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 colleagues[1]) 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.

Bastian Tugemann
tugemann@mailbox.org

Munich, Germany

1 Ho P-R, Koendgen H, Campbell N, Haddock B, Richman S, Chang I. Risk of natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: a retrospective analysis of data from four clinical studies. *Lancet Neurol* 2017; **16:** 925–33.

2 Hunt D, Giovannoni G. Natalizumab-associated progressive multifocal leucoencephalopathy: 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.

4 Bloomgren G, Richman S, Hotermans C, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy. *N Engl J Med* 2012; **366:** 1870–80.

5 Plavina T, Subramanyam M, Bloomgren G, et al. Anti-JC virus antibody levels in serum or plasma further define risk of natalizumab-associated progressive multifocal leukoencephalopathy. *Ann Neurol* 2014; **76:** 802–12.

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

risk stratification factors are being incorporated into clinical practice and affecting the incidence of PML.

P-RH, NC, and IC are employees of and hold stock or stock options, or both, in Biogen.

*Pei-Ran Ho, Nolan Campbell, Ih Chang
peiran.ho@biogen.com

Biogen, Cambridge, MA 02142, USA

1. Ho P-R, Koendgen H, Campbell N, et al. Risk of natalizumab-associated progressive multifocal leukoencephalopathy in patients with multiple sclerosis: a retrospective analysis of data from four clinical studies. *Lancet Neurol* 2017; **16:** 925–33.
2 Tysabri (natalizumab) summary of product characteristics. Cambridge, MA: Biogen, 2018. https://ec.europa.eu/health/documents/community-register/2018/20180802142037/anx_142037_en.pdf (accessed Jan 22, 2019).
3 Physician information and management guidelines for multiple sclerosis patients on Tysabri therapy. June 24, 2016. https://www.hpra.ie/docs/default-source/3rd-party-documents/tysabri-physician-information-and-management-guidelines-(version-15-27th-april-2016).pdf?sfvrsn=2 (accessed Jan 19, 2019).

Optimal stroke prevention in patients with PFO

We read with interest Bernhard Meier's Comment[1] on the Article by Scott E Kasner and colleagues,[2] suggesting that current recommendations on the treatment of patients with stroke patients and patent foramen ovale (PFO) should be reconsidered. Meier states that "in patients with a stroke and PFO as the presumed cause, PFO closure with a device should be considered first, oral anticoagulation (eg, with rivaroxaban) second (due to the accumulating bleeding risk), and aspirin should not be considered at all".[1]

As members of the editorial committee of the Italian National Guidelines on Stroke, in December 2018, we summarised the available evidence for PFO closure compared with medical treatment, that shows the very low risk of events in the medical group that included patients treated with anticoagulation or antiplatelet therapy (1% per year), and published our rapid recommendations.[3] We recommend percutaneous closure of PFO in highly selected patients with cryptogenic ischaemic stroke or transient ischaemic attack, defined after accurate diagnostic screening. That is, when uncontrolled vascular risk factors are absent, in patients aged younger than 61 years, and in patients with particular anatomical features of PFO (large size or association with aneurysm of the interatrial septum), also taking into account patient preferences. We also published a comment in the same report, to document the risk of atrial fibrillation and draw attention to the need to inform patients of this risk. Atrial fibrillation or flutter after PFO closure occurred in 4·4% of patients in the RESPECT trial, 4·6% of patients in the CLOSE trial, and 6% in the GORE-REDUCE trial.[4]

When considering the strengths and limitations of existing clinical trials to inform the selection of patients for PFO closure, the importance of actively involving patients in the treatment decision and of informing them of the potential risks and benefits of treatment should not be overlooked.

Based on current evidence, we disagree with Meier's statement that aspirin should not be considered.[1] In agreement with the 2018 European consensus paper on the management of patients with PFO,[5] we believe that, when a medical therapy is chosen, the individual risk of bleeding should be weighed against the risk of PFO-related stroke recurrence, in close collaboration with the patient. When the patient has a high haemorrhagic risk, is poorly compliant, or when proper anticoagulant monitoring cannot be guaranteed, or the risk of stroke recurrence is deemed to be low, an antiplatelet therapy should be prescribed.

We declare no competing interests.

*Maurizio Melis, Stefano Ricci, Danilo Toni, on behalf of the editorial committee of the Italian National Guidelines on Stroke
mauriziomelis@aob.it

Neurology and Stroke Unit, Neuroscience and Rehabilitation Department, Azienda Ospedaliera G Brotzu, Cagliari 09134, Italy (MM); Neurology Unit, USL Umbria 1, Città di Castello, Italy (SR); and Neurovascular Treatment Unit, Department of Human Neurosciences, Sapienza University, Rome, Italy (DT)

1 Meier B. Optimal stroke prevention in patients with patent foramen ovale. *Lancet Neurol* 2018; **17:** 597–608.
2 Kasner SE, Swaminathan B, Lavados P, et al. Rivaroxaban or aspirin for patent foramen ovale and embolic stroke of undetermined source: a prespecified subgroup analysis from the NAVIGATE ESUS trial. *Lancet Neurol* 2018; **17:** P1053–60.
3 Raccomandazione Rapida "Ictus criptogenetico e forame ovale pervio". Italian National Guidelines on Stroke. www.iso-spead.it/index.php?azione=contatti (accessed Jan 8, 2019; in Italian).
4 Turc G, Calvet D, MD, et al. Closure, anticoagulation, or antiplatelet therapy for cryptogenic stroke with patent foramen ovale: systematic review of randomized trials, sequential meta-analysis, and new insights from the CLOSE study. *J Am Heart Assoc* 2018; **7:** e008356.
5 Pristipino C, Sievert H, D'Ascenzo F, et al. European position paper on the management of patients with patent foramen ovale. General approach and left circulation thromboembolism. *EuroIntervention* 2018; published online Aug 25. DOI:10.4244/EIJ-D-18-00622.

Primum non nocere: a call for balance when reporting on CTE

As clinicians and researchers in traumatic brain injury and neurodegeneration, we are concerned by the tone of reporting on chronic traumatic encephalopathy (CTE) that has developed over the past decade, highlighted in an article in *The New York Times*.[1] Misleading reporting can have unintended, negative consequences and we call for balance from the medical and scientific communities and the media when communicating on issues related to CTE.

Contrary to common perception, the clinical syndrome of CTE has not yet been fully defined,[2] its prevalence is unknown, and the neuropathological diagnostic criteria are no more than preliminary.[3] We have an incomplete understanding of the extent or distribution of pathology required to