Natalizumab Succeeds in Post-Marketing Trial

VITALS

Major Finding: "Real-world" multiple sclerosis patients treated with natalizumab had rates of adverse events and reduction in relapses similar to those observed in patients in phase III trials.

Data Source: Ongoing postmarketing observational study of 1,011 patients.

Disclosures: Study funded by Biogen Idec Inc.; Dr. Trojano, consulting or speaking fees from Biogen Idec and research funding from Merck Serono.

BY MICHELE G. SULLIVAN

BANGKOK, THAILAND — The effects and adverse event profile of natalizumab in multiple sclerosis patients seen in highly controlled phase III trials continue to be observed in patients who are participating in an ongoing, postmarketing observational trial of the drug.

The Tysabri Observational Program (TOP) is an ongoing evaluation of the drug's effect in 1,011 patients, whose baseline characteristics were quite different from those of patients included in the AFFIRM (Natalizumab Safety and Efficacy in Relapsing Remitting Multiple Sclerosis) trials, on which the drug's approval was based, said Dr. Maria Trojano, who presented the results at the World Congress of Neurology.

The AFFIRM trial lasted 2 years, and showed a 68% reduction in the relapse rate among all patients, as well as a 42% reduction in sustained EDSS progression. Natalizumab (Tysabri) was also effective in patients with highly active disease, reducing the annual relapse rate by 81%, and the EDSS progression rate by 53%. Safety was good, with a 4% rate of adverse events, 1% of which were considered serious.

The TOP study (www.clinicaltrials.gov/ct2/show/NCT00493298) began in June 2007 and is slated to finish in 2015, for a full 8 years of observation. It was designed to examine natalizumab's effects in a "real-world" setting, Dr. Trojano said. Now that the drug is commercially available, the group of patients using it will vary much more widely at baseline than those included in the more narrow confines of AFFIRM's patient selection criteria, she said.

The question TOP must answer, Dr. Trojano said, is: "Does natalizumab in real life produce a similar highly reducing effect on disease activity and progression, while keeping the same safety?"

At baseline, TOP's cohort was significantly older than those in AFFIRM (38 vs. 36 years), with a longer mean duration of disease (7.5 vs. 5 years), and a worse mean score on the Expanded Disability Status Scale (EDSS; 3.7 vs. 2.3). TOP patients also had a higher annual relapse rate than did AFFIRM patients (2.03 vs. 1.53), noted Dr. Trojano of the University of Bari, Italy.

As of July 2009, patients in TOP had taken a mean of 7 doses of natalizumab, giving a base of 556 person-years to evaluate.

Natalizumab was associated with a steep decline in annualized relapse rate, dropping from a mean of 2 to less than 0.5 in the first month of therapy. Throughout the next 12 months, the mean relapse rate stayed below 0.5. This pattern mirrors that seen in the AFFIRM trial, which found relapse rates below 0.5 throughout its 24-month follow-up period.

The 292 TOP patients who have completed a full 12 months of follow-up have remained clinically stable, with an EDSS score of 3.6, compared with 3.8 at baseline.

As of July 14, there had been 46 serious adverse events reported in TOP patients (4.3%). Those included 10 infections (including 4 cases of herpes zoster and 2 pneumonias); 9 hypersensitivity reactions; 19 "miscellaneous" events; and 8 events that were not yet coded.

However, Dr. Trojano said, since TOP lacked a randomized control group, an independent 5-year study will create an external patient cohort to be used for a comparison to TOP patients.

The Multiple Sclerosis Comparator Study of Efficacy of Treatment (MSCOMET) trial will provide more reliable information about the effectiveness of natalizumab.

MSCOMET will prospectively assesses clinical effectiveness of interferon-beta or glatiramer acetate in a cohort of patients with relapsing-remitting MS.

Patients will be recruited from some centers participating in the International MSBase Registry in Melbourne, Australia. The external cohort will be selected in the MSBase Registry by a propensity score-matching technique. ■

Potential Methods for PML Surveillance Programs Outlined

BY JEFF EVANS

BALTIMORE — Surveillance programs for progressive multifocal leukoencephalopathy have many hurdles to clear before any become a reality in federal agencies or state health departments, despite concern over new cases that are associated with the use of monoclonal antibody therapies.

Dr. James J. Sejvar of the Centers for Disease Control and Prevention said that in addition to a lack of funding, attempts to conduct surveillance for progressive multifocal leukoencephalopathy (PML) are hampered by a lack of clear diagnostic criteria, a definition for a confirmed case, and case validation methods.

Dr. Sejvar, a neurologist and epidemiologist with the division of viral and rickettsial diseases at the CDC's National Center for Zoonotic, Vector-Borne, and Enteric Disease, described potential benefits and limitations of various approaches to PML surveillance at the annual meeting of the American Neurological Association.

Reports thus far have estimated that PML occurs in 1 of every 1,000 patients exposed to natalizumab (Tysabri), 1 of every 500 exposed to efalizumab (which has been taken off the U.S. market), and at an unknown, but probably lower, rate in patients exposed to rituximab (Rituxan).

National surveillance for PML could be conducted by making it a nationally notifiable infectious disease, establishing a national registry, or by gathering information from physicians, states, or laboratories.

A mechanism for surveillance still would need to have the capacity to determine a case definition of PML, which samples of patient data should be analyzed, the level of diagnostic certainty necessary for prompt reporting/confirming of cases, who should analyze patients' samples and data, and how it would be funded, Dr. Sejvar said.

NNIDs Designation

The CDC could add PML to the list of nationally notifiable infectious diseases (NNIDs), which are normally restricted to diseases with significant risk to public health. Although a rough infrastructure is already in place to add PML, and the condition would gain greater attention from physicians if it were added to the list, Dr. Sejvar said that "making it reportable doesn't mean it will be reported."

Diagnosing PML is difficult in part because of inaccurate reporting of cases, which points to the need for methods for validating cases. PML is probably also underascertained in clinics, he said, noting that no simple laboratory test for it is available.

One option would be for PML to be tracked in a national registry, which would 'allow for the collection of detailed clinical information.'

Dr. Sejvar said state governments are unlikely to view PML as a public health imperative that is worthy of the investments that would have to be made to conduct surveillance.

National Registry for PML

Another option would be for PML to be tracked in a national registry by the Agency for Toxic Substances and Diseases Registry (ATSDR). The congressionally mandated national amyotrophic lateral sclerosis registry that was recently developed with the ATSDR could serve as a template, Dr. Sejvar said.

"This would provide for an infrastructure to start to get a handle on PML and also allow for the collection of detailed clinical information."

The registry would rely on self-reports by patients and entries from physicians, and would need funding and endorsement from various stakeholders, he said. Congress would have to be actively lobbied for a national PML registry.

Active, Physician-Based Surveillance

Surveillance for PML under the CDC's Emerging Infections Program, a network formed by the CDC and 10 state health departments covering 44 million people, would provide a relatively accurate estimation of incidence and prevalence. The EIP contains sites with many tertiary neurologic care institutes where patients with PML would be best diagnosed, Dr. Sejvar noted.

The proactive outreach approach of the EIP would provide direct contact with the neurologic community, but it is limited by the resources of its partners. Adding PML surveillance would require endorsement by principal investigators at all EIP sites, who are unlikely to view PML as important enough to add.

State-Based Surveillance

State-based surveillance by the CDC or ATSDR, performed in cooperation with the Council of State and Territorial Epidemiologists (CSTE), "may be one of the best options," Dr. Sejvar said.

The CSTE is already involved in surveillance for Creutzfeldt-Jakob disease, another rare neurologic disorder that is difficult to diagnose. If PML surveillance was performed with CSTE, state surveillance officers would identify and report cases to the CDC. The CSTE would need to receive a proposal to add PML to its surveillance list and then endorse it.

There is also potential for collaborating with the National Prion Disease Pathology Surveillance Center to confirm cases pathologically, Dr. Sejvar said.

Laboratory-Based Surveillance

A system of laboratory-based surveillance is already used for other infectious diseases, particularly ones that can be readily identified in the lab and then reported to state health departments and the CDC. If a lab-based system was assembled, investigators could collect data rapidly from the relatively few labs that perform JC virus polymerase chain reaction assays, requiring minimal resources, Dr. Sejvar said.

However, lab-based surveillance would produce many false-negative results. Clinical data, which would be hard to obtain, would be necessary to interpret the lab data. ■