Rare Demyelinating Disorder Tied to MS Drug

BY ELIZABETH MECHCATIE
Senior Writer

Prospects for the eventual return of the multiple sclerosis treatment natalizumab (Tysabri) became more uncertain when a second case of progressive multifocal leukoencephalopathy was confirmed in a patient who had been treated with the drug for more than 2 years, in combination with interferon beta-1a.

On Feb. 28, Elan Corporation and Biogen Idec announced that marketing of the monoclonal antibody, which had received U.S. Food and Drug Administration approval months earlier for relapsing forms of multiple sclerosis (MS), was being suspended because of one confirmed case of progressive multifocal leukoencephalopathy (PML) in a patient who had died and a second suspected case.

In early March, the companies announced that this second case had also been confirmed. The patient was a woman who, like the first patient, had been on the drug for over 2 years in combination with interferon beta-1a (Avonex), another Biogen product that was approved for MS in 1996.

One patient had been treated for 38 months, the other, 27 months. No cases of PML, a rare, usually fatal, progressive demyelinating central nervous system disease, have been reported in patients with MS who have used natalizumab as monotherapy, or in the Crohn's disease or rheumatoid arthritis trials. In addition, no cases of PML have been reported in patients who have been treated with interferon beta-1a monotherapy since its approval in 1996.

In March, the FDA suspended clinical trials of all MS drugs that are in the same class as natalizumab, as a precaution. One drug affected is 683699, an investigational agent developed by European drugmaker GlaxoSmithKline, which was in phase II trials at the time of the FDA action.

Since approval in late November, about 5,000 people have been treated with natalizumab, but most had received only a few doses since it is administered intravenously once every 4 weeks. About 3,000 patients had received natalizumab in clinical trials, largely for MS. The drug was also stopped in patients enrolled in smaller trials of rheumatoid arthritis and Crohn's disease.

In the companies' efforts to determine the association between natalizumab and PML, and to determine whether MS patients who may be at risk for developing PML can be identified, the two companies are working with a panel of PML experts, and are reviewing clinical information and MRI scans of all patients in clinical trials. These patients will also undergo physical exams, and will undergo MRIs to look for early signs of PML.

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The companies hope to find "a path back for this drug," Al Sandrock, M.D., vice president of medical research at Biogen Idec, said during a Webcast sponsored by the National MS Society in New York City after the suspension. He would not speculate on when or if it would become available again, but added that the companies recognize the benefits of the drug. Within days of learning about the two cases, the companies decided to suspend marketing, "to step back and assess the risk."

In a "dear health care professional" letter, the companies advised physicians to evaluate their patients who have taken natalizumab for signs of PML, and to report any suspected cases. Impaired cognition, cortical blindness, and hemiparesis are usually among the presenting symptoms, and characteristic lesions are usually present on MRI scans.

PML primarily affects those who are immunocompromised, with the vast majority of cases today seen in patients with AIDs or HIV. It is caused by the activation of a human polyomavirus, JC virus, which is latent in more than 80% of healthy adults, and can be similar in presentation to MS although the cause of demyelination differs.

The FDA approved natalizumab for reducing the frequency of exacerbations in people with relapsing forms of MS. The accelerated approval was based on the first year of efficacy and safety data from two ongoing international trials of over 2,000 patients, under the condition that the companies complete the second year of the trials.

During the first year of treatment, those on monotherapy had 66% fewer relapses than those on placebo, and in the second trial, those on the combination had 54% fewer relapses than those on interferon beta-1a alone. No major safety concerns were raised in these studies.

During the National MS Society Webcast, Aaron Miller, M.D., said that although PML and MS are both demyelinating diseases, the mechanisms of demyelination are different and PML is "not at all related to MS," he said. With PML, the virus destroys oligodendrocytes in the brain, which make myelin; but in most if not all cases of MS, an inflammatory process destroys myelin, said Dr. Miller, chief medical officer of the society and medical director of the Corinne Goldsmith Dickinson Center for MS, at Mt. Sinai Medical Center, New York.

Dr. Miller described the PML cases and subsequent suspension of the drug from marketing as "a great tragedy for the entire MS community. We certainly hope that after the dust has cleared, we will be able to find a way to safely bring this drug back to patients," he said, but added, "that remains to be seen." ■

The FDA's public health advisory regarding natalizumab can be found at www.fda.gov/cder/drug/advisory/natalizumab.htm. More information can be found on the Elan Web site at www.elan.com.

When It Comes to Sedation, Antiepileptics Not Created Equal

BY DAMIAN McNAMARA
Miami Bureau

MIAMI BEACH — Some antiepileptic drugs cause more sedation than do others, according to a study presented at the annual meeting of the American Academy of Neurology.

Sedation is a common side effect of antiepileptic drugs (AEDs). However, the relative prevalence of sedation associated with each AED is unknown, David B. Weintraub said.

Mr. Weintraub and his associates performed a head-to-head comparison of epilepsy drugs commonly used at the Columbia Comprehensive Epilepsy Center at New York–Presbyterian Hospital in New York City, where he is a research coordinator.

Researchers reviewed charts for 1,088 adult patients treated at the center since January 2001. They assessed the overall rate of sedation attributed to a particular AED and whether sedation led to drug discontinuation.

They also looked at subpopulations taking an AED as monotherapy and patients beginning a particular agent, or "new starts." In each comparison, the drug was compared with the average rate of sedation of all other agents using chi-square analysis.

Investigators reviewed the Columbia AED database for patients' background, medical history, and AED use, including AED efficacy and side effects.

In addition, the investigators recorded all physician or patient reports of sedation or sleepiness, tiredness, lethargy, drowsiness, or fatigue associated with an AED.

Overall, 34% of the participants experienced sedation from one or more AEDs. An average of 15% of patients starting a new AED experienced sedation. In almost 5% of participants, the sedation was cited as a reason the patient discontinued the drug.

Elan, GlaxoSmithKline, Pfizer, Ortho-McNeill, and UCB Pharma provide funding for the Columbia AED database. Mr. Weintraub has received financial support from UCB Pharma.

The incidence of both sedation and drug discontinuation were highest among patients taking phenobarbital (39% and 15%, respectively). Phenytoin had a higher than average incidence of sedation (32%), as did levetiracetam (20%), but discontinuation rates among patients taking these drugs were average.

"Phenytoin and levetiracetam were the only ones that reached statistical significance for increasing sedation," coauthor and presenter Lawrence J. Hirsch, M.D., said. (The 13 patients taking phenobarbital in the study were too few to reach statistical significance.)

Dr. Hirsch, of the department of neurology at Columbia University, has received personal compensation from Elan, GlaxoSmithKline, Ortho-McNeil, and UCB Pharma; he has also received financial support from these four companies as well as from Pfizer.

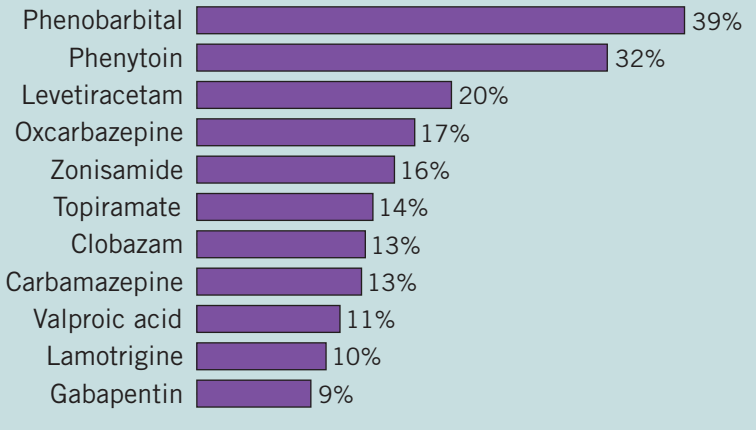
Intermediate rates of sedation were associated with oxcarbazepine (17%), zonisamide (16%), topiramate (14%), carbamazepine (13%), clobazam (13%), and valproic acid (11%).

The researchers found that lamotrigine (10%) and gabapentin (9%) had the lowest consistent sedating effects in the study.

The investigators also looked at the 254 patients taking an AED as monotherapy. The average rate of sedation was 21% in this subpopulation.

"These were smaller numbers," Dr. Hirsch said. "Nothing reached statistical significance here." ■

Percentage of Patients Newly Started on AEDs Who Experience Sedating Effects



Note: Data include patients on both mono- and polytherapy.
Source: Mr. Weintraub