Risk Plan Gearing Up

Natalizumab *from page 1*

were halted when two cases of progressive multifocal leukoencephalopathy (PML) were reported; its link to a third PML case was confirmed shortly thereafter. The removal of natalizumab from the market and clinical trials of its safety and efficacy in the treatment of rheumatoid arthritis and Crohn's disease came only 3 months after its approval for management of relapsing MS. Its approval in November 2004 was remarkable for having been the first time the FDA had ever approved a drug based on data from clinical trials that were only halfway completed.

The stringent risk management plan is expected to include mandatory enrollment of physicians and patients in a registry, and a monthly pre-infusion checklist with questions designed to pick up any neurologic symptoms that could be signs of PML.

Natalizumab's approval in November 2004 was the first time the FDA had given the nod to a drug based on data from uncompleted clinical trials.

Immunosuppression, such as occurs in transplant recipients or other patients with compromised immune systems, is associated with activation of the usually latent human polyomavirus—JC virus—that can cause PML.

Panel members unanimously agreed that natalizumab should become available again—considering the currently available safety data—and that its use should be limited to patients with relapsing features of the disease, and only as monotherapy. The FDA usually follows the advice of its advisory panels.

Administered in a monthly infusion, natalizumab—a selective adhesion-molecule inhibitor—is thought to work by inhibiting the migration of leukocytes to sites of inflammation within the CNS. At the time the first cases of PML were reported, the degree of risk was uncertain. More than 3,000 patients who had been exposed to a mean of 18 monthly doses of natalizumab underwent evaluations, which included MRIs and testing of CSF for JC virus DNA. No new cases of PML were found, and the risk of PML was estimated at 1 in 1,000.

But whether the risk changes after 3 years of treatment is not clear; this uncertainty will be addressed in the mandatory registry of all patients and prescribing physicians, which is aimed at determining the incidence and risk factors for PML and other serious opportunistic infections.

During a press conference held at the meeting, Dr. Russell Katz, director of the FDA's neuropharmacological drug products division, pointed out that very little is known about the risk of PML after 3 years of treatment. The hope is that by enrolling patients in the risk management program, "we'd quickly learn if [the risk] increases after 3 years."

Currently, there is no solid evidence that detecting PML early will affect outcome, although there are good reasons to detect it early, he added.

"We believe clinical vigilance by the neurologist is the most important means of screening," and that monthly interactions between the health care provider and patients before infusions will enhance this vigilance, Dr. Michael Panzara, vice-president of neurology at Biogen Idec, told the panel. He said that the three patients with PML had clinical signs early in the course that had been noticeable to them, or to family members or their clinicians, but that the symptoms had been attributed to MS.

Under the terms of the proposed registry, enrolled physicians will be required to report any PML case to Biogen Idec immediately, and physicians will be queried every 6 months by the company about any patient deaths, discontinuations of treatment, or PML cases. If physicians do not comply, their enrollment in the program and access to natalizumab will be discontinued. Other elements of the risk minimization plan include mandatory registration of infusion centers and physician offices where infusions are administered; a controlled centralized distribution system, which would ship Tysabri vials only to the registered and compliant infusion centers and physicians; and a mandatory patient-physician informed consent form.

Under the risk minimization plan, any clinical change in a treated patient "will be viewed as PML until proven otherwise," and will result in stopping treatment and a full evaluation, Dr. Panzara said. However, whether early identification can affect the course of PML is unclear. There is some evidence from the HIV population and transplant patients that suggests that early recognition and discontinuation of immunosuppressive therapies can improve survival, he said.

Despite some initial optimism that plasma JC viral DNA levels would be useful in detecting PML early, its sensitivity and positive predictive values are uncertain, and while CSF testing for JC virus is specific at the time of diagnosis, the literature indicates that it tends to be negative in early disease and it is invasive; so it is not considered to be a good screening tool, he explained.

The company will also conduct an 5-years observational cohort study of a 5,000 MS patients in the registry. ■

CV Risks Unchanged by Infliximab Therapy

BY JONATHAN GARDNER
Contributing Writer

Infliximab therapy for rheumatoid arthritis improves patients' levels of high-density lipoprotein but does not make them any less vulnerable to cardiovascular disease because it also raises their levels of low-density lipoprotein, according to a new study.

Infliximab therapy had the effect of increasing serum levels of total cholesterol and both HDL and LDL cholesterol, correlating with a decrease of joint inflammation.

But infliximab does not reduce the risk of cardiovascular disease, the most common cause of premature death in rheumatoid arthritis patients.

Researchers at Cochin Hospital in Paris analyzed the cholesterol levels of 56 consecutive rheumatoid arthritis patients undergoing infliximab therapy. The researchers compared their cholesterol levels with those of a group of 56 rheumatoid arthritis patients not receiving infused infliximab and a control population of 56 without rheumatoid arthritis.

The researchers found that because the infliximab therapy did not change the ratio of HDL to LDL or total cholesterol, the cardiovascular risk did not change for the infliximab therapy patients (Clin. Chim. Acta. 2006;365:143-8).

At baseline, both of the rheumatoid arthritis groups had significantly higher atherogenic profiles than the control group, both in their ratio of LDL to HDL and HDL to total cholesterol. They also had significantly higher HDL levels.

After treatment at baseline, 2 weeks, 6 weeks, and every 8 weeks thereafter, total cholesterol levels in the study group increased from 5 mmol/L at baseline to 5.9 mmol/L at 6 weeks and 6 mmol/L at 30 weeks.

The mean ratio of LDL to HDL did not change significantly, however—2.6 at baseline, 2.7 at 6 weeks, and 2.5 at 30 weeks.

The mean ratio of total cholesterol to HDL did not change, either: 4.3 at baseline, 4.8 at 6 weeks, and 4.4 at 30 weeks.

The results are a departure from those from classic disease-modifying antirheumatic drugs, which have been shown to lower patients' atherogenic profiles, coauthor Dr. Didier Borderie said in an interview.

The study results show that "physicians have to be attentive to the lipid profile of their patients and to evaluate the atherogenic ratio of their patients before and regularly during infliximab therapy," according to Dr. Borderie, of Cochin Hospital. ■

Any Extraarticular Disease in RA Ups Risk for Early Death

BY TIMOTHY F. KIRN
Sacramento Bureau

Snowmass, Colo. — Extraarticular disease occurs in almost half of all rheumatoid arthritis patients, and greatly increases the risk of premature mortality, Dr. Eric L. Matteson reported at a symposium sponsored by the American College of Rheumatology.

In a review of 609 incident cases of rheumatoid arthritis occurring in Rochester between 1955 and 1995 and followed through 2000, Dr. Matteson of the Mayo Clinic, Rochester, Minn., and his colleagues found that 46% of patients with rheumatoid arthritis developed some extraarticular disease.

The most common extraarticular manifestations in patients included subcutaneous nodules (34%), Sjögren's syndrome (11%), pulmonary fibrosis (7%), pericarditis (5%), and pleuritis (5%). The least common—occurring in 1% or fewer of patients—included neuropathy, xerostomia, and amyloidosis.

A woman with RA and vasculitis, pericarditis, pleuritis, or pulmonary fibrosis would likely have a life span that was 13-15 years shorter than a healthy peer's.

Their review also found that the likelihood of premature mortality was greatly increased by extraarticular disease; for example, a female rheumatoid arthritis patient aged 50 years with vasculitis, pericarditis, pleuritis, or pulmonary fibrosis had a life expectancy that was 13-15 years shorter than that of a healthy peer. Male patients with the same manifestations were found to have a life expectancy 15 years shorter than that of healthy peers.

When Dr. Matteson and his colleagues plotted the survival curve of the patients against that of the general Rochester population, there was a significant difference in survival. But when they took out the patients with extraarticular disease and compared only patients with rheumatoid arthritis without extraarticular disease, there was no difference. "The impact is profound," he said.

Analysis of data showed that the relevant factors most associated with extraarticular disease in patients were antinuclear antibody positivity, male gender, and smoking.

Extraarticular disease was reported by 60% of the rheumatoid arthritis patients who reported having ever smoked. The association has been noted before in other investigations, and some of that evidence suggests that smoking actually drives the disease process, he said.

Rates of extraarticular disease may be different now in the era of biologic treatment, Dr. Matteson allowed. However, during the time of this review, there was no improvement in the incidence rate of extraarticular disease. ■

Family Health History Tracking Tool Available

The U.S. Surgeon General and the U.S. Department of Health and Human Services have launched an initiative to encourage families to learn more about their family health history. The initiative features a Web-enabled tool to help users organize family medical information and present this information to family physicians. The tool can be accessed at https://familyhistory.hhs.gov.