Rituximab Use Associated With PML in Arthritis

BY MARY ANN MOON

FROM ARCHIVES OF NEUROLOGY

Physicians considering the use of rituximab treatment of rheumatic diseases including rheumatoid arthritis should be aware that there is "a potential, albeit modest, risk of developing progressive multifocal leukoencephalopathy," a study has shown.

In addition, rheumatology patients who are already taking the drug should undergo "aggressive evaluation of new and progressing neurologic deficits … to allow early diagnosis" of progressive multifocal leukoencephalopathy (PML), said Dr. David B. Clifford, professor of neurology and medicine at Washington University in St. Louis, and his associates.

PML is a serious, often fatal demyelinating infection of the brain, usually caused by reactivation of latent JC virus in people who are immunocompromised. It also has been reported as a complication of treatment with monoclonal antibodies such as natalizumab and efalizumab, among patients taking the drugs for disorders including multiple sclerosis, inflammatory bowel disease, and chronic plaque psoriasis.

The mechanism by which these agents facilitate the development of PML is not yet known, but it is presumed that some suppressive effect they exert on the immune system allows latent JC virus to reactivate. Primary JC virus infection usually occurs unnoticed during childhood and is very widespread; most adults are seropositive for JC virus, and many carry latent virus in kidney epithelial cells, lymphoid tissues, bone marrow, and possibly the brain.

"Until very recently, treatment of RA with rituximab had not been associated with development of PML," the investigators wrote. There was one case reported in 2009, but that "was complicated by a history of malignancy that had been treated with chemotherapy and irradiation a short time before PML onset," so the connection with rituximab was unclear, they noted.

VITALS

Major Finding: Patients given rituximab for refractory RA are at "modest" risk of developing progressive multifocal leukoencephalopathy, with an estimated incidence of 1 case of PML per 25,000 drug exposures.

Data Source: Case studies of five RA patients who developed PML after receiving rituximab.

Disclosures: This study was supported by the National Institute of Mental Health, the National Institute of Neurological Disorders and Stroke, and the National Institute of Allergy and Infectious Diseases. Dr. Clifford and his associates reported ties to Bavarian Nordic, Biogen Idec, Bristol-Myers Squibb, Genentech (maker of rituximab), Genzyme, GlaxoSmithKline, Lilly, Millennium, NeurogesX, Novartis, Pfizer, Schering-Plough, Tibotec, and Wyeth.

Dr. Clifford and his colleagues now report four additional cases of PML in RA patients treated with rituximab. To characterize the disorder in this patient population, they summarized their findings along with those for the previously reported case.

All of the patients were women aged 51-73 years who had moderate to severe RA of at least 3 years' duration. All began taking rituximab after failing to respond adequately to other interventions including methotrexate, other biologics, or corticosteroids.

In all cases, rituximab was given at the recommended dose for refractory RA: Each course comprised two 1,000-mg infusions administered 2 weeks apart. Two patients received only a single course, and the maximal number of courses was five. In two cases, patients may have been at increased risk of PML because of cancer. One woman had a history of breast cancer treated with surgery and chemotherapy; the other was the previously reported case in which the patient developed superficial squamous cell carcinoma of the oropharynx and received chemotherapy and irradiation after rituximab had been administered.

Symptom onset occurred at 5-7 months after a rituximab infusion in three cases. This timing is "interesting" because it occurs during the process of immune reconstitution, rather than earlier, when CD20 cells reach their nadir.

In a fourth case, PML onset was delayed until 16 months after rituximab infusion. However this also proved to be during immune reconstitution, as this patient had an unusually prolonged interval of CD-cell suppression. This suppression "only began to normalize after PML onset, when a clear immune reconstitution inflammatory syndrome (IRIS) was well documented on MR scans," the investigators said.

It appears that the immune reconstitution inflammatory syndrome may often complicate rituximab-associated PML, as it developed in three of these five cases. "This factor is critical for clinicians, since it impacts diagnosis and management," they added.

These five patients presented with a variety of central nervous system symptoms including dysesthesias, ataxia, dysphasia, cognitive decline, focal dystonic tremor, and segmental myoclonus. JC virus DNA frequently was not detectable in the cerebrospinal fluid at presentation, "and was found only after repeated lumbar punctures as the disease progressed." In fact, one case required a brain biopsy to confirm PML.

Genentech, the maker of rituximab, estimates that these five cases of PML occurred against a background of approximately 129,000 exposures among RA patients. This puts the incidence of rituximab-associated PML at 1 in 25,000 exposed RA patients, Dr. Clifford and his associates said (Arch. Neurol. 2011 May 9 [doi:10.1001/archneurol.2011.103]).

This may be an underestimate because it's likely that more patients have not been accurately diagnosed or reported to the company, they added.

This "modest" incidence is lower than that reported for natalizumab-associated PML (1 in 1,000 patients exposed for more than 2 years) or for efalizumab-associated PML (1 in 400 exposed patients).

The need for effective treatments of rituximab-associated PML is "urgent." Antiviral therapy has not been shown to be effective. Some clinicians still try using cytosine arabinoside and cidofovir, "in spite of significant evidence that they are not effective."

Mefloquine hydrochloride has shown in vitro activity against JC virus and was used "in several of our cases," but failed to show efficacy in a recent clinical trial. "Similarly, clinicians continue to prescribe mirtazapine on a theoretical basis, related to its potential efficacy in blocking serotonin receptors used for viral entry, despite absence of documented clinical efficacy," they said.

Plasma exchange has become standard practice for natalizumab-associated PML, but it is only likely to speed immune recovery in RA patients taking rituximab if PML is discovered shortly after an infusion of the drug.

If patients develop immune reconstitution inflammatory syndrome, that "provides an additional potential therapeutic avenue." High-dose corticosteroid pulses – "often 1 g of IV methylprednisolone daily for 5 days, which is repeated if symptoms respond and then recur" – may halt neurologic decline and initiate recovery. "Physicians should be aware that this may be required even when the CD20 count suggests ongoing immune compromise" from the rituximab therapy, they added. ■

Short-Term NSAID Use Raises Death/Recurrent MI Risk

BY ELIZABETH MECHCATIE

FROM CIRCULATION

For patients with a history of myocardial infarction, any length of treatment with nonsteroidal anti-inflammatory drugs poses an unacceptably high risk for death or recurrent heart attack, based on findings from a Danish study using hospital and pharmacy registry data.

The risk elevation began during the first week of therapy and continued throughout the course of treatment, with some differences in the magnitude of risk between NSAIDs.

"These results challenge the view that NSAIDs are not harmful during short-term [1-week] treatment and indicate that a revision of current recommendations regarding NSAID treatment in patients with established cardiovascular disease is required," concluded Anne-Marie Schjerning of the department of cardiology, Copenhagen University Hospital in Gentofte, Denmark, and her coauthors. (Circulation 2011 May 9 [(doi: 0.1161/CIRCULATIONAHA.110.004671]).

The significant increase in death and recurrent myocardial infarction associated with the use of NSAIDs in a study of people with a history of myocardial infarction indicates that current recommendations regarding NSAID use in patients with cardiovascular disease need to be revised, the study authors concluded.

Although international guidelines state that NSAID use should be discouraged in people with established cardiovascular disease, they say that if such use is unavoidable, the duration of NSAID treatment "should be as short as possible," the authors pointed out.

The investigators conducted the study to address the paucity of information on the association between the duration of treatment with NSAIDs and the risk of cardiovascular disease, in this population of patients. Of the 83,675 people aged 30 years and older who had had their first MI from 1997 through 2006 identified in the national registries (mean age, 68 years), 42% had received NSAIDs.

Overall, treatment with NSAIDs was associated with a 45% greater risk of death/recurrent MI during the first 7 days of treatment, which persisted and was increased by 65% over a 30- to 90-day period of treatment.

The greatest risk identified was with diclofenac (hazard ratio, 3.26; 95% confidence interval, 2.57-3.86 for death/MI at day 1-7 of treatment). Diclofenac is available over the counter in many countries, the authors noted.

A significant increase in risk was seen after 1 week of treatment with ibuprofen, in the first week of treatment with rofecoxib (which has been withdrawn from the market), and after 14-30 days with celecoxib.

The risk associated with ibuprofen was lower than the risk associated with the two cyclooxygenase-2 (COX-2) selective inhibitors, rofecoxib and celecoxib, and it was lower than the risk associated with the use of diclofenac.

There was no increased risk of death or recurrent MI associated with naproxen for the entire treatment duration, which exceeded 90 days in some cases. However, naproxen has been associated with an increased risk of GI bleeding, compared with rofecoxib, in one study, the authors noted.

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