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An overview of Multiple Sclerosis

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Multiple sclerosis (MS) is an immune-mediated demyelinating disorder of the central nervous system. This chronic disease is categorized into patterns of acute symptom onset and remission, with or without chronic progression of associated disabilities. MS is the most common demyelinating disease in high-income countries [1,2] and the most common cause of disability in young adults [3].

Prevalence is highest in North America and Europe, at 140 and 108 per 100,000, respectively [2]. According to the National MS Society, in the United States, approximately 1 million people suffer from this condition, a number which has increased in the past few decades, where it was previously half that number [4]. It mainly affects younger Caucasian adults between the ages of 20 and 50, with a female to male predominance of 3:1 [1]. Other ethnic groups suffer from the condition as well.

Genetic and environmental risk factors each play a role in disease manifestation. A multitude of environmental factors have been explored, with the strongest evidence supporting a link with smoking, anti-EBNA IgG sero-positivity, and infectious mononucleosis [2]. High latitude also carries a positive association with MS. Recent research has connected this environmental factor with decreased vitamin D as a result of low sun exposure [2,3]. Fifty-percent of individuals with MS have a positive family history for the disease, often with one or more family members affected.

Additionally, identical twins of those affected have a one in three chance of developing the disease.1 Genetic susceptibility has been demonstrated in individuals with major histocompatibility complex (MHC) alleles. Interestingly, this includes HLA-DRB1, a gene which has been shown to express alleles containing a vitamin D response element [5]. Gut Microbiome is probably linked with MS. Recent work has shown that mice with experimentally eliminated gut flora are protected from an MS-like condition, while those colonized with different bacterial species can be either predisposed or protected from it, depending on the bacterial species [6].

The exact pathophysiologic etiology of MS is unknown, and the mechanism is not fully understood. Generally, the mechanism is characterized by CNS tissue damage caused by immune mediated inflammation, leading to demyelination and subsequent axonal degeneration. Possible autoimmune epitopes have been identified, including myelin basic protein. On a cellular level, MS has classically been

associated with T lymphocytes, specifically the T helper 17 cells. These cells are frequently found in MS plaques, as well as in the CSF and peripheral circulation [7]. The role of B lymphocytes in MS pathophysiology has been increasingly explored, as new MS drugs specifically targeting B lymphocytes have shown promising results in recent studies [8-10].

The clinical manifestations of MS depend on the location and severity of a given inflammatory lesion or lesions. Often, patients will initially complain of blurred vision or a focal neurologic deficit, while later complaints may present as cognitive difficulties and urinary incontinence. Diagnosis of MS is made with magnetic resonance imaging (MRI) of the brain and spinal cord, which will show specific distributions, such as Dawson finger-like projections in the peri-ventricular white matter, as well as juxtacortical and infratentorial lesions. Some of these lesions may be enhancing with gadolinium, which would demonstrate active disease. CSF studies may show elevated protein, cell count, IgG index, and oligoclonal bands [7,10].

The disease course varies from patient-to-patient. There are three different types, including relapsing-remitting (RRMS), primary progressive (PPMS), and secondary progressive (SPMS). The relapsing-remitting is the most common type, and presents as an acute clinically isolated syndrome that remits, leaving no or minimal persistent disability. Later, disability accumulates, which defines the clinical syndrome of secondary progressive. The primary progressive type presents initially with acute flares and persistent residual disability from the onset that continues to progress indefinitely [11].

The basis of MS treatment is to decrease inflammation via immune modulation. Therefore, the goal of these medications is to decrease the annualized relapse rate (ARR) by decreasing number of relapses, accumulation of disability, and MRI CNS lesion load. The desired endpoint, is the achievement of "NEDA," or No Evidence of Disease Activity. This is marked by no new, enlarging, or enhancing lesions on MRI, no relapses, and no progression of disability. To this point, no medication has achieved NEDA.

Most MS medications require blood count (CBC) and liver function (LFT) monitoring, with few exceptions. Virtually all render patients susceptible to common as well as rare infections. Progressive multifocal leukoencephalopathy (PML), caused by activation of latent JC virus, has also been associated with these drugs. This disease may occur in patients who have been on prior immune suppression by another agent and are later given MS disease modifying treatment. Incidence of PML also depends on the length of therapy. Some MS medications may carry a slightly increased risk for developing cancers compared to the general population.

The classical treatment for MS is Interferon B, an immune modulator that suppresses antigen presentation and promotes T cell apoptosis. Side effects include flu-like symptoms [12]. Multiple other therapies have been researched and are available for treatment of MS, though most have utility with only RRMS. Glatiramer Acetate is an injectable drug that reduces myelin-reactive T-cells. It does not require CBC or LFT monitoring. Injection site reactions are common with this drug. Fingolimod is an oral drug that works by binding sphingosine-1-phosphate (S1P) receptors to prevent lymphocytes from leaving secondary lymph organs.

It requires first dose observation due to possible bradycardia and precipitation of heart block. Periodic eye check-up is also necessary due to macular edema [12]. Notably, Fingolimod has recently been approved for the pediatric population, ages 10 years and older [13]. Dimethyl Fumarate is an anti-inflammatory that functions within the nuclear factor erythroid 2 (NrF2) pathway. It requires confirmation of VZV immunity and absence of latent tuberculosis, as its mechanism predisposes patients to infection with both [12] Teriflunomide is an oral agent that prevents lymphocyte differentiation by inhibiting pyrimidine synthesis [14].

It is a category X teratogen that should not be given to men or women of reproductive age who are attempting to have children, [12] as it has been found in semen and other tissues for up to 2 years after the last dose. Mitoxantrone was studied as a disease modifying agent for SPMS and PPMS. It functions by inhibiting lymphocyte production, cytokine release, and antigen presentation. Unfortunately, it was found to have significant risk for development of therapy-related acute leukemia and cardio toxicity [14,15]. It has been taken off the market in Europe. Daclizumab is another drug that has been removed from the market due to incidence of autoimmune hepatitis [16].

Natalizumab binds cell surface integrins to prevent lymphocytic migration into the CNS. It is an intravenous (IV) infusion given every 28 days. Natalizumab carries a high risk of PML, with an incidence of 1/1000, compared to Fingolimod at 1/18,000 and dimethyl fumarate at 1/50,000. Alamtuzumab acts by triggering apoptosis via CD52 on lymphocyte cell surfaces. It is an infusion given for 5 days and repeated 1 year later for 3 days [14]. However, it requires close monitoring for up to 4 years from the last dose due to autoimmune side effects that may lead to thrombocytopenia, glomerulonephritis, and thyroid storm [12].

Ocrelizumab is relatively new to the market. It is a fully humanized monoclonal antibody targeting CD20+ B lymphocytes. It is given as an IV infusion every 6 months [14]. Side effects include infusion reaction, which requires close monitoring for a period of time due to the frequency of occurrence [9]. In this author's practice, many patients have reported recovery from prior disabilities, with some regaining functions such as the ability to walk with assistance from previous wheelchair bound status.

While post-marketing research for Ocrelizumab is still ongoing, early results from the phase II trial demonstrated an annualized relapse rate (ARR) of 80% over 24 weeks [17]. This number can be compared to approximately 68% for Natalizumab, approximately 33% for injectables, and approximately 42% for oral medications [14]. Additionally, the OPERA I and OPERA II trials demonstrated a 46% and 47% lower ARR with Ocrelizumab compared to Interferon beta-1a [9].

Perhaps more interestingly, Ocrelizumab has proven to be a promising drug in the setting of primary progressive MS, a disease process which has limited options for disease modification. In the Oratorio trial, Ocrelizumab was shown to have a statistically significant decrease in disability progression at 12 weeks as a primary endpoint (32.9% vs 39% with placebo), and at 24 weeks as a secondary endpoint (29.6% vs. 35.7% with placebo). Also noted was a change from baseline on timed 25-foot walk of 38.9% with Ocrelizumab compared to 55.1% at 120 weeks. With Ocrelizumab, MRI CNS lesion load decreased by 3.4%, compared to 7.4% with placebo. Ocrelizumab also demonstrated a brain volume decrease of 0.9%, compared to brain volume decrease of 1.09% with placebo [9].

Medications currently being developed include Ozanimod, Siponimod, and Ibudilast. Like Fingolimod, Ozanimod and Siponimod are S1P receptor blockers [18]. Ibudilast is a non-selective phosphodiesterase inhibitor [19]. High dose biotin is also being explored, however it has since been removed from the European market [20]. These therapies are all under continued investigation.

Overall, since the interferon-1B was first approved in the early 1990s, MS treatment has progressed significantly. New pharmacological targets have led to successful disease modification, while also advancing the fundamental understanding of the pathophysiological mechanism of the disease itself. Continued research into new drugs based on recent successes of drugs like Ocrelizumab carries great optimism for the future of MS treatment, and ultimately CURE.

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