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Journal of Neuroscience and Neurological Surgery
Theodore Eric , J Neuroscience and Neurological Surgery

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Review Article

Multiple Sclerosis: A Systemic Review of Drugs and Therapeutics

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Received date: March 10,2017 ;Accepted date : March 20,2017; Published date: March 25,2017.

Citation: Theodore Eric, Bates Archer, Multiple Sclerosis: A Systemic Review of Drugs and Therapeutics, J Neuroscience and Neurological Surgery. **Doi:** 10.31579/2578-8868/018

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. No agents are FDA approved for the primary progressive version of MS. FDA approved agents include four preparations of interferon β (Avonex, Rebif, Betaseron and Extavia), glatiramer acetate (Copaxone), mitoxantrone (Novantrone), natalizumab (Tysabri) and fingolimod (Gilenya). There are several drug undergoing phase II and III trials. The heterogeneity of the MS disease process, individual patient response, and medication toxicities continue to challenge the treating physician.

Keywords

Multiple sclerosis, Pathogenesis, Immune Response.

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.

Table 1

Types of Multiple Sclerosis	
Type	**Disease Course**
Relapsing/Remitting Multiple Sclerosis (RRMS)	Most common type, accounts for approximate 85% of cases. Characterized by discrete attacks that evolve over days to weeks followed by some decree of recovery over weeks to months. In between attacks, the patient has no worsening neurological function.
Secondary Progressive Multiple Sclerosis (SPMS)	Characterized by initial relapses, followed by gradual neurological deterioration not associated with acute attacks.
Primary Progressive Multiple Sclerosis (PPMS)	Characterized by steady functional decline from the onset of the disease. No relapses ever.
Progressive Relapsing Multiple Sclerosis (PRMS)	Characterized by steady functional decline from onset of the disease with later superimposed acute attacks. PRMS and PPMS cannot be distinguished during early stages, until the relapses occur

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

On its website the National MS society listed more than 136 ongoing clinical trials testing different treatments for 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.

Monoclonal Antibodies

Monoclonal antibodies (mAbs) have been studied since the 1980's. There are three different types of monoclonal antibodies differentiated by their structural similarity to human antibody structure. Humanized antibodies consist of more than 90% human components with the balance from the original murine structure. These antibodies include natalizumab, alemtuzumab and daclizumab. Chimeric antibodies are at least 66% human structure and structure, and rituximab belongs to this class of antibodies. Fully human antibodies have no murine structural components Each mAb is developed to bind to a specific target molecule. mAb mechanism of action depends on the distribution of the targeted molecule, efficacy of the antibody in reaching the target, the interaction between the antibody and target, and the effector functions of the interaction. The mAbs may interact with their target by binding, blocking or signaling. The type of interaction depends on its Fab activity. A binding mAb can mark a target for destruction through is effector function or through conjugation of the mAb to a toxin. Another mechanism is by blocking the epitope needed for ligand interaction, thus preventing signaling. Both natalizumab and daclizumab are blocking mAbs. Monoclonal antibodies can also mediate cytotoxic immune responses and destroy targeted cells. This effector function depends on the Fc domain of the antibody. To date the four monoclonal antibodies most studied for MS are natalizumab, daclizumab, alemtuzumab and rituximab.

Natalizumab

Natalizumab (*Tysabri*) is a humanized monoclonal antibody with an IgG4 framework. It was specifically designed for the treatment of MS and was FDA approved on 2004. It was temporarily withdrawn from the market in 2005 after several cases of fatal progressive multifocal leukoencephalopathy were reported in patients treated with natalizumab. It was reapproved on 2006 as a monotherapy for the treatment of RRMS. Its target molecule is CD49, the α4 subunit of very late antigen-4 (VLA-4) receptor.

Alemtuzumab

Alemtuzumab (*Campath-1H*) is a humanized antibody that was initially approved for the treatment of B-cell chronic lymphocytic leukemia. It remains an investigational agent for MS. Its target molecule is CD52, a glycoprotein expressed widely throughout on T and B cells, natural killer cells, dendritic cells, monocytes, macrophages and granulocytes with the exemption of neutrophils. Alemtuzumab causes a complete depletion of CD52 bearing cells. It depletes cells that mediate Ab-dependent cellular cytotoxicity, i.e. natural killer cells. Studies have shown that the depletion of these immune cells is associated with a decrease in contrast enhancing lesions in MS, thus suggesting stabilization of the blood brain barrier.

Rituximab

Rituximab (*Rituxan*) is a chimeric murine/human IgG1 monoclonal antibody. Its target is CD20, an antigen produced only on mature B cells and not on the Ab-producing plasma cells. This monoclonal antibody is FDA approved for the treatment of rheumatoid arthritis and B cell lymphoma and it remains an investigational agent for treatment of MS.

Daclizumab

Daclizumab (*Zenapax*) is a humanized monoclonal antibody with an IgG1 framework. It was used initially for the prevention of allogenic tissue transplantation. Its target molecule is CD25, the IL-2 binding epitope of the α-chain of the IL-2 receptor. IL-2 plays an important role both in the regulation of lymphocyte expansion and contraction.

Mitoxantrone

Mitoxantrone (*Novantrone*) is a synthetic anthracenedione that intercalates into DNA. It causes cross-linking and strand breaks and inhibits topoisomerase II, thus interfering with DNA repair. Besides causing generalized immunosuppression, mitoxantrone inhibits monocyte and lymphocyte migration, induces apoptosis of dendritic cells, decreases the secretion of proinflammatory cytokines such as tumor necrosis factor, interleukin-2 and interferon-g.

Corticosteroids

Corticosteroids inhibit lymphocyte proliferation and the synthesis of most pro-inflammatory cytokines. Because of their potent anti-inflammatory effects, corticosteroids have been used to treat MS for the last 50 years. Today corticosteroids are standard treatment for patients with acute relapses, however it is not yet clear if they are as efficacious as a long term treatment. Ciconne did a Cochrane review to study the long term effect of corticosteroids in patients with all types of MS. The analysis showed that overall there was no clear evidence that corticosteroids slowed or reversed disease progression.

Conclusion

The unknown etiology, probable disease heterogeneity, and immune system complexity will continue to provide challenges for clinicians treating MS. To date there is no cure for MS, and medications which decrease immunologic functions may have significant risks. The short term efficacy and safety of newer agents is being explored however the long term risks of these agents, particularly when used in combination or succession will remain uncertain. Moreover, physicians are faced with the treating potentially pregnant woman and at times even children.

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