

## JC Virus May Flag PML

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Natalizumab, a treatment for multiple sclerosis, was withdrawn from the market in February after it was linked to progressive multifocal leukoencephalopathy (PML).

The safety evaluation includes data on more than 2,000 MS patients who had received the drug either in clinical trials or after approval in 2004 had been completed, and no more cases of PML had been identified. The evaluation of the smaller number of patients in the Crohn's disease and rheumatoid arthritis trials, which had been halted once the drug was withdrawn, was almost finished.

A spokesperson for the FDA's Center for Drug Evaluation and Research in Rockville, Md., said that after the agency reviews the data submitted by the companies, the FDA will hold a public advisory committee meeting to seek "broader input and advice" from experts in the area and consumer and patient representatives.

Aaron Miller, M.D., medical director of the Corinne Goldsmith Dickinson Center for Multiple Sclerosis (MS), at Mount Sinai Medical Center, New York, said that from his perspective, "if the drug is allowed back on the market, then individual practitioners will have to weigh very carefully the risks and potential benefits for an individual patient."

Based on the currently available information, uncertainties about the risk will remain, so if natalizumab becomes available again, it will be imperative to be "extremely vigilant and closely observant" of patients who receive the drug, to clearly establish the risks, said Dr. Miller, who is also chief medical officer of the National MS Society in New York City. While current MS therapy is clearly an advance from what was available over a decade ago, there is "clearly tremendous room for improvement and better drugs," he noted.

Natalizumab, administered intravenously every 4 weeks, was approved in late 2004 for relapsing forms of MS, and was marketed as Tysabri by Biogen Idec and Elan. Approval was based on 1-year data in two 2-year trials, under the condition that the manufacturers complete the trials.

To date, the two cases of PML, a rare, usually fatal, progressive demyelinating central nervous system disease, have been confirmed in patients with multiple sclerosis, according to the companies. The fatal case had been confirmed when the drug was withdrawn in February, and a second suspected case was subsequently confirmed.

In March, the companies announced that a third case had been identified, in a patient in the open-label Crohn's disease trial, who

had been diagnosed with a malignant astrocytoma, but a reevaluation of the case confirmed that the diagnosis was PML. The patient, who died in 2003, had received eight courses of natalizumab over 18 months and had received multiple courses of immunosuppressive therapy in the past, but was not on interferon  $\beta$ -1a (Avonex), as were the two MS patients. Both patients had been on the drug for over 2 years, in combination with interferon  $\beta$ -1a (Avonex), in a trial evaluating combination therapy.

These three cases were described in detail in the July 28 issue of the *New England Journal of Medicine*, which included observations that PML may be preceded by JC virus viremia, and that PML was not necessarily life threatening.

This finding raises the possibility that natalizumab could be stopped in time to prevent PML from developing into a life-threatening illness if patients were appropriately monitored. PML is caused by the activation of JC virus, a human polyomavirus, which is latent in most healthy adults (*N. Eng. J. Med.* 2005;353:362-8).

In a response to the cases that appeared in the same issue, Biogen Idec officials wrote that it "is possible that testing for the appearance of JC virus in plasma, along with a high degree of clinical suspicion, will permit early diagnosis and discontinuation of natalizumab therapy and allow patients to recover." They noted that similar findings have been reported on a related polyomavirus that infects transplant recipients.

The FDA will have to make a decision based on the available efficacy information combined with the information now available on the three confirmed cases of PML in patients treated with natalizumab to date, said Dr. Miller.

In a statement released Aug. 9, Whaijen Soo, M.D., Ph.D., senior vice president for medical research at Biogen Idec, said that "given the high unmet need in MS and the therapeutic benefit we have seen with Tysabri, we are encouraged by these safety findings."

Alosetron, approved in 2000 for women with diarrhea-predominant irritable bowel syndrome, is an example of a drug that was withdrawn from the market for safety reasons but brought back with a risk management plan: Months after approval, it was voluntarily withdrawn because of cases of fatal ischemic colitis and severe complications of constipation associated with the drug. But it was reintroduced in 2002, with a narrower indication, a lower recommended starting dose, and a risk management program in place. ■

## TNF Blockade May Trigger CNS Demyelination in Some

BY BRUCE K. DIXON  
Chicago Bureau

CLEVELAND — Tumor necrosis factor- $\alpha$  blockade should not be instituted in patients with known multiple sclerosis and should be used with caution in patients with family histories or other risk factors for MS, according to Jeffrey A. Cohen, M.D., a neurologist at the Cleveland Clinic, Ohio.

Physicians should also be alert to uncommon CNS manifestations in patients receiving tumor necrosis factor (TNF) blockade for their inflammatory diseases, he said at a meeting on the treatment of autoimmune and inflammatory disorders.

TNF inhibitors currently approved by the Food and Drug Administration include the monoclonal antibodies infliximab (Remicade) and adalimumab (Humira) and the fusion protein etanercept (Enbrel).

TNF blockade both prevents and abrogates demyelinating disease in vitro and in animal studies. In humans, TNF blockade actually increased MS activity, said Dr. Cohen, citing data from two studies of infliximab and the discontinued lenercept. "In addition, treatment of other diseases for which TNF inhibitors are highly effective, including rheumatoid arthritis, Crohn's disease, and psoriasis, on rare occasions leads to CNS inflammatory demyelinating syndromes," Dr. Cohen said at a summit sponsored by the Cleveland Clinic.



Failure of anti-TNF therapy in MS may be due to pleiotropic aspects of TNF actions, he noted. "In the CNS, TNF mediates cellular apoptosis and tissue damage, has important immunoregulatory functions, and is involved in tissue repair and regeneration. This experience reminds us that in the development of novel therapeutics, one must be cautious in extrapolating from animal models to human disease and from the results in one human disease to another," he said. CNS demyelination can occur anytime after an

**TNF blockade increases MS activity in humans but prevents demyelination in animals.**

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anti-TNF agent is started. Demyelination appears to be a class effect of all TNF antagonists.

Dr. Cohen recommends avoiding TNF blockade for patients with or at risk for MS. Withhold TNF inhibitor infusions from patients who have had a previous clinically isolated CNS syndrome and have cranial MRIs that look suggestive of MS but do not yet have clinical manifestations, advised Dr. Cohen.

Dr. Cohen, a neurologist, advised against looking for MS in every patient prior to starting a TNF inhibitor for treatment of inflammatory bowel disease, rheumatoid arthritis, or psoriasis. "In particular, I would not obtain an MRI unless there was some clinical suggestion of potential (for MS)." However, uveitis is a different story: "Uveitis is a manifestation that can occur in MS, so I would look very carefully for any indication of MS involvement" before beginning TNF blockade. ■

## Demyelinating Polyneuropathy May Be Triggered by TNF Blockade Therapy

BY BRUCE K. DIXON  
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CLEVELAND — Treatment with a tumor necrosis factor- $\alpha$  inhibitor may trigger a demyelinating polyneuropathy with Guillain-Barré-like symptoms, according to MaryAnn Mays, M.D., of the Cleveland Clinic Foundation.

The case in point, presented in a poster at a symposium on the treatment of autoimmune and inflammatory disorders sponsored by the clinic, was that of a 56-year-old man with seropositive rheumatoid arthritis who became severely disabled after infliximab infusions were added to his methotrexate therapy.

Dr. Mays, a neurologist, said in an interview that following his first anti-TNF treatment in 2002, the patient's rheumatoid arthritis symptoms lessened dramatically, but following an infusion in late 2003, he had dizziness and hearing loss for a week. The symptoms recurred and lasted longer following a third infusion 2 months later.

The next infliximab infusion in April 2004 produced worsening neurologic symptoms, including blurred vision, headaches, dysarthria, hearing loss, ataxia, dysphagia requiring percutaneous endoscopic gastrostomy for nutrition, and progressive weakness, according to Dr. Mays.

"Initial evaluation included cerebrospinal fluid WBC of 123, protein 79, and electromyograph consistent with demyelinating polyneuropathy.

But the overall pattern was not typical of Guillain-Barré syndrome [GBS]," Dr. Mays said. "He had high white count and normal protein. Auditory evoked potentials showed a right central conduction disturbance. His detrusor urinae muscle were unresponsive, which is typical of GBS. His right Babinski sign was atypical of GBS."

Feyrouz Al-Ashkar, M.D., the lead investigator and a rheumatologist, noted in an interview that by the time the patient was brought to the clinic, he "could not walk, use his hands, lift his head, or feed himself, although he could still breathe on his own."

"He received intravenous immunoglobulin [IVIg] and steroids before we saw him. When he got here, he again received intravenous steroids and another course of intravenous immunoglobulin, and slowly but surely, he recovered completely," Dr. Al-Ashkar said.

Dr. Mays noted that the patient's response to IVIg supports the diagnosis of a demyelinating polyneuropathy other than GBS."

Dr. Al-Ashkar said that the onset of neurologic deficits or demyelinating diseases in patients on infliximab is a red flag to stop TNF blockade. "In such cases, our experience would suggest that there is potential for worsening of neurologic deficits with each infliximab treatment, and that continuing treatments after onset of neurologic symptoms would be relatively contraindicated," according to the poster. ■