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Discrepant findings in immune responses to JC virus in patients receiving natalizumab

Chen S Tan, Yiping Chen, Raphael P Viscidi, R Philip Kinkel, Marion C Stein, and Igor J Koralnik

Division of Infectious Disease (CST), Division of Viral Pathogenesis (CST, YC, IJK), Department of Medicine, Division of NeuroVirology (CST, IJK), and Department of Neurology (RPK, MCS), Beth Israel Deaconess Medical Center, Boston, MA, USA; and Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA (RPV)

We read with interest both the paper by Jilek and colleagues,¹ which describes immunological and virological findings in a cohort of patients with multiple sclerosis before and during the course of natalizumab therapy, and the associated commentary² comparing their results with our recent study of similar design.³ Whereas we found a decrease in the magnitude of the cellular immune response against JC virus in natalizumab-treated patients, and an increased incidence of JC virus in the urine and blood, Jilek and colleagues¹ found an increase in cellular immune responses to JC virus, Epstein-Barr virus and cytomegalovirus, stable incidence of JC virus in the urine, and no JC virus in the blood.

We have difficulties integrating the humoral and cellular immune response data presented by Jilek and colleagues.³ They reported that only 12 of 24 patients treated with natalizumab and six of 14 treated with interferon beta had antibodies against JC virus, and one additional JC virus-seronegative patient in the natalizumab group had detectable JC virus in the urine. None of the patients seroconverted for JC virus during the study. Based on these data, the 11 of 24 patients treated with natalizumab and eight of 14 treated with interferon beta who had negative JC virus serology might not have been exposed to JC virus, and therefore would not be expected to have a cellular immune response to this virus. The inclusion of JC virus-seronegative patients along with the seropositive patients might have altered the final analysis of cellular immune responses. Similarly, serological assays for Epstein Barr virus and cytomegalovirus should have been done and only seropositive patients should have been tested for their cellular immune response against those viruses.

Conversely, Jilek and colleagues¹ noted that 20 of 24 patients treated with natalizumab and ten of 14 treated with interferon beta had a detectable cellular immune response against JC virus that was mediated by T lymphocytes. Therefore, the authors should comment on whether their JC virus serology assay underestimated the proportion of their patients who were exposed to JC virus. Indeed, if the cellular immune response assay represents true JC virus exposure, the sensitivity of their serology assay for JC virus might be as low as 60%. The sensitivity and specificity of a JC virus serology assay is of substantial interest because such an assay is now being considered as a means to assess the risk of progressive multifocal leukoencephalopathy (PML) in patients treated with natalizumab.⁴

Several methodological differences might explain the discrepancies between the two studies.^{1,3} We detected either anti-IgG or anti-IgM antibodies to JC virus in all of the patients in our study, which confirmed their exposure to the virus. Although T-cell

responses specific to JC virus are low and difficult to detect ex vivo, they are robust after in-vitro stimulation of cells with JC virus antigens and are predictive of clinical outcome in patients with PML.^{5,6} We therefore did an enzyme-linked immunosorbent spot assay after in-vitro stimulation of peripheral blood mononuclear cells with JC virus peptides³ and, unlike Jilek and colleagues,¹ we did not use frozen samples. The amplitudes of the measured T-cell responses were several orders of magnitude above those reported by Jilek and colleagues, and many data points from their study fall below the positive threshold in our assay. Furthermore, our JC virus peptide library was more comprehensive and consisted of 15-mers overlapping by 11 amino acids instead of by ten, as used by Jilek and colleagues. Finally, we used a different kit to extract DNA from urine and plasma and our PCR assay was more sensitive.

As of April 6, 2010, 46 cases of natalizumab-associated PML had been reported worldwide.⁷ International studies and standardisation of methods are therefore urgently needed to devise strategies to mitigate the risk of PML in natalizumab-treated patients.

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