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Personal Viewpoint

Does risk stratification decrease the risk of natalizumab-associated PML? Where is the evidence?

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Abstract: The use of natalizumab has likely been limited by its association with progressive multifocal leukoencephalopathy (PML), an infection caused by the human polyomavirus John Cunningham (JC). Three factors were recently identified that contribute to the overall risk of natalizumab-associated PML: (1) Positive serostatus for anti-JCV antibodies, (2) prior use of immunosuppressants, and (3) duration of natalizumab therapy. This risk stratification algorithm has not led to a reduction in the incidence of PML in natalizumab-treated patients with multiple sclerosis between April 2010 and February 2014. This observation may appear perplexing, as treatment duration and JCV serostatus are modifiable risk factors. Potential reasons for the lack of success of companion diagnostics that determine the overall risk of natalizumab-associated PML are discussed.

Keywords: Disease-modifying therapies, multiple sclerosis, outcome measurement

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Natalizumab is a very effective therapy for patients with relapsing forms of multiple sclerosis (MS), which was recently approved as a first-line therapy by the Food and Drug Administration (FDA). Its use has likely been limited by its association with progressive multifocal leukoencephalopathy (PML), an infection caused by the human polyomavirus John Cunningham (JC). Currently, more than 400 patients with MS treated with natalizumab have been diagnosed with PML.[1] While PML under natalizumab is not universally fatal, many survivors have serious morbidity and permanent disability.[2] Thus, identification of patients at risk for PML prior to initiation of therapy or during therapy is critical in guiding treatment decisions.

In 2010, preliminary testing with an enzyme-linked immunosorbent assay (ELISA) designed to detect JCV-specific antibodies suggested that JCV seropositive patients with MS have an increased risk of natalizumab-associated PML.[3] Subsequently, three factors were identified that contribute to the overall risk: (1) Positive serostatus for anti-JCV antibodies, (2) prior use of immunosuppressants, and (3) duration of natalizumab therapy, alone or in combination.[4] Patients with MS who are JCV antibody seronegative carry a negligible risk for PML. A more recent study suggests that patients with low JCV antibody titers are at lower risk of developing natalizumab-associated PML than patients with high antibody titers.[5] In January 2012, the FDA approved the clinical use of a revised, more sensitive JCV antibody test. This assay is provided through the manufacturer of natalizumab.

The risk stratification algorithm and the test for JCV serology have provided limited insight into the pathogenesis of natalizumab-associated PML. More importantly, and perhaps surprisingly, it appears that the incidence of PML in natalizumab-treated MS patients between April 2010 and February 2014 has remained essentially unchanged regardless of natalizumab treatment duration.[1] This observation appears perplexing, as treatment duration and JCV serostatus are modifiable risk factors. Presumably, neurologists discuss these risk factors with their patients, and one would expect some impact via risk mitigation. Consequently, eliminating some of those at higher risk (informative censoring) should result in a reduction in the risk of PML. Further increased differential drop-out or weaning from therapy of incident JCV-positive patients and patients who have been treated with natalizumab for a long time should also lower the risk and subsequent rates.

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Given that the sole obvious purpose of these companion diagnostics is the selection of patients with MS for natalizumab therapy based on their own biology, it appears that the risk stratification algorithm may not have been a success. The reason for this failure is unknown. Possible explanations are:

- It is possible that neurologists have difficulties interpreting the risk stratification algorithm. Also, the fact that natalizumab treatment cessation is associated with MS disease reactivation makes the risk assessment of PML versus that or MS quite complex in some instances.[6]
- Any protein detection assay has a defined lower limit of detection, and there are numerous cases of natalizumab-associated PML that had previously tested negative for JCV with the above-mentioned ELISA.[7] Thus, these cases either represent de-novo infections, or the test results were false negative.
- Neurologists may primarily focus on the JCV serostatus when assessing the overall risk of natalizumab-associated PML, and neglect other risk factors. As stated above, prior pharmacological immunosuppression increases PML susceptibility in patients who at the time of natalizumab initiation are JCV-negative, but subsequently seroconvert undetected.
- It may simply be too soon to detect a possible impact of risk stratification due to the fact that a high number of person years of patients on natalizumab treatment is dominated by the first year of exposure, during which potential risk changes are more difficult to detect due to the lower incidence.
- With incident rates in the range of 1–10 per thousand, it theoretically only takes a single case to maintain the current event rates.
- It could be that patients are willing to forego the risks in favor of the drug despite the excess risk

Examining rates by initial JCV-positive and negative status would help clinicians be sure that this risk mitigation strategy is benefiting their patients, and indeed worth the cost.

Conflict of interest

Gary Cutter: Consulting and/or DSMB commitments in past 24 months.
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Apotek, Ascendis, Biogen-Idec, Cleveland Clinic, Glaxo Smith Klein Pharmaceuticals, Gilead Pharmaceuticals, Modigenetech/Prolor, Merck/Ono Pharmaceuticals, Merck, Neuren, PCT Bio, Teva, Vivus, NHLBI (Protocol Review Committee), NINDS, NMSS, NICHD (OPRU oversight committee).
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References

1. Biogen Idec. https://medinfo.biogenidec.com.
2. Clifford DB, De LA, Simpson DM, et al. Natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: Lessons from 28 cases. *Lancet Neurol* 2010; 9: 438–446.
3. Gorelik L, Lerner M, Bixler S, et al. Anti-JC virus antibodies: Implications for PML risk stratification. *Ann Neurol* 2010; 68: 295–303.
4. Bloomgren G, Richman S, Hotermans C, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. *N Engl J Med* 2012; 366: 1870–1880.
5. Plavina T, Bloomgren G, Richman S, et al. Anti-JCV antibody index further defines PML risk in natalizumab-treated MS patients. *27th Annual Meeting of the Consortium of Multiple Sclerosis Centers*, Orlando, FL, 2013.
6. O'Connor PW, Goodman A, Kappos L, et al. Disease activity return during natalizumab treatment interruption in patients with multiple sclerosis. *Neurology* 2011; 76: 1858–1865.
7. Fine AJ, Sorbello A, Kortepeter C, et al. Progressive multifocal leukoencephalopathy after natalizumab discontinuation. *Ann Neurol* 2014; 75: 108–115.