Natalizumab and Immune Cells

UNDERSTANDING THE MECHANISMS UNDERlying the unfortunate occurrence of progressive multifocal leukoencephalopathy (PML), a disease caused by reactivation of the JC polyomavirus, in a small subset of patients during treatment of autoimmune disease with natalizumab is important at several levels. The most important and immediate outcome would be a more complete appreciation of the risk of PML, not only with natalizumab therapy but also with other immunomodulatory therapeutic strategies currently in development. The second most important outcome would be the potential for the development of approaches for monitoring patients treated with natalizumab and other therapies that may have similar risks, in turn allowing for the safer use of these treatments. Finally, an understanding of the mechanism(s) contributing to the association of PML with natalizumab therapy may provide new insights into the disease processes in multiple sclerosis and PML.

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Two general mechanisms have been suggested to explain the association between natalizumab treatment and PML. The first is that blocking α4 integrin decreases lymphocyte trafficking, and the subsequent reduction in immune surveillance allows for the activation of a latent infection in the nervous system. The second suggested mechanism is associated with the finding that deletion of α4 integrin is associated with increased numbers of B cells and immature progenitor cells released from the bone marrow.[1] Both of these populations may be reservoirs of latent JC virus. At present, there is little direct evidence supporting either of these possibilities.

The results described by Stüve et al[2] in this issue of the ARCHIVES, while based on the study of a small number of patients and retrospective in design, raise several important issues relating to the use of natalizumab in treating autoimmune disease. The results indicate that in the cerebrospinal fluid, the ratio of $CD4^+/CD8^+$ T cells is reduced to a level similar to that seen in human immunodeficiency virus infection. In human immunodeficiency virus infection, the reduction in the cerebrospinal fluid $CD4^+/CD8^+$ ratio is secondary to the decreased ratio seen in peripheral blood and reflects the marked reduction in $CD4^+$ T cells. Stüve and colleagues found that the $CD4^+/CD8^+$ ratio in peripheral blood was normal, although a trend toward a decreasing ratio was seen in relation to the duration of the treatment. They interpreted the findings as reflecting a decreased migration of $CD4^+$ T cells into the central nervous system. In addition, data on a separate cohort of patients demonstrated that the amount of expression of unbound α4 integrin remaining during treatment with natalizumab is less on $CD4^+$ T cells than on $CD8^+$ T cells. This suggests that the impairment of migration is more marked with $CD4^+$ T cells, resulting in a relative decrease in $CD4^+$ T cells in the cerebrospinal fluid. These findings are consistent with the hypothesis that a reduction of $CD4^+$ T-cell surveillance may result in reactivation of JC virus that could potentially lead to subsequent disease. Although Stüve and colleagues did not provide the absolute numbers of $CD4^+$ and $CD8^+$ T cells in either peripheral blood or cerebrospinal fluid, the most likely interpretation is that the decreased ratio is due to a decrease in $CD4^+$ T cells and not an increase in $CD8^+$ T cells.

What is the significance of these findings? First, the hypothesis by Stüve and colleagues that the findings reflect decreased transmigration of $CD4^+$ T cells into the central nervous system and consequent decreased surveillance by $CD4^+$ T cells is reasonable and consistent with the previous suggestions[3] of a relationship between decreased immune surveillance and PML. The evidence that the explanation for the decreased ratios is the decreased levels of unbound α4 integrin on $CD4^+$ T cells as compared with $CD8^+$ T cells is indirect because measurement of the $CD4^+/CD8^+$ ratio was not performed on these same patients. Also, information about the relationship of the unbound α4 integrin to the time after treatment is missing. The data in the study by Stüve and colleagues report levels immediately following infusion. Does the level of unbound α4 integrin remain at a similar low level that is sufficient to explain the decreased migration? Probably the most striking aspects of the data are the magnitude of the decreased ratios and the consistency in the finding in the study cohort. Again, the data would be more easily analyzed if the reader were provided the absolute cell counts underlying the decreased ratios. However, the findings suggest a profound abnormality that apparently occurs very rapidly, as it was observed in 1 patient who had received only a single dose. If the risk of PML is related to the decreased $CD4^+/CD8^+$ ratio, the data would represent a need for caution. Decreased immune surveillance would not necessarily be specific for JC virus, and the possibility exists that other commensal human viruses may also be reac-

tivated. However, it is not clear that decreased surveillance alone is sufficient for the development of PML. Controversy exists with respect to the reservoirs for latent JC virus in healthy individuals. Although some investigators[4] have found JC virus DNA in normal brain tissue, many others[5] have failed to do so and have indicated that the reservoir may be in the bone marrow and kidney. If correct, infection of the brain would require transport of the virus to the central nervous system. Because, as mentioned earlier, treatment with natalizumab produces mobilization of B cells and progenitor cells from the bone marrow, these cells may represent a reservoir of latent JC virus that could be transported to the central nervous system. Consequently, the disease may require the combined events of decreased surveillance and delivery of latent virus to the nervous system.

The most important aspects of the findings may be that they lead to a specific hypothesis that can be tested and they reinforce the need for careful biological monitoring of patients as they return to treatment with natalizumab. More detailed measurements of immune surveillance can and should be done in a prospective manner. In addition, studies of transient changes in the viral load in peripheral blood cells can and should be done, again in a careful prospective manner. It will be unfortunate if the opportunity to design careful prospective measurements of immune function and viral activation is not initiated as treatment with natalizumab resumes. The results will be central to understanding the potential risks, and they have implications for not only natalizumab but also other therapies that may have similar mechanisms.

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