

Tysabri Is Again Available—With Conditions

BY ELIZABETH MEHCATIE
Senior Writer

Tysabri, the monoclonal antibody withdrawn from the market in February last year after progressive multifocal leukoencephalopathy was diagnosed in three patients receiving the drug in clinical trials, will be made available again for patients with relapsing forms of multiple sclerosis, under a restricted distribution program.

The Food and Drug Administration announced in June that the agency had approved Biogen Idec's application for resuming the marketing of natalizumab (Tysabri), with the risk minimization plan, a detailed multistep program called the TOUCH prescribing program by Biogen Idec, the manufacturer of Tysabri.

The FDA now requires prescribing physicians, infusion centers (or physicians' offices that provide infusions) and pharmacies that provide Tysabri to enroll in a risk-minimization program.

The purpose of the detailed, multistep

program is "to ensure that physicians and patients are educated about the risks and the benefits of treatment with Tysabri and that only appropriate patients receive treatment," Dr. Russell Katz, director of the FDA's division of neurology products, said during a teleconference held by the FDA to announce the approval to reintroduce the drug.

The program is also designed to collect information about additional cases of progressive multifocal leukoencephalopathy (PML), and other serious infections "in real time so that we can as rapidly as possible understand both what the true rate of this infection is, but also possibly whether there are any other factors" that may increase a patient's risk of PML, he added.

Currently, it is not clear how to predict who will develop PML, how to prevent it, or how to treat it should it occur during treatment with Tysabri, other than to stop treatment as soon as possible, Dr. Katz said. The best estimate currently available is that the risk is about 1 per 1,000 patients treat-

ed for up to 2 years, which is based on clinical trial data on use of the drug in patients with multiple sclerosis or Crohn's disease. Little is known about the risk in a larger population or when treatment is continued for longer than 2 years, he noted.

Even with the program in place, other cases of PML are expected, including fatal cases, he said.

"This is balanced against the significant benefits that we believe the drug confers," Dr. Katz said.

The main elements of the program are that Tysabri can be prescribed, distributed, and infused only by physicians, infusion centers, and pharmacies enrolled in the program, a process that is designed to "minimize the risk of PML, minimize death and disability due to PML, and promote informed risk-benefit decisions" regarding the use of Tysabri, according to the FDA.

A baseline MRI must be obtained in patients before treatment is started to help distinguish multiple sclerosis symptoms that may appear in the future from PML, and

physicians are required to evaluate patients 3 and 6 months after the receiving the first infusion, followed by every 6 months; information from these evaluations needs to be sent to the company regularly.

Infusion centers need to inform the company each time a patient has an infusion.

Prescribing physicians are required to be able to diagnose and manage opportunistic infections and PML, or to be prepared to refer patients to an appropriate specialist.

Tysabri was approved in November 2004, and withdrawn by the manufacturer in February 2005; no new cases of PML were reported. The FDA allowed clinical trials to resume earlier this year. ■

More information on Tysabri, including the new label and a summary of the risk-minimization action plan, is available at www.fda.gov/cder/drug/infopage/natalizumab/default.htm. Information on the program can also be obtained by calling the company at 800-456-2255.

Cognition Impaired in 30% With ALS

BY MARY ANN MOON
Contributing Writer

Cognitive impairment was found in 30% of patients with amyotrophic lateral sclerosis in a study designed to assess the prevalence of cognitive involvement in what used to be considered a disease restricted to the motor system, according to Dr. Gregory A. Rippon and his associates.

In an editorial comment accompanying this report, Dr. Michael J. Strong of the University of Western Ontario, London, said that the 30% prevalence of dementia found in this study may actually underestimate the prevalence in the general population.

These subjects were evaluated "long before the institution of detailed tests of frontotemporal lobe dysfunction," which would likely have detected dementia in more of them. Moreover, subjects with a family history of neurodegenerative diseases were excluded from this study, which again may have led to an underrepresentation of dementia cases, he said.

Dr. Rippon agreed that estimates must be considered unreliable at best, since the studies from which they were derived were flawed by small sample sizes, selection bias, widely varying definitions of cognitive impairment, and very different methods for assessing cognition.

As ALS is increasingly recognized as a multisystem neurode-

generative disorder, researchers have revised their estimates of cognitive involvement from 2% up to as much as 52%.

In what Dr. Rippon and his associates at Columbia University College of Physicians and Surgeons, New York, described as one of the largest studies of the issue to date, the researchers assessed 40 consecutively treated patients with classic ALS seen in a 1-year period at the university's Neurological Institute. These patients, along with 80 control sub-

A small study of patients with classic amyotrophic lateral sclerosis found cognitive impairment in 30% of the patients and dementia in 23%.

jects matched for age, sex, and education level, underwent a battery of neuropsychologic tests that evaluated learning and memory, executive function, attention and psychomotor speed, language, and visuospatial ability.

Twelve of the ALS patients (30%) showed cognitive impairment, including 9 (23%) who met the criteria for dementia.

Free recall, executive function, and naming were the areas of most severe impairment, while language comprehension was preserved and attention, processing speed, and visuospatial function remained normal.

This pattern is consistent with frontotemporal lobar dementia, the investigators said (*Arch. Neurol.* 2006;63:345-52).

Among the ALS patients, there was no difference between those with and without dementia in terms of age, sex, education level, site of symptom onset, emotional lability, subjective memory loss, or family history.

This finding is contrary to that of other researchers who suggested that patients with bulbar-onset ALS are particularly susceptible to dementia, Dr. Rippon and his associates noted.

ALS symptom severity did not seem to affect test performance.

As a group, the ALS patients performed better than control subjects on most of the tasks tested.

Survival was the same in ALS patients with dementia as in those without dementia, but this study was underpowered to detect a survival difference of less than 3 years.

Previous studies have demonstrated a shorter survival time in ALS patients with frontotemporal dementia.

"Larger prospective studies with interval cognitive assessments would more fully address the possibility of differential survival," they added.

In his editorial, Dr. Strong noted that the study's findings may provoke controversy over the clinical relevance of cognitive impairment in most ALS patients (*Arch. Neurol.* 2006; 63:319-20).

Most cognitive impairment associated with ALS in the literature is "subtle," not a fulminant dementia. ■

History May Offer Clues in Neuropsychiatric Lupus

GLASGOW — When acute nonspecific symptoms might represent neuropsychiatric lupus, it is necessary to carefully review a patient's past medical history, because the presenting symptoms of systemic lupus erythematosus are manifold, may mimic other disorders, and can evolve over time, Dr. Hala Y. Sadik reported in a poster.

This is particularly the case when the onset is acute, as happened in a case treated by Dr. Sadik of the Academic Rheumatology Unit, University Hospital Aintree, Liverpool, England.

In August 2005, a 57-year-old woman presented with hypothermia, bradycardia, confusion, a low score on the Glasgow Coma Scale, and hyponatremia. The patient's plasma sodium level was low (120 mmol/L), as well as her plasma osmolality (235 mOsm/kg), while urinary sodium and osmolality levels were both high. A diagnosis of inappropriate antidiuretic hormone secretion was made, Dr. Sadik reported in a poster session at the annual meeting of the British Society for Rheumatology.

Initial management included fluid restriction and administration of double-strength normal saline, which normalized the plasma sodium level, reported Dr. Sadik. Initial MRI of the head raised the possibility of neurosarcoidosis, but serum angiotensin-converting en-

zyme levels and chest x-ray were normal. A repeat MRI with gadolinium suggested demyelinating disease or systemic lupus erythematosus. Immunology profile findings included positive antinuclear antibody (ANA) and double-stranded DNA antibody. Thrombocytopenia and lymphopenia also were present.

Upon review, her previous case records from another hospital revealed that she had been admitted in 1992 with a 2-week history of arthralgias, Raynaud's phenomenon, thrombocytopenia, lymphopenia, and positive ANA. A diagnosis of lupus had been considered at that time, and she was followed for several years as an outpatient, but ANA remained weakly positive and double-stranded DNA was persistently negative, so the diagnosis had been dismissed, Dr. Sadik wrote.

With improvements on the Glasgow Coma Scale during her current admission, it became apparent that the patient was profoundly depressed, so she was treated with mirtazapine.

After a diagnosis of neuropsychiatric lupus, the patient began treatment with intravenous methylprednisolone and cyclophosphamide. Significant improvements were seen in her disabling depression, and her hematologic parameters normalized.

—Nancy Walsh