Journal of the American Pharmacists Association 57 (2017) 551–554

Contents lists available at ScienceDirect

Journal of the American Pharmacists Association

journal homepage: www.japha.org

NEW DRUGS

Ocrelizumab, edaravone, and valbenazine

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Agent for multiple sclerosis

Multiple sclerosis (MS) is a chronic, inflammatory autoimmune disease of the central nervous system that affects approximately 400,000 people in the United States. It occurs more often in women than in men, and most individuals first experience symptoms between the ages of 20 and 40 years. Relapsing-remitting MS, also designated as relapsing MS, is the most common form of the disease in which patients experience episodes of worsening function (relapses) that are followed by recovery periods (remissions) of varying duration. As the disease continues, remissions may be incomplete and, eventually, some patients become disabled and experience cognitive decline. Approximately 15% of patients with MS have primary progressive MS (PPMS) that is characterized by steadily worsening function from the onset of symptoms, sometimes without early relapses and remissions.

The treatment of MS includes the use of disease-modifying drugs, as well as medications for the treatment of specific symptoms, such as pain, and corticosteroids for acute exacerbations. The disease-modifying drugs have been of value in reducing the frequency and severity of relapses, but they are of limited benefit in more progressive disease. Interferon beta was the first disease-modifying drug to be approved for the treatment of MS, and it continues to be used often in several forms and products, including interferon beta-1a (Rebif), pegylated interferon beta-1a (Plegridy), and interferon beta-1b (Betaseron) that are administered subcutaneously, and a formulation of interferon beta-1a (Avonex) that is administered intramuscularly. Other drugs that have been approved for the treatment of patients with relapsing-remitting MS include glatiramer acetate (Copaxone), alemtuzumab (Lemtrada), natalizumab (Tysabri), mitoxantrone, fingolimod (Gilenya), teriflunomide (Aubagio), and dimethyl fumarate (Tecfidera). The latter 3 agents offer the convenience of oral administration and are often used as a first-line treatment for MS. Natalizumab may be the most effective of these drugs, but there is concern about rare but serious adverse events, including progressive multifocal leukoencephalopathy (PML), a potentially fatal opportunistic viral infection of the brain. In addition to these agents, rituximab (Rituxan) has been used off-label for the treatment of patients with more severe forms of MS.

Ocrelizumab (Ocrevus; Genentech) is a humanized monoclonal antibody that, like the chimeric monoclonal antibody rituximab, is directed against CD20-expressing B cells. CD20 is a cell surface antigen present on pre-B and mature B lymphocytes. Following cell surface binding to B lymphocytes, ocrelizumab causes antibody-dependent cellular cytolysis and complement-mediated lysis. It is administered by intravenous infusion and is indicated for the treatment of patients with relapsing or primary progressive forms of MS. As the first drug to be demonstrated to be effective in the treatment of PPMS, ocrelizumab represents an important advance for patients with more severe forms of the disease.

The effectiveness of ocrelizumab in the treatment of relapsing MS was established in 2 studies of 1656 patients that were conducted for a period of 96 weeks. The new drug was compared with interferon beta-1a (Rebif) in both studies, in which the primary endpoint was the annualized relapse rate. The annualized relapse rate for the patients treated with ocrelizumab was 0.156 and 0.155 in the 2 studies, compared with rates of 0.292 and 0.290 for those treated with interferon beta-1a. In addition, 83% and 82% of the ocrelizumab-treated patients were relapse-free compared with 71% and 72% of the interferon beta–treated patients. The proportion of patients with 12-week confirmed disability progression was 9.8% with ocrelizumab treatment and 15.2% with interferon beta.

Ocrelizumab was evaluated in patients with PPMS in a placebo-controlled trial with 732 participants that continued for at least 120 weeks. There was a longer time to the worsening of disability in patients treated with the new drug, with the proportion of patients with 12-week confirmed disability progression being 32.9%, compared with 39.3% for those receiving placebo. In all 3 studies, the MRI evaluations (e.g., number and volume of MS-associated

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http://dx.doi.org/10.1016/j.japh.2017.06.008
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brain lesions) indicated greater effectiveness of ocrelizumab, compared with interferon beta-1a or placebo.

Infusion reactions are an important concern with the use of ocrelizumab; they occurred in 40% of patients in the placebo-controlled study, with the highest incidence being associated with the first infusion. Manifestations ranged from relatively mild dermatologic events to serious reactions, such as bronchospasm and hypotension. Although there were no fatal infusion reactions in the clinical studies, 0.3% of patients experienced serious reactions and some required hospitalization. Ocrelizumab is contraindicated in patients with a history of life-threatening infusion reactions to the drug. If such reactions occur during treatment, the infusion should be stopped immediately and permanently, and appropriate supportive treatment initiated. To reduce the frequency and severity of infusion reactions, a corticosteroid and antihistamine should be administered as premedications. The addition of an antipyretic can also be considered.

Many patients treated with ocrelizumab experience infections, the most common of which are upper respiratory tract infections (49%), skin infections (14%), lower respiratory tract infections (10%), and herpes virus–associated infections (5%). These infections were also commonly reported, but at a lower incidence, in patients receiving placebo. In the clinical studies, there were no reports of reactivation of hepatitis B virus (HBV) infection or PML. Because the other anti-CD20 antibody rituximab has been associated with reactivation of HBV infection, ocrelizumab is contraindicated in patients with active HBV infection. Vaccination with live or live-attenuated vaccines is not recommended during treatment with ocrelizumab, or following treatment until B cell repletion. Immunizations according to guidelines should be administered at least 6 weeks before initiating treatment with ocrelizumab.

An increased risk of malignancy, including breast cancer, may be associated with the use of ocrelizumab. Breast cancer occurred in 6 of 781 females treated with the new drug, and in none of the 668 females treated with interferon beta-1 or placebo. Patients should follow standard breast cancer screening guidelines.

There are insufficient data to assess the risk of using ocrelizumab in pregnant and nursing women. The results of animal studies suggest a potential for harm to the unborn child if used during pregnancy. Although this risk with ocrelizumab may be less than with certain other agents used for the treatment of MS (e.g., teriflunomide, mitoxantrone), glatiramer acetate appears to have a lower risk of problems if used during pregnancy. The effectiveness and safety of ocrelizumab in pediatric patients have not been established.

The concomitant use of ocrelizumab and other immune-modulating or immunosuppressive medications, including corticosteroids, may increase the risk of immunosuppression. Caution must be observed when these agents are used concurrently and sequentially, in consideration of the long duration of action of the new drug and certain other medications.

A potential exists for immunogenicity with the use of ocrelizumab, but only approximately 1% of patients tested positive for antidrug antibodies, and only 2 of 1311 patients tested positive for neutralizing antibodies.

Before ocrelizumab treatment is initiated, patients should be screened for active HBV infection and, before each dose, the presence of active infection of any type should be excluded. If an active infection exists, the infusion of ocrelizumab should be delayed until the infection resolves. Before each infusion, patients should be premedicated with an antihistamine (e.g., diphenhydramine) approximately 30-60 minutes before infusion and 100 mg of methylprednisolone (or an equivalent corticosteroid) administered intravenously approximately 30 minutes beforehand. The addition of an antipyretic (e.g., acetaminophen) may also be considered.

Ocrelizumab injection is supplied in single-dose vials containing 300 mg of the drug in 10 mL. The vials should be stored in a refrigerator. The intravenous infusion must be prepared by a health care professional and administered under supervision. Patients should be observed for infusion reactions during the infusion and for at least 1 hour after the completion of the infusion. The intended dose should be withdrawn from the vial and diluted into an infusion bag containing 0.9% sodium chloride injection, to a final drug concentration of approximately 1.2 mg/mL. The diluted infusion solution should be administered through a dedicated line using an infusion set with a 0.2- or 0.22-μm inline filter.

The initial dose of ocrelizumab is 300 mg in 250 mL of diluted solution, followed 2 weeks later by a second 300-mg infusion. Each of these infusions should be started at a rate of 30 mL/h that can be increased by 30 mL/h every 30 minutes to a maximum of 180 mL/h, for a total infusion duration of 2.5 hours or longer. Subsequent doses are administered as a single 600-mg infusion (in 500 mL) every 6 months. These infusions should be started at a rate of 40 mL/h that can be increased by 40 mL/h every 30 minutes to a maximum of 200 mL/h for a total infusion duration of 3.5 hours or longer. The product labeling should be consulted for recommended dosage modifications if infusion reactions occur. If a planned infusion is missed, it should be administered as soon as possible. The dosage schedule should then be adjusted so that the next scheduled dose is administered 6 months after the missed dose is administered. Doses of the drug must be separated by an interval of at least 5 months.

Agent for amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS), commonly known as Lou Gehrig's disease, is a progressive, neurodegenerative disease that affects 12,000-15,000 Americans, with approximately 5000 cases diagnosed this year. It is characterized by the destruction of nerve cells that control voluntary muscles that are involved in functions such as chewing, walking, breathing, and talking. As the activity of the nerve cells declines, the muscles become weaker and paralysis results. Most patients with ALS die from respiratory failure, usually within 3-5 years from when symptoms first appear.

Riluzole (Rilutek) was approved by the U.S. Food and Drug Administration in 1995, and it has been the only drug available that is indicated for the treatment of ALS. It is thought to act by reducing glutamate release and reducing the accumulation of this amino acid in nerve cell synapses. This agent has been demonstrated to prolong survival and time to tracheostomy, but it prolongs survival on average by only 3 months.

Edaravone (Radicava; Mitsubishi Tanabe) is the second drug to be

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