Multiple Sclerosis: A Review and Treatment Option Updates

Authors:
Abby L. Adams, PharmD, 2013, Harrison School of Pharmacy, Auburn University;
Michael R. Morgan, PharmD 2013, Harrison School of Pharmacy, Auburn University;
Wesley T. Lindsey, PharmD, Associate Clinical Professor, Drug Information and Learning Resource Center, Harrison School of Pharmacy, Auburn University

Universal Activity #: 0178-0000-14-102-H01-P  |  1.25 contact hours (.125 CEUs)
Initial Release Date: August 31, 2014  |  Expires: April 1, 2016
EDUCATIONAL OBJECTIVES
After the completion of this activity pharmacists will be able to:

• Describe four different courses of multiple sclerosis.
• Review McDonald Criteria for diagnosis of multiple sclerosis.
• Discuss FDA-approved treatment therapies for multiple sclerosis.

INTRODUCTION
Multiple sclerosis (MS) is an autoimmune disease that involves an attack on the central nervous system (CNS). Myelin, which is a substance that surrounds and protects the nerve fibers, is damaged which leads to the formation of scar tissue, or sclerosis. Although MS was first described in the late 1800s, the cause of the disease still remains a mystery, and there is no known cure. Due to the time frame in which MS typically develops, there is a large economic burden associated with this disease. This can be in terms of treatment costs, or in terms of a patient’s lost wages due to their reduced ability to work. One study estimated that in 2009, the annual cost of MS was about $24,000 per patient in treatment costs alone.

MS is a disease that affects more women than men at about a 2:1 ratio, and about 250,000 to 350,000 people total are diagnosed with MS in the United States, with about 10,000 new cases diagnosed each year. When it comes to determining the risk of developing the disease, the most important factors to consider include: geography, age, environmental influences, and genetics. MS is typically diagnosed between the ages of 15 to 45 years. One of the unique aspects of this disease is its apparent uneven distribution across the world. Traditionally, the disease affects white people of Nordic origin who live in temperate climates. In general, the prevalence of MS increases the further one goes away from the equator. In the United States, there is a higher prevalence in states above the 37th parallel, which is roughly anything north of the Oklahoma panhandle. Other factors that have been implicated include environment and viruses. In terms of environmental influences, studies have shown that people who live in a high-risk area (above the 37th parallel in the United States) before the age of 15 for at least two years are at a higher risk of developing the disease. This suggests that an exposure to some environmental agent before puberty may possibly influence an individual to develop MS later on in their life. Some other researchers believe that a reduced vitamin D level may affect the risk of developing MS. Vitamin D is naturally produced when a person’s skin is exposed to sunlight, and people who live closer to the equator are exposed to greater amounts of sunlight which may reduce the risk of MS. Familial recurrence rate of MS is about 5% with the most commonly reported relationship being that of siblings. This too is consistent with the idea that an environmental agent is important in the etiology, but it also hints that one or more genes may play a role as well.

There have been several viruses proposed as a trigger for MS which include: measles, herpes virus (HHV-6), rubella, canine distemper virus, and Epstein-Barr virus. Although these viruses have been proposed, studies have not demonstrated any one of them as a definitive trigger for MS. Out of all of these, the greatest evidence exists with the Epstein-Barr virus and in current studies is the leading candidate for causation; however, the role of Epstein-Barr virus in the pathogenesis of MS remains unknown at the present time. The predominant theory as of now is that this virus is capable of causing latent infection with B cells and T cells. This infection within the T cells could possibly be a trigger for MS. Due to the severity of the disease and the cost associated with it, this article will review MS and provide an update on newer agents available as well as potential therapies in the future.

FOUR DIFFERENT COURSES OF MS
Neurologists group patients into four major categories based on the course of the disease. The four major categories are: relapsing-remitting, secondary progressive, primary progressive, and progressive-relapsing.

1. Relapsing-remitting: this is the most common form of MS with about 85% of patients initially diagnosed with this course. It is characterized by flare-ups (exacerbations) of symptoms followed by periods of remission. These exacerbations are clearly defined attacks of worsening neurological function. In remission, the symptoms either improve or are not present.

2. Secondary-progressive: this course of the disease follows an initial period of relapsing-remitting MS. After this initial period, the disease begins to worsen steadily, with or without periods of remission. The time to conversion from relapsing-remitting MS varies from person to person, but an average time frame is 20-25 years after initial onset and diagnosis. Since this presentation of the disease is not initially diagnosed, there are no information regarding the percentage of patients who will develop this course of the disease.

3. Primary progressive: This course is characterized by slowly worsening neurologic function from the onset of the disease with no distinct period of remission. About 10% of patients are initially diagnosed with this course of the disease, and it is most commonly diagnosed in individuals who are older than 50 at the time of onset. This form of MS is more resistant to the medications typically used to treat the disease. The rate of the progression of the disease varies from person to person.

4. Progressive-relapsing: this is the rarest course of the disease with about 5% of patients initially diagnosed. This course is characterized by being progressive from the start with intermittent exacerbations present along the way. This course of the disease differs from primary progressive MS due to the presence of the exacerbations. These exacerbations are not present in primary progressive MS.

No two individuals will have exactly the same experience when it comes to their course of MS, so the courses may vary from person to person.

Figure 1 is a visual representation of the different courses of MS.
PATHOPHYSIOLOGY

Although there is little evidence to confirm an environmental trigger or virus in relation to the disease, the autoimmune hypothesis for MS is considered to be well established. This hypothesis states that the pathophysiology of MS is related to myelin antigen-specific CD4+ T cells which become activated. The exact trigger for the activation of the T cells is still unknown. One theory suggests that T cells might become activated by cross-reacting with a particular antigen, such as a microbial agent, known as “molecular mimicry”. This theory explains why some viruses (mentioned earlier) have been studied as a possible trigger for the disease. These cells then cross the blood-brain barrier, recognize myelin basic protein, attack the neuronal myelin sheaths, and trigger the onset of muscular symptoms and can lead to cognitive decline. These areas of axonal damage are known as lesions. The actual mediator of myelin and axonal destruction has not been established, but it may reflect a combination of macrophages, antibodies, cytokines, and reactive oxygen intermediates.1

DIAGNOSIS

The diagnosis of MS typically occurs between the ages of 15 and 45 years.11 There is no single specific test to diagnose MS; however, there are a variety of techniques that are used to aid in the diagnosis. These techniques include the following: magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) analysis, and the use of evoked potentials.

- MRI: this test is used to reveal areas of damage in the CNS caused by MS plaques. This is the preferred imaging technique, and it is more sensitive than computed tomography (CT) scans. Not only is this tool useful for the diagnosis of the disease, it is also useful for determining the prognosis as well.

- Evoked potentials: this test measures the electrical activity that is produced by the stimulation of certain nerve pathways. It is useful in establishing areas of demyelination. This test is considered less sensitive and specific compared to MRI or CSF analysis, but it can be useful in aiding the diagnosis.

As more information has become available about MS, the clinical guidelines have evolved as well. In the 2005 guidelines by the International Panel on the Diagnosis of MS, also known as the McDonald Criteria, a diagnosis of MS could only be made if an individual “had an appearance of a new lesion on a scan compared to a baseline scan at least 30 days after the onset of the initial clinical event.” The McDonald Criteria was revised in 2010 and now allows for the use of MRI to fulfill the criteria of a diagnosis when a new lesion is discovered regardless of when the timing of the baseline MRI occurred. The goal of this change in criteria was to diagnose patients sooner so that treatment could be initiated earlier in the course of the disease. The McDonald criteria also states that CSF findings can aid in the diagnosis and help evaluate alternative diagnoses. These findings include an elevated IgG index or the presence of two or more oligoclonal bands. With primary-progressive MS, the McDonald Criteria states that a diagnosis can be made “when there is continuous progression of neurological symptoms during a one year period with characteristic MRI and CSF findings.”

Progression of the disease varies from patient to patient and is measured using different techniques. The most common way it is measured is with the use of the Expanded Disability Status Scale (EDSS) which measures physical disability. The score is based upon neurological testing and the examination of different functional systems which include: the ability to walk, speech, swallowing, and others. The score ranges from 0-10, with 0 indicating a normal neurological exam. Many experts believe that this measuring system has flaws, one important one being that the score is complicated to calculate, so newer tools are being developed and evaluated for

Figure 1.

http://commons.wikimedia.org/wiki/File:Types_of_MS.jpg
their possible role in measuring the progression of MS. Until a stronger measuring system is developed, the use of MRI has been steadily increasing to analyze disease progression. This is done by looking for the development of new lesions or any changes in existing lesions. In research studies, this is an outcome that is being measured more frequently.

TREATMENT

The treatment of MS is subdivided into 3 categories which include: symptomatic, acute attacks, and disease modifying. Symptomatic treatment revolves around helping to maintain a patient's quality of life. This can be difficult since many of the symptoms of MS do not respond to drug therapy. The following symptoms will most likely benefit from pharmacologic management and should be initiated as the symptoms appear: spasticity, tremor, bowel and bladder symptoms, sexual dysfunction, and fatigue. Bladder frequency and urgency typically improve with oxybutynin, whereas pain and spasms typically respond to baclofen.

About half of patients diagnosed with MS will become depressed, so it is important to be aware of mood changes and treatment and counseling may be necessary.

Treatment of acute attacks is centered on the treatment of exacerbations that affects a patient's functional ability. The American Academy of Neurology recommends an IV injection of high-dose corticosteroids. The preferred agent is methylprednisolone at a dose of 500-1,000 mg/day for 3-10 days. Large doses of oral steroids may show comparable results; however, further studies are needed to validate this notion.

Disease-modifying treatment focuses on the long term management of the disease with the aim to reduce relapse rates, lessen severity, and to slow the progression of disability and cognitive decline. Treatment is highly variable and differs for patients based on disease severity, cost, side effect profiles, and patient and prescriber preference. Currently there are nine FDA-approved agents that can reduce disease activity and progression in patients with relapsing forms of MS. These agents are:

- interferon beta-la (Avonex®)
- interferon beta-la (Rebif®)
- interferon beta-1b (Betaseron®)
- interferon beta-1b (Extavia®)
- glatiramer acetate (Copaxone®)
- mitoxantrone (Novantrone®)
- natalizumab (Tysabri®)
- fingolimod (Gilenya™)
- teriflunomide (Aubagio™)

The anti-inflammatory properties of the beta interferons are thought to be beneficial, but their mechanism of action is unknown in respect to MS. Patients treated with these agents are at risk for liver function abnormalities and blood dyscrasias, so these aspects should be monitored. Liver function tests and CBC should be performed at months 1, 3, and 6 after initiation of the medication. If no clinical symptoms are present after this time, periodic assessment is recommended. Glatiramer acetate was designed to mimic myelin basic protein. By doing so, it is thought that the patient's immune system will attack this mimicked myelin as opposed to the patient's myelin. This mechanism of action is different than that of the beta interferons, so patients may respond to this agent differently. Unlike the beta interferons, this medication is not associated with liver function abnormalities or blood dyscrasias. Mitoxantrone has been shown, in vivo, to inhibit B-cell, T-cell, and macrophage proliferation. This agent should be used in patients who have worsening relapsing-remitting MS or secondary progressive MS. Natalizumab's mechanism of action with respect to MS is not well established; however, it is a monoclonal antibody that attacks molecules important to adhesion and migration of cells from the vasculature into inflamed tissues. This is thought to be beneficial in MS by blocking the T cell migration into the CNS. There is a black box warning for this agent for an increased risk of progressive multifocal leukoencephalopathy (PML) which is an opportunistic viral infection of the brain which can lead to death. The risk of PML increases the longer the patient is on the medication.

All of these agents have been shown to reduce the number of exacerbations in patients with MS. Of the medications listed above, the four beta interferons and glatiramer are generally considered as first line treatment options. The Executive Committee of the National Clinical Advisory Board of the National Multiple Sclerosis Society recommends that treatment with one of these agents be started as soon as a diagnosis has been confirmed. Natalizumab is recommended for patients who have had an inadequate response to or were unable to tolerate one of the first line treatment options. Mitoxantrone should be considered in patients with worsening disease or patients with secondary-progressive MS. This committee also recommends that changing from one medication to another should only be done for medically appropriate reasons.

Table 1 was adapted from the Multiple Sclerosis Association of America which summarizes the FDA-approved disease modifying therapies for MS.

NEWER FDA APPROVED MS THERAPIES

Fingolimod (Gilenya™)

In September 2010, the first oral disease modifying agent was FDA approved for the treatment of relapsing forms of MS. Fingolimod is a sphingosine 1-receptor modulator (S1P). S1P receptors are found on lymphoid and neuronal tissues and allow these cells to leave the lymphoid organs. The binding of fingolimod's active metabolite, fingolimod-phosphate, causes internalization of the S1P receptor into the cell. This traps the lymphocytes in the lymphoid organs and will decrease the amount of circulating activated T lymphocytes in the blood and cerebral spinal fluid, which in turn will reduce the amount of CNS inflammation and damage to nerve cells. In addition, fingolimod may also have direct effects within the CNS due to S1P receptor expression on various nerve cells resulting in neuroprotective or reparative effects.

Fingolimod is available in a capsule dosage form, and the recommended dose is 0.5mg every day. It is associated with a first dose effect of bradycardia, bradyarrhythmia, and mild reduction in forced expiratory volume in 1 second (FEV1). These effects are due to the fact that S1P receptors are located in other areas of the body that could stimulate these types of effects. Due to these effects, the FDA continues to recommends a six-hour observational period after the first dose of fingolimod.

The most common side effects associated with the use of fingolimod include: headache, diarrhea, increased liver enzymes, cough, backache, and flu like symptoms. Serious, but rare side effects to be aware of include: bradyarrhythmia, AV block, macular edema, lymphocytopenia, and malignant melanoma. During
<table>
<thead>
<tr>
<th>Name</th>
<th>Type</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avonex®</td>
<td>Interferon beta-1a</td>
<td>30 mcg intramuscular injection every week</td>
</tr>
<tr>
<td>Betaseron®</td>
<td>Interferon beta-1b</td>
<td>250 mcg subcutaneous injection every other day</td>
</tr>
<tr>
<td>Extavia®</td>
<td>Interferon beta-1b</td>
<td>250 mcg subcutaneous injection every other day</td>
</tr>
<tr>
<td>Rebif®</td>
<td>Interferon beta-1a</td>
<td>44 mcg subcutaneous injection 3 times weekly</td>
</tr>
<tr>
<td>Copaxone®</td>
<td>Glatiramer acetate; Synthetic chain of four amino acids.</td>
<td>20 mg subcutaneous injection once daily</td>
</tr>
<tr>
<td>Novantrone®</td>
<td>Mitoxantrone; Antineoplastic agent</td>
<td>IV infusion once every 3 months (2-3 years max)</td>
</tr>
<tr>
<td>Tysabri®</td>
<td>Natalizumab; Humanized monoclonal antibody</td>
<td>IV infusion every 4 weeks</td>
</tr>
<tr>
<td>Aubagio®</td>
<td>Teriflunomide; Immunomodulator</td>
<td>7 mg or 14 mg tablet by mouth once daily</td>
</tr>
<tr>
<td>Gilenya™</td>
<td>Fingolimod; S1P- receptor modulator</td>
<td>0.5 mg capsule by mouth once daily</td>
</tr>
</tbody>
</table>

**Comments for Interferon beta-1a/1b:**
- Treatment of remitting-relapsing forms of MS
- Common side effects: flu-like symptoms and injection site reactions
- Check CBC and liver function test at 1,3, and 6 months, then periodically

**Comments for Copaxone®:**
- Treatment of remitting-relapsing forms of MS
- Post injection site reaction may occur within minutes after injection that includes: flushing, chest pain, palpitations, anxiety, shortness of breath, throat constriction and hives
- Common side effect: injection site reactions

**Comments for Novantrone®:**
- Treatment of remitting-relapsing and secondary progressive forms of MS
- Patients may only be on therapy for 2-3 years due to risk of heart damage and leukemia
- Need regular testing for cardiotoxicity, liver function, and white blood cells

**Comments for Tysabri®:**
- Treatment of remitting-relapsing forms of MS
- Common side effects: headache, fatigue, pneumonia, infections, joint and abdominal pain
- Uncommon but serious side effect is progressive multifocal leukoencephalopathy, PML.

**Comments for Aubagio®:**
- Treatment of remitting-relapsing forms of MS
- FDA approved September 2012
- Common side effects: diarrhea, hair thinning, mild increase in hepatic enzymes, headache, and paresthesia
- Can cause severe liver injury and liver function should regularly be tested
- Carries a high risk of birth defects and patients should avoid pregnancy while on drug therapy

**Comments for Gilenya™:**
- Treatment of remitting-relapsing forms of MS
- FDA approved September 2010
- After first dose, a 6 hour monitoring period is advised due to possible decreased heart rate, abnormally slow heart rhythm, mild reduction in FEV-1
- Side effects: reversible increase of liver enzymes, mild blood pressure increase, macular edema, and increase in herpes infections
clinical trials, fingolimod was shown, in rare instances, to cause the development of herpes zoster infection. Patients should be checked for varicella zoster virus antibodies and vaccinated prior to initiation of therapy if needed. Fingolimod should not be used in patients with certain heart conditions or history of certain heart conditions. Patients on certain antiarrhythmic drugs should also avoid this medication. Patients should receive CBC, liver function tests, ophthalmic exams, VZW antibody testing, and ECG at baseline.

Two large, randomized, double blind, phase III trials led the FDA to approve fingolimod for use in MS patients. The FREEDOMS trial compared fingolimod to placebo. The annualized relapse rate with fingolimod was 0.18 and with placebo was 0.40. This gives a relative reduction of 54% for fingolimod compared with placebo. Fingolimod reduced the risk of disability progression over the 2 year study period with a hazard ratio of 0.70. The cumulative probability of disability progression confirmed at three months was 17.7% with fingolimod compared to 24.1% with placebo. The TRANSFORMS trial compared fingolimod to Avonex® (INF-B1a).21 Fingolimod 0.5mg group had an annualized relapse rate of 0.16 while Avonex® was 0.33. This gives a relative reduction in annual relapse rates of 38%. Fingolimod was also more effective than Avonex® at reducing lesion activity and brain volume loss on MRI.

**Teriflunomide (Aubagio®)**

In September of 2012, teriflunomide became the second oral agent available for use in MS patients.6,23 It blocks pyrimidine synthesis by inhibiting a mitochondrial enzyme, dihydorotate dehydrogenase, which is essential for pyrimidine synthesis. The inhibition of this enzyme leads to decreased proliferation of T and B lymphocytes, which reduces the concentration of activated lymphocytes in the CNS. This can reduce the inflammatory demyelination process that occurs in MS patients.

Teriflunomide is given as a 7mg or 14mg tablet orally once a day.22 For patients with suspected liver injury, in cases of pregnancy, overdose, or toxicities in which rapid lowering of teriflunomide levels are needed, cholestyramine or activated charcoal powder can be used.

The most common side effects include: headache, nausea, diarrhea, hair thinning, influenza like symptoms, paresthesia, and increased liver enzymes. Teriflunomide has a black box warning for hepatotoxicity and risk of teratogenicity. Severe liver injury could occur, and liver function tests need to be performed within six months prior to initiation and monthly for up to six months after treatment initiation. Use of this agent with other hepatotoxic drugs or in patients with severe hepatic impairment is contraindicated. Patients should not become pregnant while on this medication, and women of childbearing age should use adequate contraception. A pregnancy test should be administered prior to starting this medication.

Teriflunomide was compared to placebo in a large phase III trial (TEMSO).22 The relative risk reduction in annualized relapse rate was around 31% for both available doses of teriflunomide. MRI results such as reduction in brain lesions improved in both teriflunomide groups. The patients who experienced confirmed disability progression were 20.2% with teriflunomide 14mg, 21.7% with teriflunomide 7mg, and 27.3% with placebo. This gives a relative risk reduction of confirmed disability progression of 23.7% for 7mg teriflunomide and 29.8% for 14mg teriflunomide compared with placebo. The 7mg dose showed no significant reduction in progression of disability compared to placebo. These results are similar when compared with the older injectable agents available for MS showing that teriflunomide is an effective oral agent that is an option for use in MS patients.

**POSSIBLE FUTURE THERAPIES FOR MS**

**Dimethyl Fumarate (BG-12)**

An agent likely to be approved for the treatment of MS is BG-12 and would be the third oral agent available.24 The mechanism of action of BG-12 in MS is not completely understood, but it is thought to have its effects by activating the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway. Activation of this pathway produces anti-inflammatory effects due to the increased production of an important antioxidant, glutathione. In the body antioxidants, like glutathione, protect against cell death due to oxidative stress. Activation of the Nrf2 pathway also possesses neuroprotective properties by inhibiting neuronal damage and regulating maintenance of myelin.

BG-12 has been studied at a dose of 240mg orally two to three times a day.23-26 Adverse events that have been seen were mild to moderate in nature. The most common side effects from BG-12 include: flushing, gastrointestinal symptoms (such as nausea, vomiting, diarrhea, and abdominal pain), proteinuria, pruritus, decreased lymphocyte count, elevation of liver aminotransferase levels, and erythema. The flushing and GI symptoms appeared to be transient and seemed to decrease at or around one month of treatment. BG-12 did not show an increased risk for infection.

Two large, randomized, double blind, placebo controlled trials, the DEFINE and CONFIRM trials, were conducted to examine BG-12’s efficacy and safety in MS patients.25-27 The DEFINE trial compared BG-12 with placebo. Annualized relapse rates were 0.17 in the twice daily group, 0.19 in the thrice daily group, and 0.36 in the placebo group. Twice a day and three times a day dosing of BG-12 gave a relative reduction of 53% and 48% respectively compared to placebo on reducing annualized relapse rates. When comparing confirmed progression to disability, BG-12 had a significant risk reduction compared to placebo with 38% for twice daily and 34% for thrice daily. The CONFIRM trial looked at BG-12 compared to placebo. This study used glatiramer acetate (Copaxone®) as an active comparator and was not designed to find superiority or noninferiority. The annualized relapse rate was significantly lower in all groups compared with placebo. Annualized relapse rates were 0.22 with twice daily BG-12, 0.20 with thrice daily BG-12, 0.29 with glatiramer acetate, and 0.40 with placebo. This corresponds to a relative reduction compared to placebo of 44% for twice daily, 51% for thrice daily, and 29% for glatiramer acetate. In all groups, disability progression was not reduced significantly. Both of these studies support BG-12 use and efficacy in MS patients. BG-12 is currently awaiting FDA approval with a decision expected in early 2013.

**EXPERIMENTAL MONOCLONAL ANTIBODIES FOR MS**

Currently there are several monoclonal antibodies being looked at as possible treatment options for MS patients. Alemtuzumab, daclizumab, and ocrelizumab are humanized monoclonal antibodies and rituximab is a chimeric monoclonal antibody.28-31 All of these treatment options are in stage III clinical trials as of this writing for the treatment of MS.

**Alemtuzumab** is a monoclonal antibody that targets CD52.
Two recent phase 3 trials, CARE-MS I and CARE-MS II, have looked at alemtuzumab versus interferon beta 1a (Rebif®). In CARE-MS I, 40% of patients in the interferon group experienced a relapse compared to 22% in the alemtuzumab group. This study did not show any difference in the progression of disability between the two therapies. In contrast, the CARE-MS II trial did show that alemtuzumab decreased progression to disability significantly more than the interferon group. It also showed improvement in relapse rates with interferon beta 1a group with 51% and alemtuzumab group with 35% of patients experiencing a relapse. Side effects seen in these studies included infusion type reactions and infections that were mild to moderate in nature.

Daclizumab is a humanized monoclonal antibody that targets interleukin 2 (IL-2) receptor. IL-2 stimulates T-cell proliferation and activation. By targeting IL-2, daclizumab can inhibit activated T-cells. A phase three trial, DECIDE, is currently ongoing. It will evaluate safety and efficacy of daclizumab while comparing it to interferon beta 1a. Rituximab and Ocrelizumab are human monoclonal antibodies that target CD20 which is an antigen located on pre B and mature B cells. Targeting of this CD-12 will deplete certain B cells thus suppressing their functions. The B-cells could contribute to MS by producing antibodies against neuronal cells or functioning as an antigen presenting cell to T-cells. Ocrelizumab is currently in ongoing phase 3 trials for use in relapsing MS compared with interferon beta-1a and its use in patients with primary progressive MS.

Rituximab has also been studied for treatment of MS. In a phase 2 randomized, double blind, placebo controlled trial (HERMES trial), rituximab was shown to reduce relapse rates and inflammatory brain lesions. The OLYMPUS trial was a phase 2/3 randomized, double blind, placebo controlled trial that looked at rituximab in patients with progressive MS. This study failed to reach its primary endpoint of reduction in time to confirmed disease progression but did reach significance for the secondary endpoint of reducing T2 lesion volume on MRI.

Laquinimod is an oral immunomodulatory agent that will not suppress the immune system. It is both an anti-inflammatory and a neuroprotective agent. A potential mechanism of action in MS is the inhibition of migration of leukocytes into the CNS. Laquinimod affects cytokines by decreasing the amount of pro-inflammatory Th1 and IL-2 and increasing the amount of anti-inflammatory Th2 and IL-4. There has also been a reduction in axonal damage seen when using laquinimod. Laquinimod could additionally have neuroprotective effects due to increase in brain-derived neurotrophic factor (BDNF) levels. BDNF is needed for the development and maintenance of nerve cells in the CNS.

In a phase III trial that compared laquinimod to placebo (ALLEGRO), the annualized relapse rate was moderately low but significantly reduced by a rate of 0.30 with laquinimod and 0.39 with placebo group. The risk for disability progression was significantly decreased in the laquinimod group. MRI endpoints, which included the progression of lesions or the appearance of new lesions, also showed significant reduction for the laquinimod group. Results from another phase III trial, BRAVO, looked at patients on laquinimod, placebo, or interferon beta-1a to assess efficacy and safety. Laquinimod failed to achieve significance in reducing annualized relapse when compared to placebo. When researches accounted for differences in the MRIs of patients seen at baseline, a significant reduction was found in annualized relapse rates. Three phase III trials are currently ongoing for laquinimod for its use in MS. Two are assessing the long term safety and tolerability of laquinimod. The other trial being conducted, the CONCERTO trial, is currently recruiting patients and will assess the time to confirmed disease progression comparing two doses of laquinimod (0.6mg daily and 1.2mg daily) and placebo.

CONCLUSION

MS is an autoimmune disease involving demyelination of the CNS. It is subdivided into four different courses based on different characteristics. Currently there are nine FDA approved disease modifying therapies for treatment of multiple sclerosis. There is no cure for MS; however, in recent years there have been significant advances made towards the treatment of this disease. One such advancement is the introduction of the first oral agents used to treat the disease, fingolimod and teriflunomide. There are several agents currently in development for MS with the hope of providing more effective and safer treatment options for those affected with the disease.
REFERENCES


