

Rituximab and Progressive Multifocal Leukoencephalopathy

Introduction

On December 19, 2006, the United States Food and Drug Administration issued an ‘Alert’ (<http://www.fda.gov/medwatch/safety/2006/safety06.htm#rituxan>) regarding safety issues related to the use of rituximab in patients with rheumatologic disease. On the same day, the manufacturer of rituximab, Genentech, also issued a “Dear Healthcare Professional” letter (http://www.gene.com/gene/products/information/pdf/rituxan_DHCP_Letter.pdf). These were based on two spontaneous reports of fatal progressive multifocal leukoencephalopathy (PML) in patients with systemic lupus erythematosus who had received rituximab therapy.

PML, a rare, generally fatal demyelinating disease of the central nervous system is caused by reactivation of JC polyoma virus infection. Exposure to JC virus is endemic, with approximately 80% of healthy adults harboring latent infection. However, PML is rare (approximately 1 in 200,000 persons), and is almost always seen among profoundly immunocompromised individuals, for example AIDS patients and allograft recipients receiving strong immunosuppressive agents.

PML received wide recognition in 2005 following reports of 3 cases of PML among approximately 1,000 patients with multiple sclerosis or Crohn’s disease who had received therapy with the anti-VLA4 integrin monoclonal antibody natalizumab in clinical trials and were followed up longer-term (1). These cases, which resulted in the temporary withdrawal of natalizumab, were unexpected because treatment with this agent was not considered globally immunosuppressive, and because no prior cases of PML had been reported in MS, despite the common use of other immunomodulatory drugs.

In February 2006, the labeling for rituximab was changed to include information about patients with non-Hodgkin’s lymphoma (NHL) who developed serious viral infections after treatment with rituximab. Infections included those with cytomegalovirus, herpes simplex virus, varicella virus, and PML. As of December 2006, 23 cases of PML have been reported following rituximab therapy in patients with NHL and other hematologic malignancies, most of whom had received multiple other immunosuppressive regimens (e.g., other chemotherapy, stem cell transplant). It is estimated that more than 900,000 cancer patients have received therapy with rituximab.

There have been approximately 20 cases of PML reported in the medical literature among SLE patients not receiving rituximab (2). More than 85% of patients reported were receiving one or more immunosuppressive drugs and/or high dose corticosteroids. The outcome was fatal in approximately two thirds of cases. Although rituximab has not yet received regulatory approval for use in SLE, it is estimated that approximately 8,000 SLE patients worldwide have received therapy with rituximab to date.

Questions

What are the symptoms of PML?

The most common symptoms include paresis, cognitive impairment, and problems with coordination.

How can PML be diagnosed?

Diagnosis can be challenging. MRI findings consistent with PML include multifocal lesions, limited to the white matter, that are neither associated with enhancement with contrast material (that would be consistent with inflammation) nor with mass effect. The presence of JC virus in the central nervous system (CNS) can be established by polymerase chain reaction (PCR) on samples of cerebrospinal fluid. Histopathologic hallmarks

include enlarged oligodendroglial nuclei at the borders of demyelination; JC virus can also be shown in pathology specimens. Measurement of the viral load of JC virus in the blood can also be done. Because of the rarity of PML, the performance characteristics of these tests in different populations have not been fully defined.

What can be done for patients with PML?

Among AIDS patients, the introduction of highly effective antiretroviral therapy has resulted in a decreased prevalence of PML, suggesting that improved immune function can improve outcome. It is not clear whether or to what extent discontinuation of immunosuppressive therapy, if that is possible, might attenuate the risk or improve the outcome in other conditions. Several anti-viral agents have been tried in patients with PML (interferon, cidofovir, cytarabine), but only cytarabine, which penetrates the CNS poorly, has shown activity against JC virus.

Does susceptibility to PML vary in different diseases?

PML has been reported among patients with rheumatic diseases, including SLE and Wegener's granulomatosis (3). It had not been previously reported in MS patients, and despite the common use of immunosuppressive agents in this condition. There are a handful of reports of PML among patients with RA, and to date none among the roughly 400 RA patients treated in research studies with natalizumab (4). No cases of PML have been reported to date among RA patients treated with rituximab. Among patients with immunodeficiencies, patients with AIDS have a greater prevalence of PML than those with other immune deficiencies. This suggests that host factors may be important in susceptibility to PML.

Will other B cell directed therapies be associated with PML in SLE patients?

There is insufficient data to answer this question; it may be prudent to consider this a possibility with any B cell directed therapy. Further analysis and data from the two cases reported may provide additional information.

What do I tell my patients with rheumatic diseases treated with rituximab about their risk for PML?

PML is a rare condition. Thus far, two cases of PML have been described in patients with SLE treated with rituximab. The overall and long-term risk of PML in patients with rheumatic diseases treated with rituximab is unknown. Patients should be counseled about the potential risk, and the decision to use rituximab governed by the clinical considerations. As with any treatment, the potential risks must be weighed against the potential benefits of therapy, for example controlling disease activity in serious autoimmune conditions such as SLE and RA.

THE BOTTOM LINE

- Counsel patients on the occurrence of PML with rituximab treatment
- Consider PML in SLE patients being treated with rituximab who develop neurologic symptoms
- Report cases to MedWatch

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1. Berger JR, Korolnik IJ. [Progressive multifocal leukoencephalopathy and natalizumab – unforeseen consequences. N Engl J Med 2005;353:414-6.](#)
2. Itoh K, Kano T, Nagashio C, Mimori A, Kinoshita M, Sumiya M. [Progressive multifocal leukoencephalopathy in patients with SLE. Arthritis Rheum 2006;54:1020-5.](#)
3. Choy DS, Weiss A, Lin PT. Progressive multifocal leukoencephalopathy following treatment for Wegener's granulomatosis. JAMA 1992; 268(5):600-601.
4. Yousry TA, Major EO, Ryschkewitsch C, Fahle G, Fischer S, Hou J, Curfman B, Miszkil K, Mueller-Lenke N, Sanchez E, Barkhof F, Radue EW, Jager HR, Clifford DB. [Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. N Engl J Med 2006; 354\(9\):924-933.](#)