferon, newer drugs have acceptable side effects. Clinical evaluation and monitoring of efficacy and safety of the available drugs is necessary for achieving better quality of life for the patient. In this article recent approaches and advancements in treatment of multiple sclerosis is reviewed.

Keywords: Multiple sclerosis, Vitamin D deficiency, Immunomodulation, Anti-inflammatory

1. INTRODUCTION

Multiple sclerosis (MS) is a chronic auto immune demyelination disorder of central nervous system. An autoimmune disease means our own immune system mistakenly attacks our own healthy body parts. MS destroys the myelin sheath which is the protective covering of the nerve cells. Damaged myelin sheath causes a decrease in the flow of impulse between brain and spinal cord and from brain to the rest of the body parts. It is commonly observed in adults [1]. Patients who are diagnosed with MS are between the ages 15 to 50. Advancement of disabilities can be prevented by early diagnosis and treatment. MS is not an epidemic disease. Clinical studies have shown that in 1970 prevalence rate was found to be 0.17 to 1.33 per 100,000 in different parts of India. Current estimation stands at about 7 to 10/100,000, and this figure may still be higher than large sections of Indian population. Rough estimation has shown that in Canada 55,000-75,000 people are affected by MS. In USA over 40,000 people are effected by MS. Worldwide 2.5 million people are suffering from MS. USA, Germany, Denmark, Australia, Canada etc have a high prevalence of MS. Women's are most affected by the MS compared to men by 2:1 ratio. 80% at diagnosis have relapsing-remitting (periodic instability between relapses) form of multiple sclerosis [2, 3]. The cause of this disease is still unknown. However, scientists believe that smoking, certain infections like Epstein-Barr virus, temparate climatic conditions, certain auto immune disease like thyroid disease and type-1 diabetes, drinking beverages and Vitamin D deficiency plays an important role in the development of the disease. In its pathogenesis some risk factors have been implicated which include environment agents and genetic susceptibility. This disease develops in person with Vitamin c deficiency, smoking, season of birth, Epstein Barr virus infection, latitude etc. Stress can also be a factor for occurrence of this disease [4]. Damage to the immune system leads to tenderness and ruins myelin and oligodendroglial cells (it produces myelin in the central nervous system). Demyelination obstructs the flow of impulse which leads to a variety of manifestation. On demyelinated axons we can observe formation of plaque which leads to reduce in the transmission speed of impulse. Throughout the CNS demyelinated axons are dispersed erratically. The most repeatedly damaged areas are the optic nerve, cerebrum, brain stem, cerebellum and spinal cord. Ultimately the

axons themselves deteriorate resulting in immutable and permanent impairment.

These lesions are found in MS patients, they are only detected after post mortem (autopsy) [5] Symptoms varies from person to a person based on what part of the CNS lesion (means wound or injury of a region in an organ) form. Symptoms commonly associated with MS are numbness of skin and limbs, weakness, visual disturbance, extreme tiredness, memory loss, depression, urinary and bowel problems, double vision, muscle cramps, mood swings, ataxia (lack of muscle control) etc [6] . Advancement of disabilities can be prevented by early diagnosis and treatment. There are many number of multiple sclerosis treatments available today which show a decrease in the frequency of relapses and disease progression. Some of them are subcutaneous interferon (IFN) beta 1b, subcutaneous glatiramer acetate, natalizumab, fingolimod, oral agents such as teriflunomide and dimethyl fumarate, alemtuzumab etc. From the evidences of the recent study relapsing-remitting multiple sclerosis was found to be the most common among the Iranian population. The next common subtypes of multiple sclerosis are secondary progressive multiple sclerosis and primary progressive multiple sclerosis [7]. Relapsing-remitting multiple sclerosis is most common in women compared to men [8, 9]. The most common symptoms found in patients with RRMS include fatigue, balance problem and motor dysfunction [10- 12]. Early diagnosis is the best way to overcome multiple sclerosis. This review mainly states the recent advances used in the treatment of multiple sclerosis and how to overcome the problems caused by multiple sclerosis.

2. POSSIBLE MOLECULAR CHANGES IN MS

Mostly people are affected by RRMS followed by a decrease in neurological functions termed as secondary progressive multiple sclerosis. It causes relapses when demyelinating plaques occur in the spinal cord or brain [13]. Multiple sclerosis is an autoimmune disorder of the central nervous system mediated by T-lymphocytes.

Based on the autoimmune mechanism a number of pathophysiological observations cannot be simply explained. The 1st pathological studies have shown that progressive component of the disorder sustains despite immunosuppressive interventions that relatively stops the inflammatory disorder function [14]. The 2nd pathological studies have shown that without a preceding inflammatory reaction development of some lesions [15, 16]. The 3rd pathological studies are about the finding of a diffuse cerebral white matter hypoperfusion.

Number of studies using positron emission tomography or a single photo emission computed tomography identified decreased cerebral blood flow in the white and gray matter of patients suffering with multiple sclerosis [17-19]. MRI provides parameters of brain perfusion like cerebral blood volume, vascular mean transit time, cerebral blood flow. Using this method identify the decreased cerebral blood flow and mean transit time throughout the normal-appearing white matter in RRMS patients [20]. The cerebral blood volume and cerebral blood flow are reduced throughout the normal appearing white matter regions in both form of multiple sclerosis compared with controls.

Disconnection between the cerebral cortex and the sub-cortical structures because of white matter damage or reduced cerebral blood flow in normal appearing white matter causes hypoperfusion gray matter in multiple sclerosis [21-25].

Ge et al. explained that hypoperfusion in normal appearing white matter as a peripheral vasculopathy [26]. Microvessel thrombosis is observed within inflammatory infiltrates located around small or medium-sized veins [27] and in perivascular spaces surrounding arterioles [28, 29]. A primary vascular pathology leads to cerebral perfusion defects in multiple sclerosis patients. Astrocytes are the cells which are involved in regulating cerebral micro circulation in the CNS. Astrocytes present in the white matter are maintaining the ion balance at the Nodes of Ranvier [30, 31].

During action potential propagation potassium is released at the nodes of Ranvier which are soaked up through inward rectifying potassium channels like k_{ir} 4.1 by astrocytes. To restore the ionic balance in the axonodal region they are spatially buffered [32]. Just like gray matter astrocytes, white matter astrocytes also contain calcium-activated potassium channels in their prevascular astrocyte end feet. Buffered potassium is released in the peri-vascular space through calcium-activated potassium channels to activate inward rectifying potassium channels in k_{ir} 2.1 present in vascular smooth muscle cells.

Vasodilation occurs in the smooth muscle because of the hyperpolarization of vascular smooth muscle cells which lead to closure of voltage- dependent calcium channels [32, 33]. Therefore, reduced axonal activity leads to decreased potassium efflux at the nodes of Ranvier. Thus, represents the mechanism through which less potassium is absorbed and delivered into the perivascular space.

Astrocytes contain a number of neurotransmitter receptors [34]. Astrocytes present in normal appearing white matter and MS white matter lesions were found to be insufficient in beta 2 adrenergic receptors [35, 36]. Nor epinephrine causes activation of astrocytic beta 2 adrenergic receptors which lead to the increase in the formation of intracellular cyclic adenosine monophosphate. Cyclic adenosine monophosphate prevents the transformation of astrocytes into facultative antigen-presenting cells [35, 37], which induces brain-derived neurotrophic factors, neuregulin and growth factors for oligodendrocyctes and promotes the transformation of glycogen to lactate. Finally, it is transported as an energy source to axons.

Alternation in these mechanisms explains the occurrences of non inflammatory focal demyelinating lesions and inflammatory lesion in the progressive phase of multiple sclerosis [38, 39]. Astrocytic beta 2- adrenergic receptor is also responsible for decreased cerebral blood flow in white matter.

Systemic vascular dysregulation is another factor responsible for reduced perfusion of the white matter in multiple sclerosis, which is associated with increased endothelin-1 plasma levels. With increased endothelin-1 plasma levels the blood flow velocities in extraocular blood vessels were reduced in patients with multiple sclerosis [40].

Based on the myelin protein loss, the pattern of oligodendrocyte destruction, immunopathological audience of complement activation, and the geographical extension of plaques four different patterns of demyelination have been described in multiple sclerosis [41]. Type 3 demyelinating plaques in multiple sclerosis exhibits similarity with those found in acute ischemic stroke in the white matter, with apoptotic like oligodendrocyte destruction and preferential loss of myelin associated glycoprotein [42].

In these plaques other myelin proteins like oligodendroglia glycoprotein, myelin basic protein and proteolipid protein remains safe. Oligodendrocyte apoptosis active multiple sclerosis lesions and acute ischemic white matter lesions with myelin-associated glycoprotein loss reveal a nuclear expression of hypoxia inducible factor-1alpha in glial cells [43, 42]. Hypoxia-inducible factor-1 alpha is expressed in oxygen deficiency conditions and with hypoxia-inducible factor-1 beta forms heterodimers, which can be seen in all cells and is essential for hypoxia-induced transcription changes, but does not respond to changes in oxygen tension. Hypoxia-inducible factor-1 heterodimers acts as transcription factors when they are translocated to the nucleus and induces gene expression of a number of molecules involved in an angiogenesis, cell growth, energy metabolism and vascular control [44].

In leukoaraiosis similar upregulation of hypoxia inducible factor-1alpha in cerebral white matter has been found [45]. In RRMS patients it has been found that increased passage of blood in active plaques preceded breakdown of BBB visualized by Gd leakage in the plaque.

Subcortical ischemic brain disorder leads to leukoaraiosis which is linked with decreased cerebral flow in white matter [46] which is the common cause for occurrence of cognitive impairment. The cognitive symptoms are very similar in both leukoaraiosis and multiple sclerosis [47]. In a preliminary study, neuropsychological dysfunction in patients with both RRMS and PPMS, and relationship between perfusion changes in deep gray matter and NAWM has been found [48].

Current search in neuropathology, neuroimmunology, neurobiology, neuroimaging together with clinical neurology provide information that MS is a spectrum not a single disease. These lesions are more specifically found in MS patients, they are only detected after post mortem (autopsy) [49].

3. RECENT APPROACHES TO TREAT THESE POSSIBLE MECHANISMS

Previously multiple sclerosis is treated by some wide spectrum immunosuppressants like cyclophosphamide, methotrexate and azathioprine. Subcutaneous interferon (IFN) beta Ib was the first disease changing drug which was approved by FDA (American Food and Drug Administration). This drug created a new era in the therapy of multiple sclerosis later subcutaneous glatiramer acetate (GA), intramuscular IFN beta 1a and subcutaneous IFN beta Ib followed. These drugs have been used for nearly 30 years in the treatment of multiple sclerosis, and due to their almost perfect long-term safety they are still being used in the first line [50].

Later on after subcutaneous interferon (IFN) beta Ib and subcutaneous glatiramer acetate, the first drug which was approved by American Food and Drug administration was a humanized monoclonal antibody, natalizumab in 2004. It blocks the integrins Alfa 4 present on lymphocyte surface, later on they interfere with their attachment to the VCAM-1 or cluster of differentiation 106 (CD 106) present in the endothelial surface of the vascular system on the spinal cord and

brain, and blocks the inflammation in the spinal cord and brain.

In 2005, natalizumab approval was temporarily suspended for its progressive multifocal leukoencehpalopathy in clinical trials. For the early detection of progressive multifocal leukoencehpalopathy, touch safety system has been implemented, and finally natalizumab was re-approved in 2006. Presence of anti-John Cunningham virus antibodies, immunosuppressive treatment, use of natalizumab over two years are the three major factors responsible for developing PML under natalizumab treatment. Progressive multifocal leukoencehpalopathy risk becomes much less if the patients is negative for John Cunningham virus antibody, and if there is no prior immunosuppressant treatment.

TYGRIS-Tysabri global observational program in safety-under this program company producing natalizumab developed recording systems and globally databases to follow up infections, neoplasias (abnormal growth of tissue) and other adverse effects occurring under natalizumab treatment. But these failed to follow progressive multifocal leukoencehpalopathy cases and also malignant melanoma cases associated with natalizumab. Photographs of the patient with epidermal nevus should be taken before starting the treatment with natalizumab +and should check the changes in the nevus' appearence [51].

Use of Rituximal an anti-CD20 monoclonal antibody was considered in multiple sclerosis regarding apoptosis of B-cells in circulation, leading to reducing complement and antibody mediated cytotoxicity which may lead to the decrease in antigen presentation after understating the role of the humoral immune system in pathogenesis of multiple sclerosis. Rituximab was tested as one study for PPMS and in 3 heterogeneous studies for RRMS, and was very effective for the relapses in relapsing-remitting multiple sclerosis [52].

In many countries for these reasons it has been used off label for multiple sclerosis. Patients receiving rituximab have shown a decrease in anti-JCV antibody and this happened because of a decrease in antibody production due to rituximab [53].

Fingolimob a sphingosine 1 phosphate analogue was the 1st oral agent approved for multiple sclerosis in 2010. Sphingosine 1 phosphate receptor sub-groups are present on many cells like S1P receptors 1 to 3 are present in cardiovascular system, central nervous system, immune cells, and endothelial cells. S1P1 is present in B cells and T cells, and S1P4 is present in hematopoietic tissues and lymphoid, and S1P5 is present in CNS.

In *in vivo* conditions fingolimob is phoshorylated with sphingosine kinase. And later on with high affinity the resulting fingolimob phoshphate binds to 4 out of 5 sphingosine 1 phosphate receptor. It induces the degradation of the receptor by binding to the receptor on the surface of the lymphocytes, thus diminishes the auto aggressive lymphocytes attacking the central nervous system. In the patients with relapsing multiple sclerosis fingolimob decreases the T helper 17 cells in the peripheral blood. Memory T cells lacking L-seletin and CDR7 receptors, are expressed in intestinal lamina propria, kidney, intestinal epithelial surface, peritoneum and lungs. Clinical trials show that fingolimob diminishes the new or enlarged T2 lesions or active lesion on brain MRI, attack rate, brain atrophy, disability progression [54].

The side effects associated with fingolimob are liver function test abnormalities, back ache, cough, headache, diarrhoea, viral infection. Heart rate may decrease at first 6 hours following the 1st dose because of reduced atrioventricular transmission.

This reversible effect occurs because of receptor desensitization on atrial myocytes. The patient is kept under observation for 1st six hours, and overnight to check if there is any abnormal slow heart rate. Only 2 percent of the total lymphocytes are present in the circulation so that fingolimob does not cause lymphodenopathy. Lymphocyte levels return to normal range after the completion of treatment section. Because of a decrease in memory T cell functions fingolimob may cause increase susceptibility for viral infections, but does not show any impact on humoral immunity against bacteria or viruses [54].

In TRANSFORMS trials they are two fatal infections one is herpes encephalitis, and the other is primary varicella zoster found in 1.25 mg of dose group [54]. Since, fingolimob crosses BBB it shows effects on CNS cells and neurons. Fingolimob reduce neurodegeneration and cause endogenous repair mechanisms.

The 2nd drug which was approved as an oral medication for multiple sclerosis is teriflunomide. It is used to treat rheumatoid arthritis, and it is the active metabolite of leflunomide, In TEMSO trail 7 mg dose was compared with a 14 mg dose to placebo in relapsing-remitting attack. There were no changes regarding cerebral atrophy [55]. In TOWER trial, teriflunomide confirmed disability progression by reducing the attack rate [56].

In TOPIC trial, both 7 mg and 14 mg doses reduced the growth of relapsing-remitting multiple sclerosis in MS patients with CIS [57]. The common side effects seen in clinical trials include liver enzyme abnormalities, headache, nausea, diarrhoea and baldness. In 15% of the MS patients liver dysfunction test abnormalities was observed, so they should be continuously monitored during the treatment. Baldness is seen in 13% of MS patients and gets recovered after 1st month.

Teriflunomide may take months to get eliminated from plasma. In pregnancy or hepatotoxicity conditions elimination of teriflunomide can be increased by using activated carbon or cholestiramine [58].

Dimethyl fumarate (DMF) is the 3rd oral drug approved for relapsing-remitting multiple sclerosis. The combination 3-ethyl hydrogen fumarate and dimethyl fumarate have been used in Germany to treat psoriasis. In 2013, FDA has approved dimethyl fumarate for relapsing-remitting multiple sclerosis. Dimethyl fumarate is a first-line drug with cytoprotective and immunomodulatory effects. Dimethyl fumarate treatment increases anti-inflammatory Th 2 cells, decreases the memory T cells and decreases the Th1/ Th17 proinflammatory cells [59, 60].

In DEFINE trials patient receiving dimethyl fumarate show a decrease in new or enlarging lesion, relative risk for attacks and EDSS (expanded disability status) as compared to placebo [61]. In CONFIRM trial 2 doses of dimethyl fumarate were compared with daily subcutaneous GA and placebo, and patients who are receiving 2 or 3 times daily glatiramer acetate and dimethyl fumarate show a relative decline in attack rate. Finally there will be a decrease in the number of patients with new T2 lesions and attack [62]. Including several side effects lymphopenia is also seen in 6% of the multiple sclerosis patients.

It may also become severe and can lead to progressive multifocal leukoencehpalopathy. Periodic lymphocyte monitoring should be done because in the 1st year of treatment there will be a decrease in 30% of lymphocyte count and sometimes there may be a severe decrease which may cause infections [56-58].

Other common adverse effects associated with dimethyl fumarate are diarrhoea, dyspepsia, abdominal pain, etc. During, dimethyl fumarate use only less than 1% of patients have serious GI side effects [55-63].

Like subcutaneous injections, oral medications are also effective in the treatment of relapsing-remitting multiple sclerosis for over decades.

The disease modifying treatments for MS aiming to control the disease are available. Most DMTs target the activation of T cells and related immune reactions, immunopathology of multiple sclerosis, which is indicated by the presence of B cells in chronic and acute plaques of multiple sclerosis. These have led to the targeting of B cells to control the disease activity [64].

There are some drugs which are not approved yet by FDA and trails are still ongoing. Laquinimod is a synthetic agent and was found to be effective in multiple sclerosis in phase 2 trails [65]. It was actually modified from roquinimex. During two years of treatment peripheralmononuclear blood cells of the multiple sclerosis patients did not show any changes by both function and immune response, and concentration [65, 66].

Siponimod is a functional antagonist of SIP receptor type 1 and 5 and has a shorter half life compared to fingolimob [67]. Qzanimod is another S1P 7 and S1P 5 modulator, and its half life is 19 hours. After stopping the treatment lymphocyte levels returns to pre-treatment levels within one week [68]. Ponesiomod is a selective S1P 1 agonist, and its half life is 30 hours. After stopping the treatment there will be fast elimination within one week, which leads to fast reversibility of its pharmacological action [69, 70].

4. CONCLUSION

Worldwide 2.5 million people are suffering from multiple sclerosis. The exact cause of multiple sclerosis is still obscure. Multiple sclerosis is hardly lethal but it still induces years of pain and inconvenience for most victims. There are many advances coming in therapeutic field of medicine, health care professionals should be cautious of advances in therapy, so that the patients get the better care and improved quality of life. Research is still finding out various approaches to cure and treat multiple sclerosis.

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