

CORRESPONDENCE



Natalizumab for Relapsing Multiple Sclerosis

TO THE EDITOR: As Ropper pointed out in his editorial (March 2 issue),¹ the three articles on the use of natalizumab in that issue of the *Journal* are pivotal, but his conclusion that natalizumab is “a potent treatment for multiple sclerosis” may be too sanguine. The similar entry criteria, treatment, and methods of analysis permit clinically useful conclusions to be drawn from the placebo-controlled study of natalizumab by Polman et al.² and the study of natalizumab plus interferon beta by Rudick et al.³ A comparison of Figure 2 in both studies is illustrative. In the study by Polman et al., progression of disease at 120 weeks was decreased by 12 percent with natalizumab as compared with placebo. In the study by Rudick et al., progression of disease at 120 weeks was decreased by 6 percent with natalizumab plus interferon as compared with interferon alone. The clinical conclusion would seem to be that the efficacy of natalizumab in inhibiting disease progression is between 6 percent and 12 percent. For the clinician, this efficacy would need to be compared with that of other medications and considered along with the probability of progressive multifocal leukoencephalopathy (PML) — 1 in 1000 patients treated with natalizumab, as estimated by Yousry et al.⁴

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Dr. Tenser reports having received consulting fees or lecture fees from Berlex Laboratories, Biogen Idec, and Teva Neuroscience.

1. Ropper AH. Selective treatment of multiple sclerosis. *N Engl J Med* 2006;354:965-7.
2. Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med* 2006;354:899-910.
3. Rudick RA, Stuart WH, Calabresi PA, et al. Natalizumab plus interferon beta-1a for relapsing multiple sclerosis. *N Engl J Med* 2006;354:911-23.
4. Yousry TA, Major EO, Ryschkewitsch C, et al. Evaluation of patients treated with natalizumab for progressive multifocal leukoencephalopathy. *N Engl J Med* 2006;354:924-33.

TO THE EDITOR: I have concerns regarding the safety evaluation of natalizumab in the study by Yousry et al. These authors reviewed suspected cases of PML among patients exposed to natalizumab. Their diagnostic criteria may have resulted in the classification of patients with arrested PML as “not having PML.” A single unidentified case among patients treated with natalizumab could substantially alter the assessment of risk.

To fulfill criteria for PML, patients must have had detectable JC virus DNA in the cerebrospinal fluid on a polymerase-chain-reaction (PCR) assay. Yousry et al. state that “the sensitivity of cerebrospinal fluid detection for PML usually exceeds 90 percent.” According to the literature, the sensitivity for PML of JC virus detection in cerebrospinal fluid by PCR varies between 50 percent and 85 percent.¹⁻³ On that basis alone these authors may have classified patients with PML as not having PML.

Furthermore, the authors required that patients have progressive neurologic disease. That criterion also appears flawed. After the cessation of

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dosing, T cells reenter the central nervous system and arrest progression. Patients evaluated months after the cessation of exposure to natalizumab may have arrested PML and would not be expected to have progressive disease.

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1. Koralnik IJ. New insights into progressive multifocal leukoencephalopathy. *Curr Opin Neurol* 2004;17:365-70.
2. Gibson PE, Knowles WA, Hand JF, Brown DW. Detection of JC virus DNA in the cerebrospinal fluid of patients with progressive multifocal leukoencephalopathy. *J Med Virol* 1993;39:278-81.
3. McGuire D, Barhite S, Hollander H, Miles M. JC virus DNA in cerebrospinal fluid of human immunodeficiency virus-infected patients: predictive value for progressive multifocal leukoencephalopathy. *Ann Neurol* 1995;37:395-9. [Erratum, *Ann Neurol* 1995;37:687.]

TO THE EDITOR: Yousry et al. report that one patient treated with natalizumab (Independent Adjudication Committee [IAC] Case 28) with cognitive changes had a plasma JC virus load of 8733 copies per milliliter but was considered by the investigators not to have subclinical PML. However, one of two patients with fatal PML that they also analyzed (IAC Case 993) had plasma viral loads of the polyomavirus JC virus that rose from less than 125 copies per milliliter before treatment to 520 copies per milliliter after three treatments with natalizumab. However, two months later, the titer rose to 6600 copies per milliliter in plasma at a time when a biopsy of the brain showed that there were half a million copies per cell.¹ Since the antibodies to $\alpha_4\beta_1$ integrin are known to block cell receptors for murine polyomaviruses at the postattachment level,² it is quite possible that natalizumab induces an overwhelming JC viremia in patients by similar mechanisms, which may explain the high viral load in IAC Case 28 and other similar cases. Further research is needed.

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1. Van Assche G, Van Ranst M, Sciôt R, et al. Progressive multifocal leukoencephalopathy after natalizumab therapy for Crohn's disease. *N Engl J Med* 2005;353:362-8.

2. Caruso M, Belloni L, Sthandier O, Amati P, Garcia MI. Alpha4beta1 integrin acts as a cell receptor for murine polyomavirus at the postattachment level. *J Virol* 2003;77:3913-21.

DRS. POLMAN AND RUDICK REPLY: We agree with Tenser that it is important when prescribing natalizumab to balance the beneficial effects of the drug carefully against the risk of potentially severe adverse events. We do not agree that exclusive focus on the absolute difference in the proportion of patients with confirmed progression of disability is the optimal way to determine benefits. Doing so ignores many prespecified outcomes and underestimates treatment benefits. Natalizumab suppressed relapses by two thirds and new lesions on magnetic resonance imaging by about 90 percent and showed substantial benefits in terms of every other clinical outcome in the study, including other measures of disability and self-reported quality of life.

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DR. YOUSRY AND COLLEAGUES REPLY: Jeffery raises questions regarding the criterion for the diagnosis of PML on the basis of testing of cerebrospinal fluid for JC virus DNA and clinical progressive disease. His concern arises from confusion about the use of data for screening as opposed to diagnosis. Testing of cerebrospinal fluid for JC virus DNA is not used for screening, since it is not as sensitive as clinical evaluation and magnetic resonance imaging (MRI), the primary screening tools. JC virus DNA has not been found on cerebrospinal fluid testing before clinical signs or lesions on MRI. Our strategy required that cases with active clinical findings of possible PML or abnormalities on MRI that were consistent with PML be designated as "indeterminate" if we were unable to obtain cerebrospinal fluid or tissue for analysis for JC virus. The one patient whose case we identified as indeterminate had clinically progressive disease antedating exposure to natalizumab and was judged not likely to represent another case of PML.

Whether there was a “subclinical” occurrence of PML cannot be determined without brain-tissue analysis. However, it seems unlikely that PML would be quiescent in the three to six months after withdrawal of natalizumab during which our analysis was performed. The biologic effects of natalizumab remain for approximately three months after the end of dosing,¹ and changes in the cytology of cerebrospinal fluid remain for up to six months after withdrawal.² On the basis of knowledge about the human immunodeficiency virus and PML, if immune reconstitution occurred, it is likely that the increased inflammation would be associated with transiently more active clinical symptoms and more notable imaging changes. Thus, we believe that it is very unlikely that performing this analysis during the early months of drug withdrawal resulted in a falsely low rate of PML detection.

Meyer draws attention to the model of the murine polyomavirus.³ Unlike the murine virus, JC virus does not use the α_4 integrin as its cellular receptor.⁴ It is not likely that natalizumab blocks JC virus cell attachment that could give rise to a viremia, as seen in IAC Case 28 or Case 993. Five of 2370 plasma samples tested during risk analysis were positive for JC virus DNA in the commercial screening assay; three of the five were from patients who had never received natalizumab. However, we agree that more research is required to understand the biology of PML and its relationship to natalizumab.

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1. Rudick RA, Sandrock A. Natalizumab: α_4 -integrin antago-

nist selective adhesion molecule inhibitors for MS. *Expert Rev Neurother* 2004;4:571-80.

2. Stuve O, Marra C, Jerome KR, et al. Immune surveillance in multiple sclerosis patients treated with natalizumab. *Neurology* 2006;66:Suppl 2:A250. abstract.

3. Caruso M, Belloni L, Sthandier O, Amati P, Garcia MI. Alpha4beta1 integrin acts as a cell receptor for murine polyomavirus at the postattachment level. *J Virol* 2003;77:3913-21.

4. Eash S, Manley K, Gasparovic M, Querbes W, Atwood WJ. The human polyomaviruses. *Cell Mol Sci* (in press).

THE EDITORIALIST REPLIES: Tenser makes a valid point, but surely he would agree that the monoclonal antibodies against α_4 integrin are biologically quite potent, which was the context in the editorial. There were many end points in these trials and most were not only statistically but also clinically significant. In the published studies of Polman et al. and Rudick et al., only a minority of patients with multiple sclerosis worsened over a comparatively brief period, so the effect size for treatment would be expected to be modest at two years. However, 12 fewer patients progressed for every 100 treated; viewed alternatively, the relative risk in the Natalizumab Safety and Efficacy in Relapsing Remitting Multiple Sclerosis (AFFIRM) trial indicates that it was about half as likely that a treated patient would progress. Comparisons of the two trials are imprecise, since the Safety and Efficacy of Natalizumab in Combination with Interferon Beta-1a in Patients with Relapsing Remitting Multiple Sclerosis (SENTINEL) trial had no placebo group and the reference by Tenser to a 6 percent difference reflects only the efficacy beyond that offered by interferon. Moreover, the treatment and placebo curves in both trials were diverging during two years, and the question at hand is whether the differences between groups continue in this manner over subsequent decades. As stated in the editorial, these points only emphasize the need for information on the effects and risks of the drug over many years.

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Thalidomide for Multiple Myeloma

TO THE EDITOR: Barlogie et al. (March 9 issue)¹ report an increased response rate of multiple myeloma to thalidomide plus high-dose chemotherapy and transplantation. However, there was no

difference in overall survival between the group that received thalidomide from the beginning of the study and the control group, which received thalidomide only after relapse.