Update on the risk estimates of progressive multifocal leukoencephalopathy related to fingolimod

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Background and objective

- Progressive multifocal leukoencephalopathy is a rare opportunistic infection of the CNS caused by reactivation of a latent JCV, a widespread polyomavirus present at latent stage in healthy individuals
- Progressive multifocal leukoencephalopathy is a serious and potentially fatal complication of some MS disease-modifying therapies[1]
  - Cases of PML have been identified with natalizumab, dimethyl fumarate, fingolimod and ocrelizumab[1,2]
- Precise risk stratification for fingolimod is complicated due to the low number of PML cases, despite the robust clinical experience (by 28 February 2020, >299,600 patients were treated with fingolimod corresponding to >778,900 patient-years of exposure)

Objective **To estimate the global risk of PML in MS patients receiving fingolimod, and to investigate the effect of treatment duration and age on the risk of PML**

CNS, central nervous system; JCV, John Cunningham virus; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy

1. Berger J, et al. *Mult Scler Relat Disord*. 2017;12:59-63. 2. Sul J, et al. *Neurology* 2020;94 (15 Supplement) 4875.

Methods: Estimation of overall PML risk with fingolimod

- The Novartis safety database was searched using the search term ‘Infections (progressive multifocal leukoencephalopathy [PML]) with a data cut-off 28 February 2020
- Potential PML cases were reviewed by an independent PML adjudication committee of expert clinicians familiar with PML diagnosis
- The number of confirmed PML cases attributed to fingolimod was assessed in relation to the estimated total number of fingolimod-treated patients and patient-years of exposure

PML, progressive multifocal leukoencephalopathy

Methods: PML risk by treatment duration

- Fingolimod commercial drug exposure within each year of treatment (0–1, 1–2, 2–3, 3–4, 4–5, 5–6, 6–7, 7–8) was calculated from the average of the estimated number of patients at risk at the beginning and at the end of each period, the estimated total number of patients exposed to fingolimod, and estimates of the treatment discontinuation pattern
  - The annual exposure in periods corresponding to Years 6, 7, 8, and beyond was combined due to small numbers of reported PML cases over that period
- The incidence of PML in each period was estimated by dividing the number of PML cases attributed to fingolimod in that period with the corresponding exposure to fingolimod

PML, progressive multifocal leukoencephalopathy

Methods: PML risk by age at treatment initiation

- Five age groups were constructed to contain equal estimated numbers of treated patients
- PML cases attributed to fingolimod were categorized into these corresponding exposure quintiles

- To calculate the reporting incidence in each category, the number of PML cases attributed to fingolimod in that category was combined with the corresponding estimated number of patients receiving fingolimod

PML, progressive multifocal leukoencephalopathy

PML cases reported in MS patients while on fingolimod treatment

Total estimated exposure
(Feb 28, 2020)

>299,600 patients
>778,900 patient years

[a]Total exposure includes both commercial and clinical trial exposure

188
suspected PML cases reported and evaluated

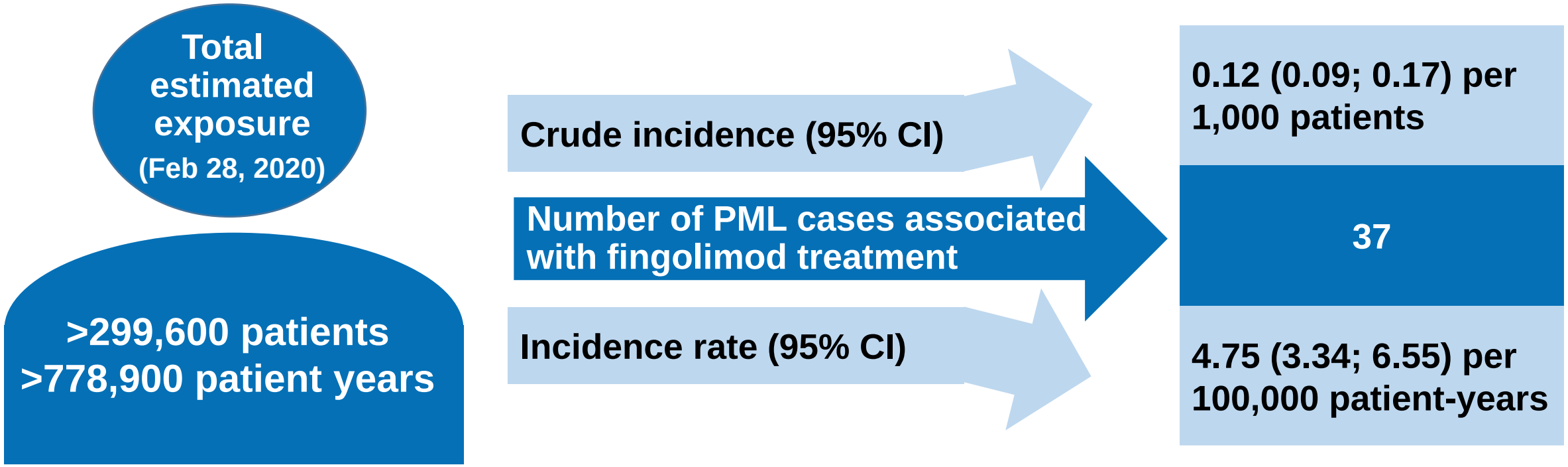
17 cases were attributed to previous natalizumab treatment

37 cases were associated with fingolimod treatment

134 cases were not confirmed as PML based on reported information

MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy

PML cases associated with fingolimod: Risk estimates



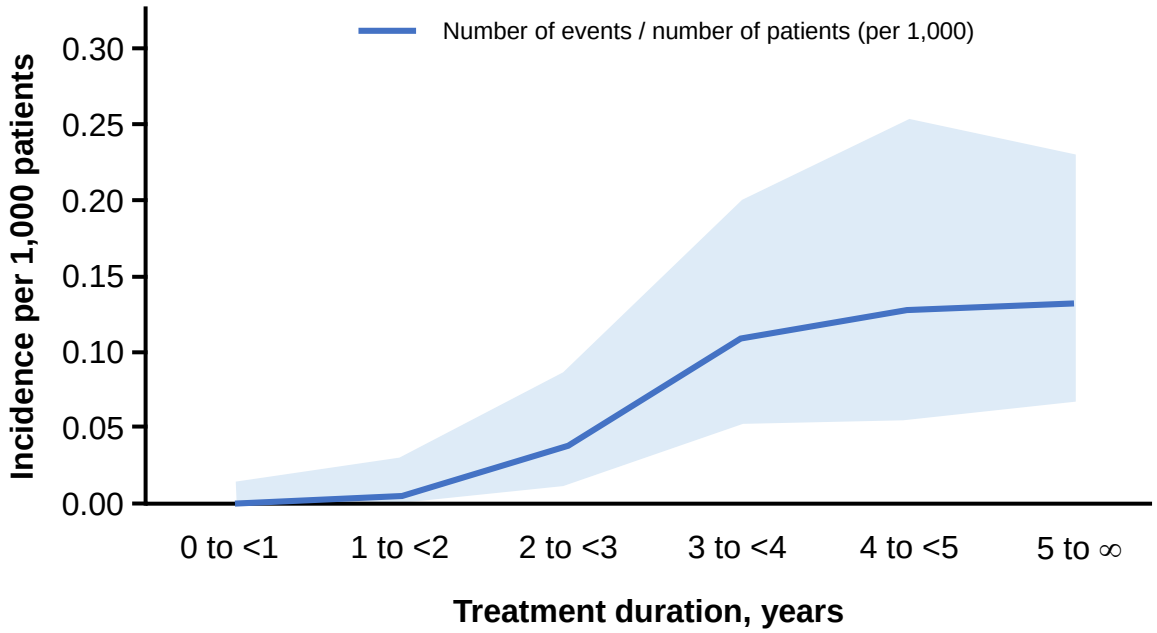
[a]Total exposure includes both commercial and clinical trial exposure

PML, progressive multifocal leukoencephalopathy

Incidence of adjudicated PML by treatment duration

- The incidence of PML appears to increase with treatment duration
  - Approached a plateau during Year 5 at ~0.13/1,000 patients with a wide confidence interval
  - Beyond Year 5 data were scarce
- The exact pattern of the relationship to duration of treatment is unclear
- The precision of incidence estimates was low due to the small number of cases

Incidence of PML per 1,000 patients by treatment duration



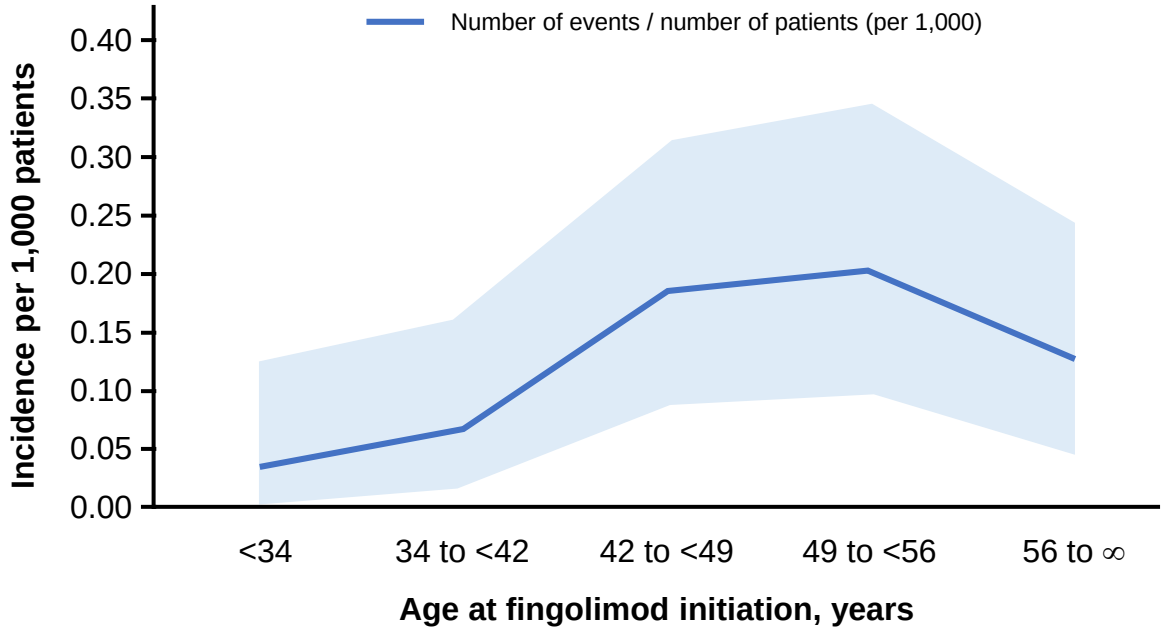
Shaded area represents 95% confidence intervals

PML, progressive multifocal leukoencephalopathy

Incidence of adjudicated PML by age at fingolimod initiation

- Incidence appears to increase between 30 and 50 years of age and then stabilize or possibly decrease
- The precision of the incidence estimates was low due to the small number of cases
- The exact shape of the relationship with age is tentative due to wide confidence intervals, uncertainties around underlying assumptions, and other unknown confounding factors

Incidence of PML per 1,000 patients by age at fingolimod initiation



Shaded area represents 95% confidence intervals

PML, progressive multifocal leukoencephalopathy

Conclusions

- The estimated PML risk associated with fingolimod:
  - Incidence 0.12 per 1,000 patients
  - Incidence rate of 4.75 per 100,000 patient-years
- This risk remains low compared with natalizumab (4.17/1000 patients[1])
- Fingolimod-associated PML risk appears to increase with cumulative exposure, however the precise pattern of this relationship remains uncertain due to the low number of PML cases despite robust patient exposure
- The estimated PML risk may increase with age from treatment initiation, although the exact pattern of this possible relationship is uncertain due to the overall low number of PML cases resulting in wide confidence intervals, as well as other unknown possible confounding factors

PML, progressive multifocal leukoencephalopathy

1. TYSABRI® (natalizumab) Safety Update. October, 2018.

Thank you