JC Virus May Flag PML

Natalizumab, a treatment for multiple sclerosis, was withdrawn from the market in February after it was linked to progressive multifocal leukoencephalopathy (PML).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 before 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number of patients in the Crohn’s disease and rheumatoid arthritis trials, which had been halted once the drug was withdrawn, was almost finished.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 “broad input and advice” from experts in the consumer and patient representatives.

Aaron Miller, M.D., medical director of the Corinne Goldsmith Dickinson Center for Multiple Sclerosis (MS) at Montefiore Medical Center, New York, said that from his perspective, “if the drug is allowed back on the market, it will have to be monitored closely and patients 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 improvement 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 that is latent in most healthy adults (N. Eng. J. Med. 2005;353:352-358).

In a response to the cases that appeared to have some common findings, 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, Whaien S. Oso, 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.”

Aloseteron, 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 lacrimal, salivary and sebaceous gland swelling and death reported to the FDA during clinical trials.

“Initial evaluation included cerebral spinal fluid WBC of 123, protein 79, and electromyograph consistent with demyelinating polyneuropathy. But the overall pattern was not typical of Guillaumin-Barré syndrome (GBS).”

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 interferon therapy is associated with drug resistance, which means 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. "Clinical demyelination can occur anytime after an 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 progressive MS. "MS patients who take TNF inhibitors are at risk for PML. " Wevusit is different story: "Wevusit is a manifestation that can occur in MS, so I would look very carefully for any indication of MS involvement before beginning TNF blockade."