

## A Brief Review Chronic Inflammatory Autoimmune Disease: Multiple Sclerosis Pathogenesis and Treatment

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### Abstract

Multiple sclerosis (MS) is a chronic inflammatory autoimmune demyelinating disease of the central nervous system. It affects approximately 400,000 people in the United States and onset is usually during young adulthood. There are four clinical forms of MS, of which relapsing remitting type is the most common. As the etiology of MS is unknown, finding a cure will remain challenging. The main mechanism of injury appears to be inflammation and 8 agents are now FDA approved to help control MS. These agents for relapsing forms of MS target different parts of the immune system, with the end goal of decreasing and avoiding further inflammation.

### Introduction

Multiple sclerosis (MS) is a chronic inflammatory autoimmune demyelinating disease of the central nervous system. Multiple sclerosis affects approximately 400,000 people in the United States alone, most of them being young adults. It expresses itself in four clinical forms: relapsing remitting MS (RRMS), secondary progressive MS (SPMS), primary progressive MS (PPMS), and progressive relapsing MD (PRMS) Approximately 87% of patients present with RRMS, characterized by acute attacks (relapses) followed by partial or full recovery (remission). Patients can manifest with a heterogeneous group of symptoms including changes in vision (unilateral visual loss, diplopia), weakness, dyscoordination, sensory loss or distortions, or changes in bowel and bladder function. Less diagnostic but also disabling symptoms include cognitive change, fatigue, and mood disturbance. Progression of disease may eventually lead to severe disability. Many medications and other measures may be used to ameliorate MS symptoms. The availability of disease modifying therapies has revolutionized the care of patients with the relapsing forms of this disease. These medications help control the underlying disease process, probably by decreasing immune mediated inflammation. They do not cure the disease or reverse the damage that has occurred with prior events. In general the effects of these agents appear more potent when they are given to patients before more severe widespread damage and disability have occurred. As the number of FDA-approved therapies continues to increase and other investigational and off label uses expands, it is helpful to review both the pathogenesis of MS and the effects of the pharmacologic agents.

### Pathogenesis Of Multiple Sclerosis

Inflammation of central nervous system is the primary cause of damage in MS. The specific elements that start this inflammation are still unknown. Studies have suggested that genetic, environmental and infectious agents may be among the factors influencing the development of MS. Many immunological studies have been done on the animal model for human MS known as the experimental autoimmune encephalomyelitis (EAE). Based on this model and observations of MS in humans, roles of several immunological pathways involved in MS are being explored. To understand these pathways it is important to first understand some basic points of the immune system in MS.

While we have learned much about the immune system by the study of EAE, our lack of understanding of the differences between EAE and MS as well as the complexity of MS (and likely different immunologic subtypes of MS) must be kept in mind when reviewing experimental and immunologic data

### Treatment Of Multiple Sclerosis

There are currently 8 FDA approved agents for relapsing forms of MS. No agents are FDA approved for the primary progressive version of MS FDA approved agents include four preparations of interferon-beta (*Avonex*, *Rebif*, *Betaseron* and *Extavia*), glatiramer acetate (*Copaxone*), mitoxantrone (*Novantrone*), and natalizumab (*Tysabri*) and the recently approved first oral medication fingolimod (*Gilenya*) Many other immunologically active agents are used off label and others are nearing study completion and FDA application. The differing types and durations of immunologic effects of these agents will increase the complexity and likely risks of future MS care.

#### Beta Interferons (*Avonex*, *Betaseron*, *Rebif*, *Extavia*)

The four beta interferon drugs—*Avonex* (Biogen Idec), *Rebif* (Pfizer), *Betaseron* (Bayer), and *Extavia* (Novartis)—are naturally occurring cytokines secreted by immune cells. These agents inhibit viral replication via a variety of immunomodulating and antiviral activities.

Although the mechanisms of action of interferons beta-1a and beta-1b in MS are unknown, these cytokines perform regulatory functions in the immune system, and their anti-inflammatory properties are thought to be beneficial. The beta interferons have been shown to reduce the incidence of relapses by approximately one-third and are recommended for patients with relapsing–remitting MS who have intolerance to glatiramer acetate. In randomized, double-blind, placebo-controlled trials, the use of beta interferons in patients with MS reduced inflammatory lesions by 50% to 80%, as shown on brain MRI scans. Moreover, there is evidence that these drugs improve quality of life and cognitive function.

#### Glatiramer Acetate (*Copaxone*)

Glatiramer acetate (*Copaxone*, Teva) is a synthesized copolymer polypeptide mixture consisting of l-glutamic acid, l-lysine, l-alanine, and l-tyrosine. The drug was originally designed to mimic and compete with myelin basic protein.<sup>2</sup> Subcutaneous (SQ) glatiramer acetate (20 mg/day) has been shown to reduce the rate of attacks in patients with relapsing–remitting MS.



### Mitoxantrone (Novantrone)

Prior to its approval for use in MS, mitoxantrone (Novantrone, EMD Serono) was used to treat certain forms of cancer. Mitoxantrone suppresses the activity of T cells, B cells, and macrophages that are thought to lead the attack on the myelin sheath. As a synthetic antineoplastic anthracenedione, it intercalates into DNA and interferes with RNA. This medication is a potent inhibitor of topoisomerase II, an enzyme responsible for repairing damaged DNA.

### Natalizumab (Tysabri)

Natalizumab (Tysabri, Biogen Idec/Elan) is a recombinant humanized immunoglobulin (IgG<sub>4</sub>) monoclonal antibody. Like the beta interferons and glatiramer acetate, its precise mechanism of action in patients with MS has not been fully defined. Natalizumab binds to the alpha 4-subunit of alpha 4β1 and alpha 4β7 integrins expressed on the surface of leukocytes (except neutrophils), and it inhibits the alpha 4-mediated adhesion of leukocytes to their counterreceptors.

### Fingolimod (Gilenya)

Fingolimod (Gilenya, Novartis) is the first orally administered, disease-modifying drug approved by the FDA to reduce relapses and to delay the progression of disability in patients with relapsing forms of MS. Fingolimod is a sphingosine-1-phosphate receptor modulator that is metabolized by sphingosine kinase to the active metabolite fingolimod phosphate, which in turn blocks the migration of lymphocytes from lymph nodes, thereby reducing the number of lymphocytes in peripheral blood. The mechanism underlying the therapeutic effect of fingolimod in MS is unknown, but it might involve the reduction of lymphocyte migration into the CNS.

## Symptomatic Treatment

### Dalfampridine (Ampyra)

Dalfampridine (Ampyra, Acorda) is the first drug approved by the FDA that has been found to improve walking in patients with any type of MS. In clinical studies, approximately one-third of dalfampridine-treated patients had faster walking speeds compared with placebo-treated patients. The average walking speed was approximately 25% above baseline.

Dalfampridine tablets contain a sustained-release formulation of 4-aminopyridine, which blocks potassium channels on the surface of nerve fibers. This blocking ability may improve the conduction of nerve signals in nerve fibers whose insulating myelin coating has been damaged by MS. Before the introduction of dalfampridine, no pharmacological treatment had been available for MS-related walking difficulty.

The maximum recommended dosage is one 10-mg tablet twice daily, taken with or without food. This dosage should not be exceeded. The tablets should be taken approximately 12 hours apart, and patients should not take double or extra doses if a dose is missed.

## Off-Label Treatment Options

### Azathioprine (Imuran)

Azathioprine (Imuran, Prometheus), an orally administered immunosuppressant agent, is administered at a dosage of 2 to 3 mg/kg per day to treat secondary progressive MS. In a meta-analysis of several small studies, azathioprine reduced relapse rates in both relapsing–remitting and secondary progressive MS.

### Methotrexate

Methotrexate (e.g., Rheumatrex, DAVA), an oral immunosuppressant, was originally developed (and continues to be used) for chemotherapy, either alone or in combination with other agents. Methotrexate is effective in a variety of cancers. It is also used to treat severe psoriasis and rheumatoid arthritis. In one study, methotrexate slowed the progression of upper-extremity dysfunction in patients with secondary progressive MS.<sup>7</sup> More studies are needed to establish the efficacy and safety of methotrexate in MS. Patients treated with methotrexate should be monitored for hepatotoxicity.

### Cyclophosphamide

Cyclophosphamide (e.g., Cytoxan, Bristol-Myers Squibb), a cytotoxic alkylating agent, was found to be beneficial in reducing the number of relapses in patients with relapsing–remitting MS when they were given with interferon beta-1a. Cyclophosphamide binds to DNA and interferes with mitosis and cell replication.

The disease-modifying agents that are currently approved for use in MS have only limited or no bioavailability in the brain and spinal cord. In contrast, cyclophosphamide readily penetrates the blood–brain barrier and the CNS parenchyma. It has been used to treat patients with MS in clinical trials and in clinical practice (in an off-label fashion) for more than 30 years. However, efficacy data for this drug have been contradictory.

### Mycophenolate Mofetil (CellCept)

The immunosuppressive agent mycophenolate mofetil (MMF; CellCept, Genentech) is relatively selective for activated lymphocytes. It is administered orally at dosages of 500 or 1,000 mg twice daily, alone or in combination with an interferon beta, for patients with relapsing–remitting and secondary progressive MS. However, its efficacy in MS is controversial.<sup>7</sup> In a preliminary study, the combination of MMF and interferon beta-1a was well tolerated in 13 patients with relapsing–remitting MS, but efficacy results after 12 months of therapy were not statistically significant compared with placebo. MMF deserves further investigation in MS, with a larger sample size and a longer follow-up period.

### Cladribine

Oral cladribine (Merck KGaA, Germany) is an adenosine deaminase-resistant purine nucleoside that is relatively selective for lymphocytes. It does not alter attack rates or the progression of MS, but it does reduce lesions in the brain. In July 2010, the FDA accepted a New Drug Application (NDA) for cladribine tablets from Merck KGaA; however, in June 2011, the company discontinued developing the drug for the treatment of MS because of a cancer risk. This discontinuation may give a boost to the oral usage of fingolimod. Merck/Serono has decided to not to pursue approval by the FDA. The drug will no longer be sold in Russia and Australia, where it had been available as Movectro. Used in the injectable form as Leustatin (Janssen), cladribine has been used to treat cancer.

## Conclusion

The FDA has approved eight medications for relapsing–remitting MS. All have been shown to reduce the number of relapses (attacks or exacerbations) and the number of new lesions (plaques or scars) on MRI brain scans. Five injectables—four beta interferons (Avonex, Betaseron, Extavia, and Rebif) and the copolymer polypeptide mixture glatiramer acetate—are generally viewed as first-line treatments for MS. Most experts recommend that treatment begin with one of these drugs as soon as the diagnosis of relapsing–remitting MS has been confirmed. Second-line therapies include natalizumab and mitoxantrone (Novantrone).

MS is a progressive disease with no cure so far. Although treatments are available to manage the disease course, they are only partially effective. Therefore, MS worsens in some patients despite everything they and their physicians do to prevent it. Patients with relapsing–remitting MS, the most common form of MS, experience attacks of worsening neurological functioning, followed by periods of remission characterized by partial or complete recovery.

A combination of drugs and physical, speech, and occupational therapies; exercise; rest; and healthful nutrition may relieve symptoms and promote a satisfactory quality of life.

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