Natalizumab's Future: Down but Not Out for MS?

BY CHRISTINE KILGORE
Contributing Writer

Soon-to-be published reports describing three patients who developed a progressive, demyelinating brain disorder during treatment with natalizumab have some experts wondering whether the drug—now under voluntary suspension from the market—might safely be given to multiple sclerosis patients if they are carefully monitored.

"Compared with what I knew before, I'm more optimistic," said John Richert, M.D., who heads research and clinical programs for the National Multiple Sclerosis Society. "We still need to hear more …, but I think there's a reasonable likelihood that the drug will be brought back."

He and others point mainly to two observations detailed in the reports—that progressive multifocal leukoencephalopathy (PML), caused by activation of the human polyomavirus JC virus, may be preceded by JC virus viremia, and that the disorder is not necessarily life-threatening—in explaining their new but guarded optimism. It might be possible to discontinue the drug in patients in time to prevent PML from developing into a life-threatening illness.

The reports, to be published in the July 28 issue of the New England Journal of Medicine, detail the clinical course of three patients who participated in clinical trials of the monoclonal antibody natalizumab (Tysabri) for MS, Crohn's disease, and rheumatoid arthritis.

Two of the patients had MS and developed PML after having taken natalizumab for over 2 years in combination with interferon β-1a. Their cases were the impetus for the drug makers' suspension earlier this year of all dosing and marketing of the drug (see CLINICAL NEUROLOGY NEWS, April 2005, p. 5).

The third patient had Crohn's disease and took the drug—which received accelerated approval from the FDA in late 2004 for the treatment of immune-mediated disorders, including MS—for a much shorter duration. He was found to have had PML after the MS cases prompted investigators to reevaluate a presumed malignant astrocytoma.

The New England Journal of Medicine, which had published some of the original studies on the efficacy of the drug, lifted its embargo early and posted the reports—as well as two editorials and correspondence from one manufacturer—on the its Web site last month after the Boston Globe reported that the FDA was investigating a possible case of PML in a fourth patient who received natalizumab. (A press report of a fifth case of suspected PML being reported to the FDA was published since then. At press time, the FDA said only that there were "no additional confirmed cases.")

In the case of the Crohn's disease patient, who had previously received other immunomodulatory agents with no reactivation of JC virus infection, retrospective analysis of serum samples showed that JC virus became detectable after only three injections of natalizumab monotherapy and 2 months before the appearance of symptomatic PML, which led to the patient's death.

Within those 2 months, the serum viral load increased by a factor of 12, Gert Van Assche, M.D., and associates at the University of Leuven (Belgium) Hospitals (NEJM [Epub ahead of print], June 9, 2005. Article DOI number:10.1056/NEJMoa051586. Available from www.nejm.org).

Biogen Idec is reviewing suspicious or ambiguous findings to evaluate them for PML, according to its letter in the New England Journal of Medicine.

Before recovering partially, one patient's condition worsened after the cessation of natalizumab therapy—despite treatment with corticosteroids, cidofovir, and intravenous immune globulin—but eventually improved (not completely, but significantly) 2 months after initiation of systemic therapy with cytarabine, which penetrates the CNS poorly.

It is possible, however, "that the extensive breakdown of his blood-brain barrier improved penetration of cytarabine into the CNS," wrote Annette Langer-Gould, M.D., of Stanford (Calif.) University, and her colleagues (NEJM [Epub ahead of print], June 9, 2005. Article DOI number:10.1056/NEJMoa051847. Available from www.nejm.org).

Such findings, Dr. Richert said, give him hope that it may be possible to fashion preventive strategies against development of PML in patients wanting to take natalizumab or similar drugs in the future. And in an editorial, Joseph R. Berger, M.D., of the University of Kentucky, Lexington, and Igor J. Koralnik, M.D., of Harvard Medical School, Boston, expressed similar optimism.

"The prospective measurement of the JC viral load in plasma and the preemptive reduction of doses or interruption of treatment if JC virus DNA appears in the blood might actually prevent the development of PML in this setting," they wrote (NEJM [Epub ahead of print], June 9, 2005. Article DOI number:10.1056/NEJMe058122. Available from www.nejm.org).

Dr. Langer-Gould and her colleagues also note in their report that "more frequent MRI monitoring of patients who receive natalizumab may be warranted."

Kenneth L. Tyler, M.D., an author on the second MS case report, cautioned that "it's exceedingly dangerous to prognosticate on the future with such a small subset (of patients." Still, he told this newspaper, he is left with the questions, "is viremia a useful warning sign? And if you discontinue the medicine, will [development of PML] subside?"

The case of the Crohn's patient, Dr. Tyler noted, is significant because it indicates "that neither concurrent use of Avonex [interferon β-1a] or underlying neurologic disease like MS is necessary" for the development of PML in patients taking Tysabri.

All agree that while the new reports clarify the association between treatment with natalizumab and the occurrence of PML, questions about the magnitude of risk need to be answered before the drug can be brought back to the market.

"There's a big interest in bringing [Tysabri] back, but the viability of the drug will depend on our ability to predict risk of PML and know how great a risk PML is for MS patients," said Michael Kaufman, M.D., director of the MS Center at Carolinas Health Care in Charlotte, N.C., and an investigator in one of the Tysabri trials.

"Two cases out of hundreds with MS … could be the tip of the iceberg, or it could be the only two who were susceptible to it," he said.

Despite her patient's partial recovery, Dr. Langer-Gould told this newspaper she fears that if the drug were prescribed for longer periods of time, "it would be highly likely we would see many more cases of PML resulting in death or significant life-long disability as well as other toxicities."

According to a short "correspondence" written by leaders at the Cambridge, Mass.–based Biogen Idec Inc., a panel established by the company is currently reviewing all suspicious and ambiguous findings to evaluate them for PML (NEJM [Epub ahead of print], June 9, 2005. Article DOI:10.1056/NEJMc055235. Available from www.nejm.com).

A spokesman for Biogen Idec and Elan Corp. told CLINICAL NEUROLOGY NEWS that once they have a better understanding of the risks of PML—perhaps later this summer—the companies will share their findings with the FDA and European regulatory agencies, and "together, the compan[ies] and agencies will make a decision about how to proceed with the drug."

In the NEJM reports, Dr. Langer-Gould, Dr. Berger, and Dr. Koralnik each report having received consulting and/or lecture fees from Biogen Idec. ■

IFN-β Products Seem Equivalent as Initial Treatment for MS

BY MICHELE G. SULLIVAN
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MIAMI BEACH — Four different interferon-β products and dosing schedules appear equally effective as initial therapy for relapsing/remitting multiple sclerosis, Volker Limmroth, M.D., reported in a poster session at the annual meeting of the American Academy of Neurology.

However, all IFN-β products were significantly less effective when used as follow-up therapy, said Dr. Limmroth, of the University of Essen (Germany), and his colleagues.

"These results suggest that patients do not gain further benefit when switching from one IFN-β product to another," according to Dr. Limmroth.

Dr. Limmroth presented the results of the global Quality Assessment in Multiple Sclerosis Therapy (QUASIMS) study which examined long-term outcomes in more than 7,000 patients from 11 countries who took different IFN-β products and dosing regimens. The study broke results down among those who took IFN-β as initial therapy and those who took it as follow-up therapy.

The patients' mean age was 36 years; about 70% were female. Their mean disease duration was about 5 years. Their mean treatment duration was about 40 months and mean Expanded Disability Status Scale (EDSS) was 2.4-2.9.

The therapies examined were intramuscular IFN-β–1a, 30 mcg once weekly; subcutaneous IFN-β–1b, 8 mIU every other day; subcutaneous IFN-β–1a, 22 mcg three times weekly; and subcutaneous IFN-β–1a, 44 mcg three times weekly. Patients had to have been on at least 2 years' uninterrupted therapy (either initial or follow-up). Overall, there were no significant differences on EDSS between the therapies at 1 or 2 years' follow-up. Some differences emerged, however, when the drugs were stratified as either initial or follow-up therapy.

All drugs were more effective as initial therapy than as follow-up therapy. Intramuscular IFN-β–1a resulted in the highest percentage of progression-free patients at 2 years (66%). For the other therapies, the percentage of progression-free patients was 62.2% for subcutaneous IFN-β–1a 44 mcg; 61% for subcutaneous IFN-β–1a 22 mcg; and 52.7% for IFN-β–1b.

Intramuscular IFN-β–1a also resulted in the highest percentage of relapse-free patients over 2 years (50.2%). The percentages for the other therapies were 42% for IFN-β–1b; 37% for subcutaneous IFN-β–1a 22 mcg; and 33.8% for subcutaneous IFN-β–1a 44 mcg.

There were no significant differences in the drugs' effectiveness when they were used as follow-up therapy.

The percentage of progression-free patients ranged from 51.7% for IFN-β–1b to 62% for subcutaneous IFN-β–1a 44 mcg. The percentage of relapse-free patients over 2 years ranged from 33.8% for subcutaneous IFN-β–1a 44 mcg to 42% for IFN-β–1b.

During the study, 18% (1,309 patients) changed therapy. The most frequent reason was perceived lack of efficacy. Switch rates were intramuscular IFN-β–1a, 45%; IFN-β–1b, 31%; subcutaneous IFN-β–1a 22 mcg, 38%; subcutaneous IFN-β–1a 44 mcg, 40%.

Dr. Limmroth is a paid investigator for Biogen Idec Inc. which sponsored the study. ■