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Mini Review

Current Therapies for Multiple Sclerosis: A Brief Review

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Abstract

Recent scientific advances have led to improved therapies for multiple sclerosis (MS). Current therapies are aimed at decreasing the damage incurred by neurons as well as attempting to restore proper function. However, all of the Food and Drug Administration (FDA) approved therapies are only indicated for treatment of relapsing remitting and/or relapsing forms of MS as they specifically target immune components, which play a main role in relapses. These drugs can reduce relapse rate and severity of relapses, as well as inhibit disease progression. This review will focus on the current and recently approved therapies for relapsing remitting MS, exploring how the main drugs target specific aspects of MS pathology so as to ameliorate disease.

Keywords: Multiple sclerosis; Drug therapies; Interferon-beta; Immune function

Abbreviations

MS: Multiple Sclerosis; RRMS: Relapsing Remitting Multiple Sclerosis; PPMS: Primary Progressive Multiple Sclerosis; SPMS: Secondary Progressive Multiple Sclerosis; PRMS: Progressive Relapsing Multiple Sclerosis; CIS: Clinically Isolated Syndrome; FDA: Food and Drug Administration; IFN-β: Interferon Beta; BBB: Blood Brain Barrier; GA: Glatiramer Acetate; PML: Progressive Multifocal Leukoencephalopathy; CNS: Central Nervous System

Introduction

Multiple sclerosis (MS) is a neuroinflammatory demyelinating autoimmune disease. It results in the loss of the protective myelin sheath surrounding the axons of neurons. This leads to inflammation and neuronal damage/death. It is thought that MS is the result of autoreactive T cells which are able to cross the blood-brain barrier (BBB) and initiate the inflammatory response. This ultimately leads to the chronic inflammation characteristic of MS pathology [1,2]. MS can be subtyped into four categories according to progression of disease: relapsing remitting (RRMS; a series of attacks followed by complete or partial recovery), secondary progressive (SPMS; worsening of neurological symptoms replaced with steady progression of disability), primary progressive (PPMS; steady decline neurological function without improvement), and progressive relapsing (PRMS; similar to relapsing remitting, but with worsening of neurological deficits during remissions).

As there is no cure for MS, caring for patients takes a multifaceted approach; addressing pathogenesis, symptoms associated with disease, and the emotional/lifestyle implications of the disease. Providers' focus is classified into five major areas as described by the National Multiple Sclerosis Foundation: modifying the disease course, treating exacerbations, managing symptoms, promoting function through rehabilitation, and providing emotional support.

Drug therapies have been shown to be more effective when implemented at early stages of disease. Previous studies have demonstrated that early introduction of drug therapy, specifically in patients with clinically isolated syndrome (CIS; individuals that have not yet developed MS but have had one attack with symptoms consistent with MS), can delay the conversion to clinically definite MS [3-6]. However, early diagnosis and treatment may be difficult as patients may not seek medical advice, may not comply with treatment regimen, or may be hesitant to start treatment.

Current Therapies

The first drugs made available were from the interferon beta (IFN-β) family, IFN- β1b and IFN- β1a. IFN- β1b was the first therapy approved by the FDA, followed by IFN- β1a [7,8]. While the precise mechanism by which IFN-β exerts all its affects on disease progression is still somewhat unclear, studies have shown that it reduces the frequency of relapses by one-third due to its antiviral, antiproliferative, and immunomodulatory properties. Inflammatory lesions, a characteristic of MS, were shown to be reduced by 50% to 80% in randomized, double-blind, placebo-controlled trials of MS patients taking IFN- β [9]. Breach of the BBB is also implicated in the pathology of MS. Studies have shown that one mechanism of action of IFN- β is to decrease permeability of the BBB thereby reducing damage to the brain [10,11]. Despite the statistical success of this treatment, there is still a risk of liver function abnormalities, leukopenia, thyroid disease, and depression [9].

Glatiramer acetate (GA) is a copolymer of four amino acids first introduced in 1996 as another first-line agent. While the exact mechanism of action is unknown, it has been shown that GA has immunomodulatory effects. GA affects antigen presenting cells, where dendritic cells from MS patients treated with GA showed a decrease in pro-inflammatory cytokines and increase in anti-inflammatory cytokines [12]. Studies suggest that GA specific suppressor T cells are produced and activated in the periphery. Its effectiveness in decreasing the inflammation associated with the disease course has been demonstrated through MRI based studies. These studies show that inflammation is reduced by one-third in patients taking GA with relapsing forms of MS [13,14]. In studies comparing the effectiveness of GA with IFN-β, there were no differences in relapses or disease progression [15-17]. GA also has a role in neuroprotection as decreased serum and cerebrospinal fluid levels of bone derived

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neurotrophic factor in MS patients is reversed following treatment [18].

Mitoxantrone was approved in 2000 for the treatment of MS and has also been shown to be effective against cancer [19]. Mitoxantrone is an immunosuppressive drug and is used for patients that have fast progressing disease and are unresponsive to IFN- β or GA treatment. Mitoxantrone is thought to address the disease course by suppressing the T cells, B cells, and macrophages that lead to demyelination [20]. It is one of the few drugs that is also effective against SPMS, thereby initially increasing its use in MS patients [21]. However, mitoxantrone has been shown to have cardiotoxic effects. Patients with SPMS in the early stages of mitoxantrone treatment have presented with left ventricular ejection fraction reduction [22], and, in larger studies, the overall incidence of cardiac dysfunction was 4.1-5.6% , with higher doses resulting in increased rates [23-26]. Due to these side effects, the frequency of use of mitoxantrone has decreased.

Natalizumab is a recombinant humanized monoclonal antibody recently approved for treatment of MS. It binds to integrins on the surface of T cells thus preventing their transmigration through the BBB. Natalizumab is effective in reducing relapse rates by 68%, disease progression by 42%, and relapse severity [27], and is prescribed for patients that cannot manage their symptoms using IFN-β or GA. One study demonstrated that patients taking natalizumab had a significantly lower relapse rate than those taking IFN-β or GA [28]. Natalizumab has also been shown to improve attention, memory, mood, and reduce vision loss in patients with RRMS [29]. In spite of these benefits, there is a major drawback to this treatment; studies have shown that patients who take Natalizumab and are seropositive for antibodies against JC virus are at an increased risk of developing progressive multifocal leukoencephalopathy (PML), a potentially life-threatening opportunistic brain infection [9,30-32]. Other risk factors for PML include having previously used immunosuppressants and having undergone longer (>2 years) durations of natalizumab treatment [33,34]. The risk of developing PML is 11.1 per 1000 patients for those that have all three risk factors, but patients without JC virus antibodies have an estimated incidence of 0.09 or less per 1000 patients [33]. When patients discontinue use of natalizumab they have disease reactivation after withdrawal, with an increase in both relapse rate and lesion formation [35]. Therefore, it is essential that patients with increased risk factors for developing PML be identified and informed before natalizumab treatment begins.

Fingolimod is a competitive inhibitor of the sphingosine 1-phosphate receptor on T cells and in 2010 was the first oral drug approved for treating MS. Fingolimod reduces relapses and delays onset of disability by affecting T cell emigration from the lymph nodes and migration into the brain, effectively reducing the amount of lymphocytes in the periphery and central nervous system (CNS) [36]. Treatment with fingolimod was associated with a significantly lower relapse rate compared to IFN-β, and the relapse rate was also lower for patients that switched from IFN-β to fingolimod [37,38]. However, there was no difference in progression of disability between patients taking fingolimod and patients taking IFN-β [37]. MRI studies of patients taking fingolimod demonstrated improved disease activity. This included a significant reduction in the number of new or enlarging T2-weighted lesions and gadolinium-enhancing lesions as well as a significantly smaller reduction in brain volume [36]. As fingolimod was only recently approved, there is limited long-term safety data. However, some risks of this drug have been identified. These include headache, diarrhea, and nausea, as well as dose-dependent decreases in heart rate [37]. It is recommended that patients have an electrocardiogram prior to and after the initial dose, as well as continue to be monitored for cardiac dysfunction.

Teriflunomide is a primary active metabolite of leflunomide and has been shown to reduce the number of relapses by more than one-third in recent studies [39,40]. It also reduced the risk of relapse or new lesion formation by more than 30% compared to placebo [40]. Teriflunomide works by inhibiting lymphocyte proliferation, thus, reducing the number of autoreactive T-cells and B-cells [41].

The most recent drug therapy, approved in 2013, is dimethyl fumarate, which has been shown to reduce relapse rate by 44-53% [42-45], as well as reduce gadolinium-enhancing lesions and T2 lesions [46]. Although its specific mechanism of action is unclear, it has antioxidant and anti-inflammatory properties. Because of this, dimethyl fumarate has also been demonstrated to be effective in chronic pancreatitis, where animals given the drug had reduced inflammation and oxidative stress [47]. Dimethyl fumarate has been shown to be associated with significantly lower relapse rate and a decreased number of lesions compared to GA [42]. As are with the previous two drugs, long term safety and efficacy data are minimal. However, adverse effects of treatment include gastrointestinal events, proteinuria, and a decreased lymphocyte count [42,43].

In 2010, dalfampridine-ER was approved by the FDA. This drug differs from those above as it targets a symptom of MS, specifically the treatment of walking impairment. At disease onset, patients with MS can experience mild walking impairment, with at least 15% necessitating some form of assistance [48]. Although the complete mechanism of action of dalfampridine-ER has not been fully elucidated, it is known that some of its therapeutic effects are due to the ability of dalfampridine-ER to restore conduction in neurons by blocking potassium channels exposed during demyelination [49].

Factors Involved in Therapy Selection

When deciding on treatment strategies, it is essential that all factors be evaluated, including efficacy and safety of the drug, biomarkers (interferon inducible genes that may predict patient-to-patient differences in IFN-β responses or the presence of JC virus-specific antibodies), patient-specific markers (gender, race, and genetics), disease severity, and cost of therapy. When looking at gender and race, studies have shown that, in response to IFN-β, female patients and African-American patients were more likely to experience relapses [50,51]. This could be due to these groups either being less responsive to IFN-β treatment or differences in disease course due to gender and race. Although, there were no gender or race differences seen in patients taking GA or natalizumab [52-54]. As previously mentioned, when the disease is in its early phase, CIS, the most effective treatments are IFN-β or GA. As the disease progresses to clinically distinct MS, therapy is dependent on the severity, with mitoxantrone and natalizumab being the preferred therapies, although each has adverse effects that must be weighed against their usefulness. However, it should be noted that there are

differences in baseline characteristics for patients among the various studies. These differences need to be accounted for when selecting the appropriate therapy. Cross study comparisons should also be done cautiously, again, taking in to account patient variability.

Conclusion

The current disease-modifying therapies approved to treat patients with MS are only effective against the relapsing forms of the disease (RRMS or SPMS with relapses), as these drugs only target essential components of the immune system actively involved in relapses. Therefore, the current therapies are ineffective against non-relapsing subtypes of MS (SPMS without relapses or PPMS). As the pathologic mechanisms of these subtypes are not well understood further research is needed to identify relevant target molecules so that new drug therapies can be developed that will ameliorate disease for these individuals as well.

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