Rituximab Use Associated With PML in Arthritis

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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 (PML), 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 unobserved 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 this was interpreted 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.

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 immunosuppressive effects of the inflammatory process of immune reconstitution, rather than earlier, when CD20 cells reach their nadir.

The investigators conducted the study to address the paucity of information on the association between the duration of treatment with NSAsIDs and the risk of PML in this population of patients. Of the 83,675 people with a history of myocardial infarction identified in the national registries (mean age, 68 years), 42% had received NSAsIDs.

Of patients treated with NSAsIDs, there was an increased 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.

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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