EDITORIAL

A link between long-term natalizumab dosing in MS and PML

Putting the puzzle together

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When an infectious serious adverse event is linked with a therapy for an underlying disease, it usually is seen in a few weeks or months, not years. This is not the case with the effective monoclonal antibody therapy for patients with multiple sclerosis (MS) natalizumab (Tysabri), the α4 integrin inhibitor preventing inflammatory T cells entering the brain. The infectious adverse event in patients with MS is another demyelinating disease, progressive multifocal leukoencephalopathy (PML), caused by lytic infection of oligodendrocytes with JC virus (JCV), a ubiquitous agent in the population. Although cases of PML are seen in patients with MS after receiving as few as 7 monthly doses, the highest incidence of PML, 1/75 or higher,[1] occurs after 24 monthly doses. Other risk factors for PML in these patients implicate prior exposure to JCV infection evidenced by presence of antiviral antibody as well as previous immunosuppressive treatments.[2]

However, many patients with MS with no natalizumab treatment as well as patients with other underlying diseases with a similar history of immunosuppressive treatment and presence of antiviral antibody have a much lower risk of PML by several orders of magnitude.[3] So the temporal pattern of PML with natalizumab treatment seems unique, making understanding of its mechanism puzzling. Interference with immunosurveillance to JCV in the periphery or in the brain has been suggested but there is little evidence for this and it does not clearly address this temporal relationship.

In a previous article by Meira et al.,[4] a family of transcription factors, POU2AF1/SpiB, was shown to be temporally upregulated by miRNA 126 in CD4+ T cells in natalizumab-treated patients with MS but only after 24 months of dosing. Prompted by this observation, the authors extended their investigation to other immune system cells shown to be affected by natalizumab treatment.

In this issue of *Neurology® Neuroimmunology & Neuroinflammation*, Meira et al.[5] may have put another important piece of this puzzle in place with the observation that natalizumab temporally regulates gene expression in immune system cells that can be targets for JCV infection prior to entry into the brain, notably B cells. Their investigation showed that the same family of transcription factors, POU2AF1, which includes the DNA binding protein SpiB, were upregulated in natalizumab-treated patients with MS over months. POU2AF1 are important regulators for B-cell differentiation. The link to JCV is SpiB with multiple binding sites on the JCV regulatory region that can be active in productive infection in CD34+ hematopoietic precursor and CD19+ B cells.[6] This natalizumab upregulation was increasingly seen over 2 years on B cells and CD8+ T cells, the latter not susceptible due to lack of viral attachment. There was an even greater natalizumab effect in PML vs non-PML patients. This temporal regulation of POU2AF1/SpiB was not seen in patients with MS not treated with natalizumab. What makes these pieces fit even better in the puzzle is that these factors return to untreated patient levels after natalizumab had been discontinued for 8 weeks or longer.

A recent study of alternative natalizumab dosing showed that extended dosing achieved an equal or better clinical effect as the standard monthly dosing. Although not statistically established, there may be a lower risk of PML in the extended dosing cohort compared with the standard dosing cohort.[7]

Can we place these observations together in order to complete this puzzle of the high incidence of PML in long-term natalizumab-treated patients with MS? Taken step by step, perhaps the figure serves the purpose by showing the pathogenesis of PML. PML occurs in patients who have been infected with JCV, indicated by the presence of anti-JCV antibody, and who may harbor a persistent/latent infection in the kidney. JCV is excreted in

See article

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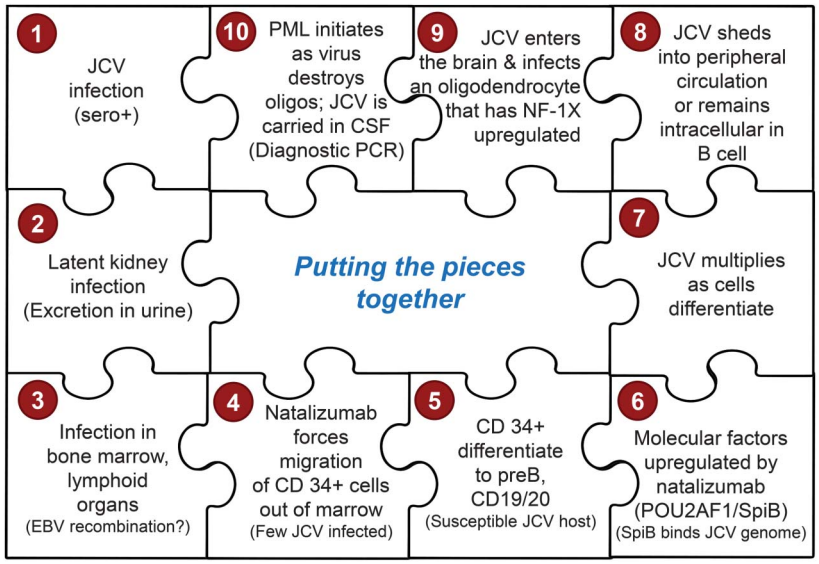
Figure Pathogenesis of progressive multifocal leukoencephalopathy (PML)



Steps 1–3 show initiation of JC virus (JCV) infection, and establish latency in kidney that can become persistent in lymphoid organs, notably the bone marrow, in which the viral regulatory region sequences become rearranged from the nonvirulent to a neurovirulent or PML variant. Steps 4–6 involve the biological effects of natalizumab treatment over time, forcing migration of CD 34+ and pre-B cells into the circulation since it prevents homing of these cells in the marrow due to blocking of binding to cell adhesion molecules. At these steps, natalizumab is associated with temporal gene regulation of a number of factors including those that augment JCV replication that may account for high incidence of PML in patients with multiple sclerosis treated with natalizumab for 24 doses or more. Steps 7–10 show progression of JCV to the brain and establishment of PML. The authors thank David Carter, In Tune Communications, Canada, for assembly of the figure. EBV = Epstein-Barr virus.

the urine as the nonvirulent variant. JCV can escape into the peripheral circulation and, in some individuals, infect lymphoid tissues including the bone marrow. It is perhaps in these compartments that the archetype variant transforms into the virulent PML regulatory region using cellular mechanism of nucleotide rearrangement or perhaps combining with other viral DNAs like Epstein-Barr virus that are also present in such tissues like marrow.[8] Then natalizumab comes into play, forcing migration of CD34+ and pre-B cells into the circulation, another unique biological effect of natalizumab by blocking homing of these cells in the marrow, where SpiB, upregulated by miRNA 126 or other factors attributed to natalizumab with long-term dosing,[5] gives JCV a boost for replication if present in these cells. JCV can be found in the peripheral circulation as free virions or in cell compartments that may enter the brain, finding highly susceptible glial cells and initiating a lytic infection.[9,10]

Based on their data and previous published work, Meira et al. suggest that temporally regulated factors like POU2AF1/SpiB could serve as biomarkers for PML risk. With 10 new PML cases reported per month in patients with MS treated with natalizumab,[2] incorporating such molecular factors to the risk mitigation strategy seems warranted.

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