EDITORIAL

Patients at Risk

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In clinical trials, the term "patients at risk" refers to the altruistic people who volunteer to participate in studies of novel treatments. In this issue of the *Journal*, three reports[1-3] provide details about patients who were participating in trials involving experimental treatment with natalizumab for either multiple sclerosis or Crohn's disease and who were affected by progressive multifocal leukoencephalopathy (PML). PML is a rapidly progressive, often fatal demyelinating brain disorder caused by infection of the central nervous system with JC virus[4]; it usually occurs in patients with diminished T-cell function. These events remind us once again of the true meaning of being a "patient at risk."

The clinical story is intriguing. Natalizumab (Tysabri) is a humanized monoclonal antibody to the T-cell adhesion molecule known as α_4 integrin; patients given the antibody have suppressed T-cell function. The agent was approved by the Food and Drug Administration for the treatment of multiple sclerosis in November 2004, but the manufacturer, Biogen Idec, has been conducting continuing clinical tests with the agent to clarify its role in the treatment of a number of medical conditions. In February of this year, two cases of PML in patients with multiple sclerosis were diagnosed among those at risk in these ongoing trials. Biogen Idec then put a halt to the sales and testing of the drug. In this issue of the *Journal*, Kleinschmidt-DeMasters and Tyler[1] and Langer-Gould et al.[2] provide the medical details of these cases of PML in patients with multiple sclerosis.

Once they were on high alert, investigators in Belgium revisited a case of what had originally been considered to be a fatal astrocytoma in a patient participating in a clinical trial of natalizumab for the treatment of Crohn's disease. As detailed by Van Assche and colleagues,[3] they quickly discovered that the patient had actually died from PML. These investigators provide strong evidence, based on a detailed chronology of recovery of JC virus from the blood, of a temporal association between treatment with natalizumab and PML.

Given these data, the association between treatment with natalizumab and the occurrence of PML seems clear. What we do not know is the magnitude of the risk of PML per year of exposure. It is our understanding that Biogen Idec has examined as many of the patients who received the drug as possible for evidence of virus in the blood or for imaging findings consistent with PML to determine whether there is a reservoir of subclinical cases. Here is where close surveillance for further active or subclinical cases of PML becomes so important. These data are needed to set provisional bounds on the risk of acquiring PML. With this knowledge, a reasonable assessment of the risk of this complication versus the treatment benefit can be made. In the case of natalizumab, there is a dilemma. On the one hand, it appears to be a promising therapy for multiple sclerosis and has raised the hopes of patients with this debilitating condition; on the other, the complication of PML can be fatal.

The bottom line is sobering. If we are to advance the art of medicine, we need patients who are willing to volunteer to be subjects in clinical trials. Despite the obstacles presented by adverse outcomes, clinical research must proceed if new therapies are to be developed. We always need to remember that these patients are "at risk." We need to be sure that research is carried out in a responsible manner and that patients who volunteer to participate are treated in an open, honest, and fair fashion; from what is currently on the public record, Biogen appears to

have honored this trust. Patients and their families expect no less, and we must always deliver on that expectation.

1. Kleinschmidt-DeMasters BK, Tyler KL. Progressive multifocal leukoencephalopathy complicating treatment with natalizumab and interferon beta-1a for multiple sclerosis. N Engl J Med 2005; 353.
2. Langer-Gould A, Atlas SW, Bollen AW, Pelletier D. Progressive multifocal leukoencephalopathy in a patient treated with natalizumab. N Engl J Med 2005;353.
3. Van Assche G, Van Ranst M, Sciot R, et al. Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. N Engl J Med 2005;353.
4. Berger JR, Koralnik IJ. Progressive multifocal leukoencephalopathy and natalizumab. N Engl J Med 2005;353.