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JC Viremia in Natalizumab-Treated Patients with Multiple Sclerosis

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To the Editor: We analyzed plasma samples for the presence of JC virus antibodies and viral DNA. The samples were obtained from separate cohorts of patients with multiple sclerosis who received monthly infusions of natalizumab. Blood samples were obtained from 26 patients immediately before the first infusion (the baseline) and for several months during the first year of treatment. Blood samples also were obtained from 23 patients once after more than 24 months of treatment. Antibody titers and viral DNA¹ were measured by means of an enzyme-linked immunosorbent assay with the use of JC viruslike particles (the Biogen Stratify assay uses similar viruslike particles).² We also used an ultrasensitive quantitative polymerase-chain-reaction (PCR) assay specific for JC virus DNA.¹ Our procedures were certified in accordance with the Clinical Laboratory Improvement Amendment. The Laboratory of Molecular Medicine and Neuroscience has provided quantitative PCR results that have confirmed the diagnosis of progressive multifocal leukoencephalopathy (PML) in approximately half the 370 cases of PML in natalizumab-treated patients with multiple sclerosis.

Overall, 17 of the 49 patients (35%) had viremia at some time. Ten of 26 patients in whom treatment was initiated had viremia; 4 were seronegative (antibody titer, <2560) and 6 were seropositive (antibody titer, ≥2560).¹ Of these patients, 4 had viremia at baseline and 3 were seropositive. Seven of 23 patients who received more than 24 infusions had viremia and 2 were seronegative. One blood sample was obtained from each of the 18 healthy volunteers; 6 were seronegative, 12 were seropositive, and none had detectable viral DNA.

Fisher's exact test was used to determine a statistical difference between the treated patients who had viremia and healthy volunteers ($P = 0.003$) (Table 1). We observed a range in viral titers from 13 to 510 copies of JC virus DNA per milliliter (mean, 43 copies per milliliter) in patients in the initial year of treatment and from 21 to 126 copies (mean, 40 copies per milliliter) in those who received more than 24 infusions. Of the 17 persons with viremia, 11 were seropositive (65%) and 6 were seronegative (35%).

Although viremia by itself is not a predictor of the risk of PML, the observation that viremia can occur in patients with negative test results for antibodies to the JC virus raises other issues. The relatively high percentage of patients who had viremia and were seronegative

appears to be greater than the false negative rate identified previously.² In some of these patients, the same blood sample showed T-cell responses to JC virus proteins but a seronegative test result.³

To establish risk-stratification algorithms for PML in patients who receive potent immunomodulatory therapies, a single measurement of viral activity such as a test for antibodies to JC virus may be useful but not sufficient to assess risk.^{4,5} The observation that some patients had viremia and were seronegative provides support for a more comprehensive risk-mitigation strategy involving periodic monitoring over the course of the treatment intervention.

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Table 1

Plasma Viremia in Patients with Multiple Sclerosis Who Were Treated with Natalizumab.*

Variable	Initial Yr of Treatment (N = 26)	Treatment >24 Mo (N = 23)	Healthy Volunteers (N = 18)
<i>number of patients</i>			
Level of JC virus DNA			
Mean, 43 copies/ml (range, 13–510)	10	0	0
Mean, 40 copies/ml (range, 21–126)	0	7	0
Seropositivity			
Seropositive (antibody titer, ≥2560)	6 [†]	5 [‡]	12
Seronegative (antibody titer, <2560)	4 [§]	2 [¶]	6

* Viremia was significantly more common in treated patients than in healthy controls (P = 0.003 by Fisher's exact test).

[†] Three patients had viremia at baseline, and one patient each had viremia at 3, 6, and 9 months.

[‡] Two patients had viremia at 25 months, and one patient each had viremia at 30, 33, and 36 months.

[§] One patient had viremia at baseline, and one patient each had viremia at 3, 6, and 9 months.

[¶] One patient had viremia at 29 months, and one patient had viremia at 33 months.