

The risk of PML from natalizumab

The Article by Pei-Ran Ho and colleagues in *The Lancet Neurology*¹ is valuable, but might have been even more clinically useful if further detail had been provided. First, given that the incidence of natalizumab-associated progressive multifocal leukoencephalopathy (PML) is much higher in Europe than in North America,² practitioners on either side of the Atlantic might find regionally stratified Kaplan-Meier curves better suited to informed decision making than the published pooled data.

Second, with regard to the additional stratification of patients without previous exposure to an immunosuppressant, four John Cunningham virus (JCV) index categories, with boundary thresholds of 0.6, 1.0, and 1.7, might be more appropriate than the three-category grouping, with thresholds of 0.9 and 1.5, chosen by Ho and colleagues.¹ The reason being that, in the study in question,³ none of the 68 patients who developed PML had a JCV index of 0.6 or less, compared with 20% of controls.¹ Moreover, patients with a JCV index in the range of 0.9–1.0 carried a risk of PML closer to that of patients in the range of 0.6–0.9 than to those in the range of 1.0–1.5. Patients with an index in the range of 1.5–1.7 had a risk similar to that of those with an index in the range of 1.0–1.5.

Third, for clinicians who view biennial evaluations^{4,5} of natalizumab therapy as sufficient, Kaplan-Meier estimates of the risk of PML during infusions 1–26, 27–52, 53–78, and 79–104 (assuming 13 infusions per year, rather than 12 as reported by Ho and colleagues¹) would be helpful, recognising that analyses in the latter range might need to be restricted to patients without previous immunosuppressant exposure because of limited availability of data.

Fourth, some clarification of the risk among JCV seronegative natalizumab users is warranted. In Ho and colleagues'

study,¹ the figure of 0.07 per 1000 was obtained by dividing the number of false-negative PML cases (one) by the number of seronegative patients in the cohort (13 996),¹ without stating the treatment interval or accounting for incomplete follow-up.

I declare no competing interests.

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- 2 Hunt D, Giovannoni G. Natalizumab-associated progressive multifocal leukoencephalopathy: a practical approach to risk profiling and monitoring. *Pract Neurol* 2012; **12**: 25–35.
- 3 Kuesters G, Plavina T, Lee S, et al. Anti-JC virus (JCV) antibody index differentiates risk of progressive multifocal leukoencephalopathy (PML) in natalizumab-treated multiple sclerosis (MS) patients with no prior immunosuppressant (IS) use: an updated analysis. *Neurology* 2015; **84**: P4.031.
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Authors' reply

We appreciate Bastian Tugemann's interest in our work. In response to the suggestion to use regionally stratified Kaplan-Meier curves, we note two important considerations. First, the smaller sample sizes would reduce the reliability of the risk estimates. Second, regional overall progressive multifocal leukoencephalopathy (PML) risk is influenced by previous immunosuppressant use and anti-John Cunningham virus (JCV) antibody prevalence. Within our study population, patients in the USA had lower rates of previous immunosuppressant use (12% vs 17%) and anti-JCV positivity (57% vs 62%) than patients outside the USA. The Kaplan-Meier curves account for these differences.

Regarding the suggestion that index thresholds of 0.6, 1.0, and 1.7 be used, we note that no PML cases with an index of less than 0.6 were observed in this dataset.¹ Use of these alternative thresholds would produce a risk estimate of zero for patients with an index of less than 0.6, which is probably an underestimate and potentially misleading for health-care providers. We aimed to balance sensitivity and specificity in choosing index cut-offs. A cut-off of 1.7 would provide optimal balance; we chose a cut-off of 1.5 to maintain PML detection sensitivity of more than 90%. These cut-offs have been thoroughly discussed with, and accepted by, numerous experts and regulatory authorities.^{2,3}

With respect to changing the reported infusion epochs, we believe that epochs of 12 infusions are more appropriate to facilitate (at minimum) annual discussions between health-care providers and patients about the risks and benefits of continuing treatment. Regarding follow-up data beyond 6 years (72 infusions), the variability of these risk estimates might become misleading because of small sample size. If the wide confidence intervals are not carefully considered, the data could lead to a perception that risk decreases after 72 months of treatment in patients without previous immunosuppressant use, which we do not believe to be the case.

The single PML case in the anti-JCV antibody-negative population occurred after 56 infusions. The Kaplan-Meier estimate of the cumulative risk in this population is thus zero up to 56 infusions, and 0.3 per 1000 thereafter. The case probably represents a false anti-JCV antibody negative, on the basis of which describing risks before and after 56 infusions seems unwarranted and inappropriate.

Finally, we note that the incidence of PML has been stable since mid-2016. This stabilisation coincides with the introduction of the risk algorithm, which suggests that the