Emerging Therapies for the Treatment of Multiple Sclerosis

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Emerging Therapies for the Treatment of Multiple Sclerosis

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Abstract
Multiple sclerosis is a neurological disease that affects millions of people worldwide, yet is not entirely understood. Symptoms of multiple sclerosis most frequently include muscle spasms and extreme fatigue, but patients can experience a wide variety of issues. There are four categories in which patients with multiple sclerosis are typically classified: relapse-remitting, primary-progressive, secondary-progressive and progressive-relapsing. The pathophysiology of the disease is largely unknown, but many theories are being researched. Currently, there are treatments that can alleviate symptoms and halt disease progression, but no cure is known at this time. Most symptomatic relief medications focus on anti-inflammatory mechanisms of action, while disease-modifying treatments have novel mechanisms which are being studied more fully. By being aware of new drug therapies, pharmacists can better counsel patients with this disease state. As new therapies are approved, it is important to understand their mechanism and reasons for use, so as to be aware of potential side effects and interactions.

Introduction to Multiple Sclerosis
Multiple sclerosis (MS) is a chronic inflammatory neurological disease that affects 2.1 million people worldwide including about 400,000 Americans. An estimated 200 Americans are diagnosed with MS every week. The hallmark of MS is a progressive autoimmune-mediated demyelination of neurons. The myelin sheath acts as an insulator, providing high resistance and low capacitance, resulting in greater impulse conduction velocity of neurons. Thus, demyelination leads to slowed or blocked signal transmission. MS is characteristically idiopathic, in that a defined pathophysiology has not been determined. However, studies suggest a strong genetic influence, as first-degree relatives of an affected individual are 20 times more likely to be diagnosed with MS than the general population. In addition, case studies have found that patients with MS have elevated levels of antibodies targeting Epstein-Barr virus proteins, suggesting the virus may initiate inflammatory responses that lead to autoimmune demyelination, characteristic of MS. The onset of symptoms and diagnosis typically occurs between the ages of 20 and 50; women are two to three times more likely to be affected by MS than men.

Symptoms
The symptoms of MS are common to many neurologic disorders and are erratic, affecting the muscles, bowel, bladder, eyes, brain and spine. The most frequent symptoms associated with MS are fatigue and muscle spasticity. However, affected individuals may also experience muscle stiffness, disequilibrium, paralysis of the limbs and bowel, mood and behavioral changes such as depression, impaired vision, slurred speech and incontinence. Symptoms range in intensity from mild to severe, with high inter-patient variability. The degree of discomfort and disability associated with MS depends on the frequency and severity of attacks, and the area of the nervous system affected. MS is typically identified by differential diagnosis due to high variability in patient presentation and symptom commonality with other neurologic disorders.

Effective management of symptoms improves quality of life and is imperative to prevent permanent damage that can result in disease progression and worsening symptoms. Pharmacological treatments may include corticosteroids to decrease inflammation in nervous tissue and reduce the duration and severity of flare-ups. Muscle relaxants, such as tizanidine (Zanaflex®) or baclofen (Lioresal®), reduce stiffness and muscle spasticity. Plasma exchange may also be used for patients who do not benefit from corticosteroid therapy and experience sudden, severe attacks of MS-related disability. The antiviral drug amantadine (Symmetrel®) or the stimulant modafinil (Provigil®) may be used for fatigue-like symptoms. An anticholinergic medication such as tolterodine (Detrol®) may be used for incontinence by blocking contractions of the bladder. Since mood and behavioral symptoms are also common, antidepressants can be used in MS patients, while non-pharmacological approaches such as physical, speech or occupational therapy may help maintain independence in activities of daily living. Individual or group therapy can help with the emotional stress of coping with the disease. Assistive devices such as a wheelchair, walker or shower chair, as well as a healthy lifestyle and planned exercise program, have also been noted to help with some of the movement issues a patient will experience. As with many diseases, avoiding illness, stress and fatigue with plenty of relaxation and rest can improve symptoms.

Clinical Classification of Multiple Sclerosis
Multiple sclerosis can be loosely classified into one of four clinical categories: relapse-remitting, primary-progressive, secondary-progressive and progressive-relapsing. The following descriptions are used for the four categories:

Relapse-Remitting MS (RRMS): Patients experience bouts of worsening neurologic function known as relapses. These flare-ups last anywhere from a few days to months and are contrasted by periods of remission characterized by full or partial recovery, during which no disease progression occurs. The flare-ups must last at least 24 hours and be separated from the previous attack by at least one month. No two flare-ups are alike. They may include just one symptom or involve multiple symptoms. Most patients are initially diagnosed in this category but many will progress to secondary-progressive MS.
Primary-Progressive MS (PPMS): The hallmark of PPMS is a worsening neurologic function from disease onset, without a clear pattern of relapse and remission.

Secondary-Progressive MS (SPMS): This classification is an example of the blurred boundaries between classifications because it is difficult to clearly distinguish it from PPMS due to their similarities. It is characterized as worsening of neurological function, with more irreversible damage occurring, with or without flare-ups and minor relapses. Thus, over time, symptoms associated with relapse become worse, while remissions are less prominent and shorter in duration, eventually becoming non-existent.

Progressive-Relapsing MS (PRMS): This classification is relatively rare. Patients experience a steady worsening of the disease from the beginning without remissions. Patients may experience clearly-defined relapses that may slow after some time; however, the disease is always continuing to progress.

Pharmacotherapy

Currently no cure for MS exists; however, treatment options are available for patients based on an anti-inflammatory strategy to slow disease progression.1,2 First-line treatments are intramuscular or subcutaneous interferon β (Rebi®) and subcutaneous glatiramer acetate (Copaxone®), both of which are indicated for RRMS. The exact mechanism of action of interferon β is unknown. However, it has been proposed to suppress the T-helper cell response, thereby diminishing T-cell migration across the blood-brain barrier, which reduces the inflammatory process. Common adverse effects consist of flu-like symptoms, depression and elevated hepatic enzymes. The mechanism of action of glatiramer acetate is not fully understood, but is thought to involve alteration of T-cell activation and differentiation. Common adverse effects are similar to those seen with interferon β, including injection-site reactions and depression, as well as lipoatrophy. These two drugs should be avoided in patients with a coexisting depressive disorder. The BEYOND, BECOME and REGARD trials compared the two first-line agents and found them to have comparable efficacy, with no significant differences regarding relapse rate, disability progression or magnetic resonance imaging (MRI) outcomes.1,8,9

Second-line agents are intravenous mitoxantrone (Novantrone®) and intravenous natalizumab (Tysabri®).2 Mitoxantrone was the first approved disease-modifying therapy indicated for multiple MS classifications (RRMS, SPMS, PRMS).1,2 Mitoxantrone works by intercalating DNA and inhibiting topoisomerase II. This results in DNA breaks and inhibition of DNA repair, causing reduced proliferation of B- and T-cells and reduced release of inflammatory cytokines. This agent is associated with rare but serious side effects of cardiotoxicity and severe bone marrow suppression, thus it is not considered a first-line agent. More common adverse effects associated with treatment include nausea, vomiting, alopecia and leukopenia. Mitoxantrone is used when patients progress from RRMS to a more severe stage of MS. The other second-line agent, natalizumab, is a humanized monoclonal antibody that inhibits leukocytes from crossing the blood-brain barrier by antagonizing α4 integrins on leukocytes.1 This monoclonal is not a first-line agent due to its association with progressive multifocal leukoencephalopathy (PML), a potentially fatal infection caused by the JC polyomavirus. The more common adverse events are headache, fatigue, allergic reaction and infection. These two treatments are reserved for patients who cannot tolerate or are unresponsive to first-line agents.

Emerging Therapies: FDA Approved

Two new agents were approved by the Food and Drug Administration (FDA) in 2010 for the treatment of MS, both with novel mechanisms relative to existing therapies—dalfampridine (Ampyra®) and fingolimod (Gilenya®).3 Dal-fampridine is the only FDA approved symptom management treatment to improve walking in all types of MS. Although there is disagreement on the exact mechanism by which dal-fampridine exerts its therapeutic effects, it is classified as a voltage-dependent potassium channel blocker that lowers the seizure threshold. Studies showed efficacy in one-third of patients and the most common adverse effects were falls, urinary tract infections, insomnia, asthenia, headache, nausea and dizziness.

The second medication, fingolimod, is considered a disease-modifying treatment, and is a sphingosine 1-phosphate receptor modulator. In vivo, fingolimod is a prodrug which has a phosphorylated active metabolite that exerts its therapeutic effects by decreasing the release of autoreactive lymphocytes. This lowers the amount of peripheral lymphocytes and sequesters lymphocytes in the lymph nodes.10 There is also potential for neuroprotective and/or reparative functions.11 Importantly, with this novel mechanism, it is the first FDA approved oral treatment for relapsing forms of MS and is now considered first-line treatment for RRMS.1,10 Fingoli-mod is metabolized by CYP4F2; however, drug-drug interactions are not likely because other drugs currently on the market are not metabolized by this enzyme.10 The most common adverse events experienced were headache, influenza, diarrhea, back pain, liver enzyme elevations and cough. Serious adverse events of bradycardia, MS relapse, basal cell carcinoma and chest pain occurred in less than 1 percent of patients. Recent reports of patient deaths after taking the first dose of fingolimod have also led to label changes guiding practitioners in appropriate patient populations. The updated FDA label for Gilenya® indicates that all patients initiating treatment with Gilenya® should have an electrocardiogram (ECG) prior to the first dose of the medicine and after the six-hour first-dose observation period in addition to hourly measurement of blood pressure and heart rate.12 Additionally, specific initiation guidance for patients is now provided to better aid health care providers. Further, there are revised recommendations on how to re-initiate therapy should Gilenya® be interrupted.

Emerging Therapies: New Labeling in Clinical Trials

In addition, several medications are under investigation for new labeling in the treatment of MS that are currently approved for different indications. These are cladribine (Leustatin®) and the monoclonal antibodies alemtuzumab...
Emerging Therapies: Orphans in Clinical Trials

Three immunomodulator medications are currently in clinical trials for new MS treatments: laquinimod, teriflunomide and dimethyl fumarate. The mechanism of action of laquinimod has not been fully defined, but is proposed to work via immunomodulatory properties with potential neuroprotection. Infiltration of leukocytes into the central nervous system (CNS) leads to destruction of white matter and neurological impairment. It is hypothesized that laquinimod acts by reducing demyelination and axonal degeneration via changes in the cytokine shift. Studies have shown laquinimod to be generally well-tolerated, with minimal differences between the placebo and laquinimod groups regarding adverse effects. Teriflunomide exerts its effects via anti-inflammatory and antiproliferative properties. Teriflunomide is the active metabolite of leflunomide, a commonly used treatment in rheumatoid arthritis. Thus far, it has exhibited a favorable safety profile and efficacy in the treatment of aspects of rheumatoid arthritis that are similar to the autoimmune reaction in MS patients. Teriflunomide exerts its effects by decreasing activation of T-cells by antigen presenting cells. Dimethyl fumarate is an orally administered immunomodulatory agent that inhibits microglia and astrocytes via the Nrf2 signaling pathway, resulting in reduced CNS inflammation. The most common side effects were abdominal pain and flushing (Table 1).

Pharmacist’s Role

With approximately 400,000 Americans diagnosed with MS, pharmacists play a critical role in improving patient outcomes. Continued development of an increasing number of novel treatment modalities make it imperative for pharmacists to be informed on the current therapies. In addition, with the recent approval of oral medications to treat MS, the

Table 1. Potential Indications for Emerging MS Therapies

<table>
<thead>
<tr>
<th>Drug</th>
<th>RRMS</th>
<th>SPMS</th>
<th>PPMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fingolimod</td>
<td>+</td>
<td>+</td>
<td>NR</td>
</tr>
<tr>
<td>Laquinimod</td>
<td>+</td>
<td>+</td>
<td>NR</td>
</tr>
<tr>
<td>Teriflunomide</td>
<td>+</td>
<td>+</td>
<td>NR</td>
</tr>
<tr>
<td>Dimethyl Fumarate</td>
<td>+</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Cladribine</td>
<td>NR</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>+</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Daclizumab</td>
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<td>+</td>
<td>NR</td>
</tr>
<tr>
<td>Rituximab</td>
<td>+</td>
<td>NR</td>
<td>+</td>
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</tbody>
</table>

NR = not reported
Adapted from Gawronski, et al. Table 3 p 921.
role of the pharmacist is no longer limited to inpatient clinical monitoring and counseling but has expanded to include the outpatient setting. Thus, it is increasingly likely pharmacists will be needed for the education of patients as well as other health care professionals on current and emerging treatments for MS.

References