Natalizumab: increased vigilance is required in treating patients with multiple sclerosis

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The recent reporting of two new cases of progressive multifocal leukoencephalopathy (PML) in patients with multiple sclerosis (MS) receiving natalizumab highlights the risks associated with this agent in patients who do not respond to conventional immunomodulatory therapy. Since the introduction of natalizumab back into the US and European markets, there had been some optimism that perhaps the use of natalizumab as a monotherapy would result in no new cases of PML. The thought that occurrence of PML would occur only when natalizumab was used in combination with interferon or following other immunosuppressive agents was proven to be false when one of the patients who developed a recent case of PML had not been on any other MS medication. Thus, while the use of natalizumab has proven to be a valuable addition in the management of some patients with MS, it appears that PML and immune reconstitution inflammatory syndrome (IRIS) are rare but significant complications that may afflict patients receiving this therapy. In addition, the recent reports of melanoma possibly being linked to natalizumab-treated MS patients suggests that infectious complications are not the only obstacles faced by patients being treated with this VLA-4 antagonist [Mullen *et al.* 2008].

It has to be emphasized that potentially fatal infectious and noninfectious complications of pharmacotherapies are not exclusive to natalizumab, but have also occurred with other experimental and approved agents [Hemmer *et al.* 2006]. For instance, the risk of acute myelogenous leukemias after exposure to mitoxantrone appears to be a rare but significant complication in

patients being treated with this chemotherapeutic agent [Hasan *et al.* 2008]. The risk of cardiac toxicity is also a significant complication that may be faced by patients receiving this therapy [Saccardi *et al.* 2004].

However, these FDA-approved agents may be joined by several new agents that also have significant risks associated with them. In the recent clinical trial examining alemtuzumab, six of 216 patients developed idiopathic thrombocytopenic purpura (ITP), with one of these patients suffering a fatal intracerebral hemorrhage. The B-cell-depleting chimeric monoclonal antibody rituximab has also been associated with the development of PML in 27 patients with different diseases. Furthermore, several of the newer agents in therapeutic development and clinical trials may also have rare but significant adverse effects.

While all of these agents have significant risks, they also offer hope to patients with MS who do not respond optimally to interferon beta or glatiramer acetate. A critical next step in defining an optimal therapy for patients with MS will be to identify (1) patients who will benefit from a particular agent, and (2) patients who will be at an increased risk of an adverse outcome. The identification of biomarkers that may include pharmacogenomics, proteomics, and more traditional laboratory assays that measure immunological responses will likely play an important role. Such tools would significantly reduce the anxiety of patients and physicians alike in terms of the use of medications such as natalizumab.

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A series of studies performed on patients enrolled in the SENTINEL and AFFIRM trials in Dallas suggest that these patients may have unexpected biological consequences that result from treatment with this agent [Stuve *et al.* 2006a; Stuve *et al.* 2006b]. While our early observations suggested a significant effect on lymphocyte entry into the cerebrospinal fluid, it was somewhat reassuring that no patients enrolled in Dallas developed any opportunistic infection. However, if natalizumab did have an adverse effect on CNS immune surveillance, shouldn't there have been evidence to suggest that viruses other than the John Cunningham (JC) virus also reactivated following natalizumab therapy?

To address this issue, we examined the CSF and serum of the Dallas natalizumab-treated cohort for evidence of human herpes virus 6 (HHV-6) reactivation, another virus thought to remain latent in the adult central nervous system [Yao *et al.* 2008]. Interestingly, natalizumab-treated patients appear to have lower serum IgG levels than MS patients that did not receive natalizumab. Among transplant immunologists, HHV-6 reactivation is considered an indicator of CNS immune suppression and increased risk for subsequent viral reactivation. Despite this low serum IgG level, we were able to detect elevated titers of antibodies in the serum of natalizumab-treated MS patients directed against HHV-6. This would suggest that conditions in natalizumab-treated patients are conducive for these patients to mount an immune response against HHV-6. It is also of interest that some investigators suggest that HHV-6 may participate in the transformation of the JC virus into a pathogenic strain capable of initiating the demyelinating pathology seen in patients with PML [Mock *et al.* 1999].

One positive aspect of the unfortunate recent events surrounding natalizumab is the heightened vigilance with regard to potential side effects of this drug. It is only through continued study of patients receiving natalizumab and attempting to understand the relationship of use of the drug to the development of risk factors for

viral reactivation that we will be able to reduce the concerns within the neurologic community about the use of these novel therapies.

Conflict of interest statement

None declared.

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