Understanding PML and Risks Associated with Biologic Therapies

A swarm of controversy has enveloped biologics due to concerns about progressive multifocal leukoencephalopathy.

Genentech announced last month a phased voluntary withdrawal of Raptiva (efalizumab) from the market, due to heightened concerns for safety issues potentially resulting in morbidity and mortality. Specifically, the drug was linked to a rare brain infection, progressive multifocal leukoencephalopathy (PML). As of June 8, 2009, the drug will no longer be available on the US market.

Given this recent chain of events, physicians may be asking a number of questions about PML, as well as how these events will affect other TNF inhibitors and systemic agents commonly used to treat psoriasis. This article will examine PML in greater detail, specifically in relation to biologics and provide a broad outlook of systemic treatments for psoriasis.

PML and Biologics

Progressive multifocal leukoencephalopathy is a rare, serious, and usually fatal demyelinating disease that occurs predominantly in severely immunosuppressed patient populations. The etiologic agent is the John Cunningham virus (JCV), a polyomavirus that is widely distributed as a latent infection in the general population in tonsillar tissue, gut, spleen, and kidney. Its activation results in dissemination to the central nervous system (CNS), where it infects myelin-producing oligodendrocytes, leading to demyelination and clinical disease. Demyelination is typically multifocal from 1mm to several cm.

PML is often fatal, and there is no effective therapy. Patients who survive this adverse advent are left neurologically impaired. PML is seen most commonly in HIV infected individuals, in addition to those with malignancies, organ transplants, systemic lupus erythematosus (SLE), and other rheumatic diseases. The critical element for survival is reversing the immunosuppressive state.

The clinical features of PML are weakness, visual loss and lack of coordination, confusion, disorientation, and personality changes. MRI changes, such as asymmetric subcortical changes in white matter, are noted. Identifying JC virus in the cerebrospinal fluid is key to diagnosis. Many of the clinical symptoms of PML, such as cognitive impairment, speech abnormalities, headache, and sensory loss are indistinguishable from multiple sclerosis (MS), neuropsychiatric SLE, and vasculitis of the CNS. A review in July 2007 reported 36 cases of PML among patients with rheumatic disease, two thirds of which had SLE.

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Raptiva Connection

The withdrawal of efalizumab from the market has prompted concerns regarding patients currently on that agent, as well as biologics in general. Importantly, duration of treatment may be linked to the likelihood of PML. Genentech disclosed that in the four reported cases of PML (including three that were fatal), each patient had been taking the drug for more than three years.

Within the last several years, PML has also been associated other biologics used for the treatment of rheumatic diseases, such as rituximab (Rituxin, Genentech), for which the FDA issued a warning in December of 2006 after two patients treated for SLE got PML. There have also been associations with natalizumab (Tysabri, Biogen), an antagonist of alpha-4 integrin for the treatment of MS, Crohn’s disease, and rheumatoid arthritis. In clinical trials, PML occurred in 0.1 percent of patients on natalizumab.

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expressed by leukocytes. These integrins serve as cell adhesion molecules and are implicated in specific homing and trafficking of leukocytes. Natalizumab essentially blocks the entry of inflammatory cells into the brain and other tissues that use alpha-4 integrin to bind with vascular cell adhesion molecules (VCAM). Similarly, efalizumab is a humanized monoclonal antibody to the LFA 1 receptor on T-cells that interferes with the up-regulation of intercellular adhesion molecule (ICAM). This results in decreased diapedesis of activated T-cells trafficking from the blood and lymph into the dermis. In fact one sees a leukocytosis with efalizumab.

**Treatment Options**

Transitioning patients who are on efalizumab to another systemic or biologic agent is imperative at this time. Importantly, simply stopping efalizumab treatment "cold turkey" is not a sound clinical measure because 10 to 20 percent of patients would have an exacerbation of their psoriasis worse than it was before they started treatment with efalizumab. In addition, upon stopping treatment, there could be a morphologic change, i.e. pustular, guttate, exfoliative erythrodermic psoriasis. The mechanism of this flare can be attributed to the mechanism of action of efalizumab, which involves inhibition of ICAM-1 with resulting inhibition of diapedesis, resulting in decreased trafficking of activated T-cells travelling from the lymph or blood into the dermis.

The challenge of transitioning from efalizumab to another biologic agent is compounded by the fact that it takes some time for the other biologic agents to kick in. Of the currently available biologics, adalimumab (Humira, Abbots) works most quickly, yielding PASI 75 at week four of 19 percent. Therefore, it is necessary to bridge patients transitioning from efalizumab with a systemic agent.

The systemic agent I prefer to bridge efalizumab to another biologic is cyclosporine 4-5mg/kg in divided doses (BID). I prefer to keep the patient on efalizumab and add cyclosporine for four weeks, then discontinue efalizumab and start either etanercept (Enbrel, Amgen Wyeth) or adalimumab. I find it best to continue cyclosporine with the new biologic for another four weeks and then taper by 1mg/kg per week for the next four weeks.

Prior to initiating cyclosporine, you will need to evaluate blood pressure, LFT, chemical screens (Creatinine), lipid levels, and magnesium. It is necessary to follow blood pressure (BP), creatinine, and magnesium every other week for the first month, then monthly. Importantly, patients should be counseled about elevations in BP, lipids, nephrotoxicity, tremors, hypertrichosis, and lymphoma.

Risks associated with other biologics used to treat psoriasis do not appear to be as strong as for efalizumab. PML is not listed as an adverse event in the Prescribing Information for alefacept (Amevive, Astellas). As of February 23, 2009, there have been no cases of PML reported in alefacept patients worldwide, including in clinical trials. No cases of PML have been reported in etanercept clinical trials, including open-label extension trials of up to 10 years. Two cases in the literature described signs and symptoms that eventually led to clinical consideration or report of PML in etanercept patients. However, neither of these was confirmed by the presence of JC virus in CSF or brain biopsy. As of March 23, 2009, no cases of PML have been reported in adalimumab clinical trials, including open-label extension trials. Finally, there were no reports of PML in infliximab (Remicade, Centocor) clinical trials. However, in a prospective rheumatoid arthritis study, one patient's death was determined to be due to PML.

**Going Forward**

The loss of efalizumab will likely influence most dermatologists’ approach to biologic treatments for psoriasis, particularly in obese patients and those with hand and foot psoriasis.

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Clinical Focus: Psoriasis