Oral Agents for Multiple Sclerosis Prove Effective

Discontinuation rates were low, but adverse event rates ranged from 8% to 14%.

BY MARY ANN MOON

Fingolimod and cladribine, the first oral formulations for treating relapsing-remitting multiple sclerosis, proved effective in three phase III clinical trials.

The two drugs have different mechanisms of action, but both target lymphocytes that are potentially autoaggressive against the CNS and both also are believed to promote neuroprotective and reparative processes. In separate multicenter, randomized, double-blind, placebo-controlled clinical trials, both oral medications reduced the rate of multiple sclerosis (MS) relapse, slowed the progression of disability, and decreased the number and severity of brain lesions on MRI.

All three trials were well conducted and 'provide a new horizon for patients with relapsing-remitting MS and a welcome increase in the range of options.'

In one of the studies, fingolimod outperformed interferon beta-1a injections, a widely used treatment for MS. "It is likely that the two oral therapies will be at least as effective as other currently available disease-modifying therapies," Dr. William M. Carroll wrote in an editorial (N. Engl. J. Med. 2010 Jan. 20 [doi:10.1056/NEJMe0912019]).

Both fingolimod and cladribine had acceptable safety profiles with low rates of adverse events leading to discontinuation of the drugs. However, these rates still were twice as high with active therapy as with placebo (ranging from 8% to 14%), and were associated with patient death in at least two cases.

"Clinicians and patients will need to evaluate the risks and benefits of each of these drugs," and long-term safety remains a concern because patients may need to take them their whole lives, according to Dr. Carroll of Sir Charles Gairdner Hospital, Perth, Australia.

In the first study, which was funded by Novartis Pharma, Dr. Ludwig Kappos of the University of Basel (Switzerland) and his associates compared two doses of daily fingolimod capsules (0.5 mg and 1.25 mg) with a matching placebo in 1,272 patients followed for 2 years at medical centers in 22 countries. The primary end point—the rate of relapse—was 54% lower with the lower dose of the drug and 60% lower with the higher dose, relative to placebo.

Fingolimod was equally effective in patients who had never been treated and those who had already received other treatments for MS. The time to first relapse was significantly longer with active treatment than with placebo, and more patients in the active-treatment group remained relapse free at 2-year follow-up.

Both doses of fingolimod also reduced the risk of disability progression and the time to progression. Scores on two measures of disability either remained stable or improved slightly with fingolimod, but worsened with placebo.

MRI scans showed significantly fewer brain lesions, as well as fewer new or enlarged lesions and a smaller overall volume of lesions, with fingolimod than with placebo. In addition, characteristic reductions in brain volume were 30% smaller with fingolimod, Dr. Kappos and his colleagues reported (N. Engl. J. Med. 2010 Jan. 20 [doi:10.1056/NEJMoa0907839]).

In the second study, which also was funded by Novartis Pharma, Dr. Jeffrey A. Cohen of the Cleveland Clinic's Mellen Center and his associates compared the same two doses of daily oral fingolimod with intramuscular injections of interferon beta-1a (Avonex). The investigators conducted follow-up for 1 year with 1,292 patients treated at 172 medical centers in 18 countries.

Compared with interferon beta-1a, the relapse rate was 38% lower with low-dose and 52% lower with high-dose fingolimod. The time to relapse, proportion of relapse-free patients, and proportion with multiple relapses also favored fingolimod.

Fingolimod-treated patients also experienced a similar rate of disability progression, time to disability progression, and MRI findings as those that were reported in the trial conducted by Dr. Kappos and his associates.

In these two studies, serious adverse events were more frequent with fingolimod than with the comparator, and they appeared to be more common at the higher dose of the drug. Adverse events tended to fall into the categories expected for any immunomodulatory agent: lymphocytopenia, CV effects, increased rates of infection, macular edema, liver-enzyme abnormalities, and neoplasms.

Fingolimod caused transient and often asymptomatic bradycardia and atrioventricular block, which likely reflects the drug's ability to bind to receptors in cardiac tissue. The long-term relevance of this effect is not yet known.

The drug also raised the rate of infection, including pneumonia. Several patients developed herpes infections, two of which were fatal, and reactivation of latent herpes remains a concern.

Both research groups emphasized that longer studies are needed to assess safety issues adequately.

In the third study, sponsored by Merck Serono, Dr. Gavin Giovannoni of Queen Mary University, London, and his associates compared two doses of oral cladribine with a matching placebo in 1,326 patients who were followed for 96 weeks at 155 centers in 32 countries.

The agents were given in two or four short courses for 48 weeks, then again in two short courses at weeks 48 and 52, for a total of 8-20 treatment days per year. This schedule allowed for an extended hematopoietic recovery period during the interval before the second round of treatment courses.

Both doses of cladribine significantly reduced the relapse rate by 55%-58%. In addition, the drug lengthened the time to relapse and decreased the rate of disability progression by approximately one-third.

Cladribine also reduced measures of MS inflammatory activity on MRI brain imaging.

The rate of serious adverse events was 8% with low-dose cladribine and 9% with high-dose cladribine, compared with 6% with placebo. The types of adverse events were similar to those with other immunomodulatory agents: lymphocytopenia, infection, and neoplasms.

Twenty patients had reactivation of latent herpes infections, and 1 had a reactivation of latent tuberculosis that proved fatal. "Cancers were isolated cases across different organ systems, and given the small number, it is not possible to establish a risk for the use of cladribine," Dr. Giovannoni and his colleagues wrote (N. Engl. J. Med. 2010 Jan. 20 [doi:10.1056/NEJMoa0902533]).

As with fingolimod, the risks of treatment with cladribine must be carefully weighed against the benefits, and longer follow-up is essential, the investigators added.

All three clinical trials were well conducted and "provide a new horizon for patients with relapsing-remitting MS and a welcome increase in the range of treatment options," Dr. Carroll noted.

All three first authors and many of their coauthors reported receiving consulting or lecture fees or research support from many manufacturers of drugs for MS, including Biogen Idec, Merck Serono, EMD Serono, and Novartis. ■

FDA Approves First Drug to Improve Walking in MS Patients

BY ELIZABETH MECHCATIE

A sustained-release formulation of the potassium channel blocker dalfampridine has been approved by the Food and Drug Administration as a treatment to improve walking in people with multiple sclerosis.

In a statement, the FDA announced that dalfampridine extended-release tablets had been approved for this indication, based on studies that found patients treated with the drug had faster walking speeds than did those treated with placebo. This is the first drug approved for this indication, according to the FDA.

Dalfampridine will be marketed as Ampyra by Acorda Therapeutics Inc. of Hawthorne, N.Y.

At a meeting in October 2009, the majority of an FDA advisory panel voted that Acorda had provided "substantial evidence" of effectiveness for this indication, although only one-third of the patients in the two pivotal trials were considered responders. Most of the panel also agreed that the drug could be considered safe for use in people with MS, but not in patients who have a history of seizures and those with severe renal insufficiency.

There is 'substantial evidence' of effectiveness for this indication, but only one-third of the patients in the two pivotal trials were responders.

The recommended dose of dalfampridine is 10 mg twice a day. However, higher doses have been associated with seizures, and the drug should not be taken by patients with moderate to severe kidney disease, whose blood levels with dalfampridine approach the levels that have been associated with seizures, according to the FDA statement.

The drug has a long history of use in the United States despite never having been approved, according to background documents filed by the FDA for the advisory panel meeting. For more than 20 years, dalfampridine has been compounded in pharmacies and used off-label to improve walking in people with various neurologic conditions. However, fampridine's narrow therapeutic range makes plasma levels difficult to regulate with the immediate-release formulation, which is associated with an increased risk of seizures. The sustained formulation was developed to overcome these limitations.

In clinical trials, the most common adverse reactions in patients taking dalfampridine included urinary tract infections, insomnia, dizziness, headache, nausea, weakness, back pain, balance disorder, swelling in the nose or throat, constipation, diarrhea, indigestion, throat pain, and skin sensations including burning, tingling, and itching.

At the meeting, representatives of Acorda said that dalfampridine improves conduction in demyelinated axons. ■