

# Oral Drugs for MS

Is it time for multiple sclerosis patients to put the needles aside? Maybe not.

BY JAMIE TALAN

Following a diagnosis of multiple sclerosis (MS) in 2001, Elissa Levy moved into her parents' building for help with her daily treatments by injection. Now, with a new generation of oral medicines on the horizon, Levy and almost a half a million other Americans may soon have an opportunity to put the needles and infusions aside. The *New Yorker* has started treatment with dalfampridine, the first oral MS drug approved by the Food and Drug Administration (FDA). Dalfampridine enhances nerve function. Levy says the drug has allowed her to walk normally for the first time in a decade.

"I walked five miles today," she says. "People wouldn't even know I have multiple sclerosis." Levy's doctor, who was involved in the clinical trial of the drug in 2006, recommended that she try a form of it made by a compounding pharmacy. Levy agreed. "I was dependent on my parents at 35," Levy says, "and two days after I started [dalfampridine] I became independent." Now 41, she is president and cofounder of MS Hope for a Cure.

Studies show that as many as 70 percent of people with MS have problems walking, according to Lauren Krupp, M.D., a neurologist at University Hospital in Stony Brook, NY. In a randomized, double-blind, placebo-controlled trial of sustained-release oral fampridine in MS (published in the medical journal *The Lancet* in 2009) dalfampridine improved walking speed in about one-third of patients.

Dalfampridine is considered a symptomatic therapy, not a disease-modifying drug. It does not affect the immune system, as do the other federally approved MS drugs, and may not alter the course of the disease.

Due to concern about the drug's adverse effects—particularly seizures, which occurred with doses greater than 10 mg—the FDA recommended that dalfampridine not be used in patients with a his-



tory of seizures or with moderate to severe kidney disease. "In these patients, blood levels with the drug approach those associated with the occurrence of seizures," according to an FDA news briefing about the approval. Still, doctors and patients are excited about the treatment option.

"There has never been anything like this before," says Dr. Krupp, who runs a number of clinical trials and has had several patients on dalfampridine.

## THE DRUG PIPELINE

Multiple sclerosis is an autoimmune disease, triggered by an immune system that is working too hard. The first disease-modifying MS drugs targeting the overactive immune system became available in the early 1990s. Every medicine approved today for MS except for dalfampridine works to suppress the immune system—and is delivered via injection or infusion.

Scientists have been trying to create a pill that delivers the right dose of medication without causing gastrointestinal problems. Until recently, nothing seemed to work. Now, there are about five different oral drugs in the pipeline that show

promise in reducing the number of MS episodes and the resulting lesions that form in the nervous system.

The first two oral disease-modifying MS drugs that are on the front burners for federal approval are fingolimod and cladribine. The FDA announced in February that fingolimod has been added to a short list of promising drugs that will be ushered through the approval process faster than normal. Cladribine is also being considered for expedited approval.

Three studies on the new oral compounds published in the February 4 issue of the *New England Journal of Medicine* (NEJM) suggest that fingolimod and cladribine are effective in reducing the relapse rates and the development of brain lesions. The trials also suggested that fingolimod may enter the brain and protect neural tissue.

However, some patients developed serious side effects—including skin and breast cancers and herpes infections—which are being studied in ongoing trials. Neurologists "will have to pay attention to these potential side effects," says Jeffrey A. Cohen, M.D., director of Experimental Therapeutics at the Mellen MS Center at

the Cleveland Clinic. Dr. Cohen was the principal investigator of the TRANSFORMS study, which tested fingolimod and was published in the Feb 4 NEJM.

Two of the three studies in the NEJM

tested fingolimod for the treatment of relapsing-remitting MS. These were all large multi-center trials. FREEDOMS1 was largely conducted in Europe and was designed to compare two doses of the oral medication to a placebo. The TRANSFORMS study compared fingolimod to injectable interferon. The third study, CLARITY, was carried out worldwide and compared cladribine to placebo.

All of the oral medicines showed a positive effect: reducing relapse rate at the end of one or two years (depending on the study design) and fewer lesions seen on repeated MRI scans.

### SAFETY PROBLEMS

The problem for moving towards approval of any of these medicines is safety. According to Dr. Cohen, the initial safety study of fingolimod (also published in the NEJM) followed 281 patients over six months. The main side effects were slowing of heart rate with the initial dose and mild elevations in liver enzymes. Those effects dissipated after the first dose. But an extension study that followed the group for almost six years found that while the benefit continued, several patients developed melanoma or basal cell carcinoma.

In the TRANSFORMS study, 1,292 patients were randomly assigned to interferon beta 1A or one of two doses of fingolimod for one year. There were significant reductions in relapse with both doses of fingolimod compared to interferon: a 52 percent reduction for the 0.5 milligram daily dose, and a 38 percent reduction for the 1.25 mil-

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ligram dose. The fingolimod also reduced lesion activity and slowed brain atrophy—hallmarks of disease progression.

However, there were two fatal herpes infections in those on the higher dose and eight

cases of skin cancers across the two doses. (Two patients in the interferon group and one patient on the placebo dose also were diagnosed with a skin cancer during the study.)

The FREEDOMS1 study, which was designed to deliver the treatment for two years to 1,272 patients, reported similar side effects as the TRANSFORMS study, such as slowing of heart rate. The researchers did not find an increase in skin cancers or herpes infections, which Dr. Cohen says is “reassuring.”

Fingolimod traps lymphocytes in the lymph nodes so that they don’t travel to the nervous system and trigger inflammation. Evidence from laboratory studies suggests that the drug enters the central nervous system to prevent damage and promote repair of cells. The other drug, cladribine, destroys B cells and T cells of the immune system and also has potent anti-inflammatory effects. Both experimental medicines were comparable in their ability to reduce relapse and brain lesions. Cladribine had similar side effects to fingolimod: herpes infections and cancers. Lymphocytopenia, an abnormally low level of white blood cells, can also be caused by cladribine.

“These safety issues will require further attention,” Dr. Cohen says. A third study of fingolimod, FREEDOMS2, will be completed in 2011. The drug is also now being studied in patients with primary progressive MS, which is characterized by a gradual but steady progression of disability. Currently there are no medicines that work for this type of MS.

### FIRST- OR SECOND-LINE THERAPY?

Neurologists are hopeful that an oral medication may soon be available, but it isn’t clear yet whether it will be a first- or second-line therapy.

“This is great news,” says Peter Calabresi, M.D., the lead investigator in the on-going FREEDOMS2 study. “We have to be cautious, however. There is a public perception that pills are safer than medicines that are injected. This may not be the case here. Until we know more about the safety profile, I don’t think we should put the majority of MS patients on this drug as a first-line therapy. If someone is doing well, I would not switch them because a pill is easier to take.”

“We are eager to see more safety data,” Dr. Calabresi adds. The 1.25 milligram dose, which had been taken by both patients who died during the TRANSFORMS study, is no longer being given to trial participants.

“The future looks bright for oral medicines,” says Douglas Jeffrey, M.D., Ph.D., director of the MS Clinic at Wake Forest University School of Medicine. “The only question is how much toxicity we will see. The first oral medicines may have no real advantages over the ones we already have.”

But Patricia O’Looney, M.D., vice president of biomedical research at the National MS Society, believes these new oral medicines will change the landscape of MS treatment. “These drugs will immediately provide patients with more choices,” she says. “It can be frustrating for people to inject themselves.”

Stony Brook’s Dr. Krupp agrees that patients hate taking shots. “They have to be in the right frame of mind,” she says. “They have to get it out of the refrigerator, let it warm down, clean the skin, then inject. It’s a ritual. We have all been waiting for an oral medicine that would provide the benefits that these injections and infusions do.”

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