Patients who receive a diagnosis of MS face numerous uncertainties, not the least of which are unknowns related to the likely progression of their disease, future disability, and long-term changes in their quality of life. But for most there seems to be one guarantee: a lifetime of therapy with an injectable disease-modifying therapy. That reality may be about to change; oral adjunctive therapy is now available, and other oral treatments are on the horizon. The following is a review of recent developments in injectable and oral therapy for MS.

**Oral Therapies**

*Dalfampridine.* At the leading edge of the new wave of oral drugs for MS, sustained release dalfampridine (Ampyra, Accorda Therapeutics) garnered FDA approval in January to improve walking ability in patients with MS. Previously also called fampridine, dalfampridine SR is a broad-spectrum potassium channel blocker that is not shown clinically to affect the duration of the QRS interval and does not prolong the QTc interval. It increases the conductivity of demyelinated nerve fibers. Based on its narrow but important indication, dalfampridine is most likely to be used as an adjunct to disease-modifying therapy, although it was tested and shown effective in clinical trials in patients who were not receiving immunomodulatory therapy.

Fampridine is not a new agent in neurology, points out Douglas Jeffery, associate professor in the department of neurology at Wake Forest University Baptist Medical Center. Physicians have been ordering compounded fampridine for many years, but these compounded products lack consistency and do not have reliable safety—a concern, given potential effects on the QT interval.

In two Phase III placebo-controlled clinical trials involving a total of 540 patients with MS, significantly more of those who received 10 mg of dalfampridine twice daily showed an increase in walking speed, regardless of whether or not they were...
using an immunomodulatory drug simultaneously.

In one randomized, multicenter, double-blind, controlled Phase III trial, 301 patients with any type of MS were randomized to 14 weeks of treatment with either fampridine 10mg twice daily (n = 229) or placebo (n = 72). Among timed-walk responders, walking speed improved 25.2 percent among treated patients and 4.7 percent among controls. Timed walk responders showed greater improvement in 12-item multiple sclerosis walking scale scores (6.84) than timed walk non-responders (0.05).2

In clinical trials, the most commonly reported adverse event was urinary tract infection. Other frequently reported adverse events included dizziness, GI upset, headache, insomnia, stuffy nose, throat pain, and weakness. Dalfampridine is contraindicated in patients with moderate to severe kidney impairment.

The label contains a warning that dalfampridine can cause seizures, and it is contraindicated in patients with a history of seizure. Dalfampridine should be discontinued in any patient who has a seizure. The sustained-release formulation was developed in efforts to minimize seizure risk: Improvement in neurological deficits is primarily related to the total fampridine dose, according to pharmacokinetic studies, while seizure induction is related to peak serum levels.3

The recommended dose of dalfampridine is one 10mg extended-release tablet taken twice daily with

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**Natalizumab Update**

New label changes for natalizumab indicate that an individual’s risk of developing progressive multifocal leukoencephalopathy (PML) increases along with the duration of therapy. For neurologists, this has long been accepted. In announcing the label change, which also includes a notice regarding Immune Reconstitution Inflammatory Syndrome (IRIS), FDA indicated that the available data show “that the clinical benefits of Tysabri continue to outweigh the potential risks.” The agency also indicated that in addition to identifying new PML cases, “Revisions to the drug label and patient Medication Guide, with the continued use of the TOUCH Prescribing Program, are intended to maximize the safe use of Tysabri.”

Data from a recent study indicate that viral reactivation in the peripheral blood is not evident after one year of natalizumab therapy. (Lancet Neurol. 2010 Jan 28. Epub) Among 24 MS patients who received natalizumab, JC virus DNA was not detected in the blood at any timepoint; JC virus DNA was present in the urine of six patients (most concentrations were stable over time).

Another study indicates that serial plasma and cerebrospinal fluid (CSF) screening for polyomavirus could help identify patients with laboratory evidence of viral infection prior to the development of clinical PML. (J Neurol. 2010 Jan 7. Epub) The study involved 200 MS patients who had pre-treatment CSF/plasma screening for JC virus (JCV) and BK virus (BKV) DNA, and then following every six treatments of natalizumab. If a patient tested positive, therapy was discontinued, and the patient was followed up with clinical examinations and plasma/CSF JCV/BKV tests until all evaluations were normal. Although eight of 200 patients had detectable JCV or BKV DNA (five positive for BKV DNA in the CSF, three positive for JCV DNA (one plasma, two CSF)), no patient developed clinical evidence of PML. After cessation of natalizumab treatment, all patients converted to undetectable viral DNA.

Thomas Leist, MD, PhD Chief, Division of Clinical Neuroimmunology and Director, Comprehensive MS Center at Thomas Jefferson University in Philadelphia has previously addressed the decision to initiate natalizumab therapy in patients, given the possible risks. “It is very important that the patient is part of any treatment decision. The patient is the one ultimately who will need to be compliant,” he notes. “The patient is the person who ultimately gives consent to make the switch.” He has noted that three possible reasons to switch to natalizumab include 1.) patient desire, because he or she perceives it as more effective and/or more convenient, 2.) the patient is intolerant to current therapy, or 3.) the patient has incomplete response to current therapy. Approaching therapeutic decisions with patients in this way, he says, and comparing risks and benefits of natalizumab relative to current therapy allows the patient to bring in their own judgment of risk tolerance.
or without food. The film-coated tablets are designed to be taken whole and not divided, crushed, or chewed.

Dr. Jeffery says that based on the data, roughly one quarter of patients are expected to respond to therapy, and those who do should see significant benefits. Noting that not all patients will respond to dalfampridine, he suspects that it will be tried in a number of MS patients. The treatment is attractive because it can be combined safely with standard disease modifying therapies, and if the patient does not see a benefit, he or she can simply discontinue it, he adds.

**Cladribine.** The leading candidates for oral disease-modifying therapy are fingolimod (Novartis) and cladribine (Merck), despite recent regulatory setbacks for the latter. Late last year, FDA notified Merck that it had refused to file the NDA for cladribine on the basis that it was incomplete. Cladribine has been used parenterally for the management of MS and for indications in oncology for more than 15 years, and its efficacy in relapsing remitting MS is well established, Dr. Jeffery notes. It has not proven as beneficial in progressive MS. In RRMS, IV cladribine has provided MRI outcomes similar to those of the interferons, Dr. Jeffery says. However, the agent has been associated with safety concerns related to its immunosuppressive action. Specifically, there appears to be an increased risk of herpes zoster, as also documented with oral cladribine in recent trials. The drug is teratogenic, Dr. Jeffery notes, and there are at least theoretical concerns about effects on a patient’s fertility.

Merck has undertaken three trials for oral cladribine, which would be administered eight to 10 days a year. The CLARITY (CLAdRibine Tablets Treating MS Orally) two-year, placebo-controlled trial was designed to evaluate the efficacy and safety of cladribine tablets as a monotherapy in patients with RRMS. The study also had a two-year extension designed to provide data on the long-term safety and efficacy of extended administration of cladribine tablets for up to four years. Recently reported were data on 1,326 patients randomized in an approximate 1:1:1 ratio to receive one of two cumulative doses of cladribine tablets (either 3.5mg or 5.25mg/kg) short courses starting at week 48 and week 52 (for a total of eight to 20 days per year). Among treated patients, there was a significantly lower annualized rate of relapse than in the placebo group [0.14 and 0.15, respectively, vs. 0.33], a higher relapse-free rate (79.7 percent and 78.9 percent, respectively, vs. 60.9 percent), a lower risk of three-month sustained progression of disability, and significant reductions in the brain lesion count on MRI. Treated patients also had a higher frequency of lymphocytopenia (21.6 percent in the 3.5mg group; 31.5 percent in the 5.25mg group, vs. 1.8%) and herpes zoster (eight and 12 patients, respectively, vs. no patients).

Merck maintains that it will continue to pursue approval and is working with the FDA to complete its NDA. Dr. Jeffery notes several practical questions potentially associated with oral cladribine, including concerns about the ideal duration of therapy to optimize response while minimizing risks associated with immunosuppression. He also notes that immunosuppression associated with cladribine will limit patients’ access to rescue therapies, such as natalizumab (Tysabri, Biogen-Idec).

**Fingolimod.** Fingolimod (FTY720, Novartis) is currently completing phase III trials for MS. Fingolimod activates S1P1, an extracellular lipid mediator that plays a key role in the immune system, regulates and prevents lymphocyte migration from lymphoid tissues, and reduces autoaggressive lymphocyte infiltration into the CNS. Fingolimod may have direct CNS effects—it crosses the blood-brain barrier—and prophylactic administration to animals with experimental autoimmune encephalitis (EAE) completely prevents development of EAE features. Therapeutic administration to mice with EAE significantly reduces clinical severity of EAE.

In a 12-month, double-blind, double-dummy study (TRANSFORMS), 1,292 patients with relapsing-remitting MS and a recent history of at least one relapse were randomly assigned to receive either oral fingolimod 1.25mg daily, 0.5mg daily, or intramuscular interferon beta-1a 30mug. A total of 1,153 patients completed the study. The annualized relapse rate was significantly lower among fingolimod-treated patients [0.20 in the 1.25mg group; 0.16 in the
0.5mg group) than among those receiving interferon (0.33). MRI findings supported the primary results.

Two fatal infections occurred in the group that received the 1.25mg dose of fingolimod: disseminated primary varicella zoster and herpes simplex encephalitis. Other adverse events among patients receiving fingolimod were nonfatal herpesvirus infections, bradycardia and atrioventricular block, hypertension, macular edema, skin cancer, and elevated liver-enzyme levels.

A total of 1,272 patients completed a longer 24-month, double-blind, randomized study (FREE-DOMS). Patients received oral fingolimod 0.5mg or 1.25mg daily or placebo. The annualized relapse rate was 0.18 with fingolimod 0.5mg, 0.16 with fingolimod 1.25mg, and 0.40 with placebo. Fingolimod significantly reduced the risk of disability progression over the 24-month period; the cumulative probability of disability progression was 17.7 percent with fingolimod 0.5mg, 16.6 percent with fingolimod 1.25mg, and 24.1 percent with placebo. MRI-related measures were higher with treatment than placebo. Bradycardia and atrioventricular conduction block at the time of fingolimod initiation, macular edema, elevated liver-enzyme levels, and mild hypertension led to therapy discontinuation in some subjects.

According to Dr. Jeffery, the positive effects on MRI measures along with the effect on disability progression make fingolimod a potentially attractive treatment option. Associated adverse events, particularly breast cancer, basal cell carcinoma, and malignant melanoma are concerning, but appear to be dose-dependent: “The signals were less with lower doses,” he says.

Fingolimod is not shown to have long-term effects on the immune system, so patients could transition easily from the oral agent to another MS therapy.

Laquinimod. Phase II trials of laquinimod (Teva) suggest “a lot of potential,” Dr. Jeffery says, noting that the agent is associated with a favorable safety profile. There may be a moderately increased risk of HSV and HVZ associated with treatment.

The broad-spectrum immunomodulatory agent received fast-track designation from the FDA last year. Laquinimod is a quinolonecarboxamide shown effective in animal models of several autoimmune diseases, including MS. It appears to modulate a Th1/Th2 shift without producing immunosuppression. In Phase II studies in relapsing MS, laquinimod produced a dose-response effect on the number of active lesions on brain MRI with favorable tolerability and safety.

Recently reported data from the 25th Congress of the European Committee for Treatment and Research in MS show that laquinimod reduced inflammation, demyelination, and axonal damage in EAE. In human subjects with RRMS, three months of treatment with laquinimod 0.6mg produced up to an 11-fold increase in brain derived neurotrophic factor (BDNF) serum levels compared to baseline and placebo, suggesting possible neuroprotective effects.

Balancing Safety and Efficacy

Determining a clinical role for the various oral disease-modifying therapies—once they reach market—will depend on balancing documented efficacy with safety, Dr. Jeffery suggests. He notes that injectables have established benefits: they work fairly well, are generally safe, and their risk profiles are fairly well-known. But tolerability is sometimes a concern, as are injection site reactions, and patient convenience/compliance.

Oral agents could, theoretically, obviate some of these concerns. The challenge is deciding whether the benefits and efficacy outweigh the risks—which may not be fully known as of yet.