Updated Incidence of Natalizumab-Associated Progressive Multifocal Leukoencephalopathy and Its Relationship with the Pattern of Natalizumab Exposure over Time

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Discussion

- The overall incidence of natalizumab-associated progressive multifocal leukoencephalopathy (PML) has been stable since mid-2016.
  - This stabilisation has coincided with the introduction of new PML risk estimates,[1,2] suggesting that risk stratification factors are being incorporated into clinical practice and may continue to influence future PML incidence.
  - These data confirm and extend previous assessments of changes in PML incidence as of December 2017[3] with an additional 21 months of data.
- Over the past 4 years, the number of patients treated for longer durations (>36 infusions) has increased,[3] while PML incidence in higher-exposure epochs (37–48, 49–60, and 61–72 infusions) has decreased.
  - Increases in the number of patients with longer exposures is expected over time, corresponding to the time natalizumab has been available as a treatment option.
- The decrease in PML incidence within each exposure epoch over time suggests that other risk factors (anti–JC virus [JCV] antibodies and prior immunosuppressant use) may be decreasing in the natalizumab-treated population, which is consistent with physicians' utilization of risk stratification in their clinical practices.
  - A limitation of this analysis is that risk factor information for anti-JCV antibodies and prior immunosuppressant use is not included.
- Taken together, these results underscore the importance of PML risk stratification as part of the patient management guidelines for natalizumab.

Introduction

- Natalizumab is a highly efficacious therapy for the treatment of multiple sclerosis (MS).
- Treatment with natalizumab is associated with an increased risk of developing PML, an opportunistic infection of the central nervous system caused by JCV.[5,6]
- Three known risk factors for developing natalizumab-associated PML are the presence of anti-JCV antibodies, prior immunosuppressant (IS) use, and longer treatment duration, especially beyond 2 years.[5]
- Following validation of an anti-JCV antibody test for use in PML risk stratification,[7,8] the first risk estimates of natalizumab-associated PML risk were published in 2012.[5]
- Updated risk estimates, which incorporated use of the anti-JCV antibody index, and associated patient management guidelines became available in 2016.[1,2]
- Understanding how natalizumab-associated PML incidence may have changed over time following risk stratification is of interest to clinicians and patients.

Objectives

- To update assessments of the incidence of natalizumab-associated PML in the global postmarketing setting since the introduction of the anti-JCV antibody assay and changes in PML incidence stratified by natalizumab exposure over time.

Methods

- The incidence of confirmed PML cases in Biogen's global safety database from November 2009 to September 2019 was evaluated retrospectively.
- Overall incidence in all exposed patients was determined using the estimated total number of patients ever exposed to natalizumab and the number of PML cases.
- Changes in natalizumab-associated PML incidence over time were evaluated in epochs of 12 infusions.
  - The evaluation period started in 2011, before risk stratification had been introduced but at a point at which patient numbers were sufficient to allow robust analyses.
- As individual-level data for anti-JCV antibody status and history of prior IS use are often not available in the postmarketing setting, this analysis focused on overall PML incidence and exposure (within postmarketing data).

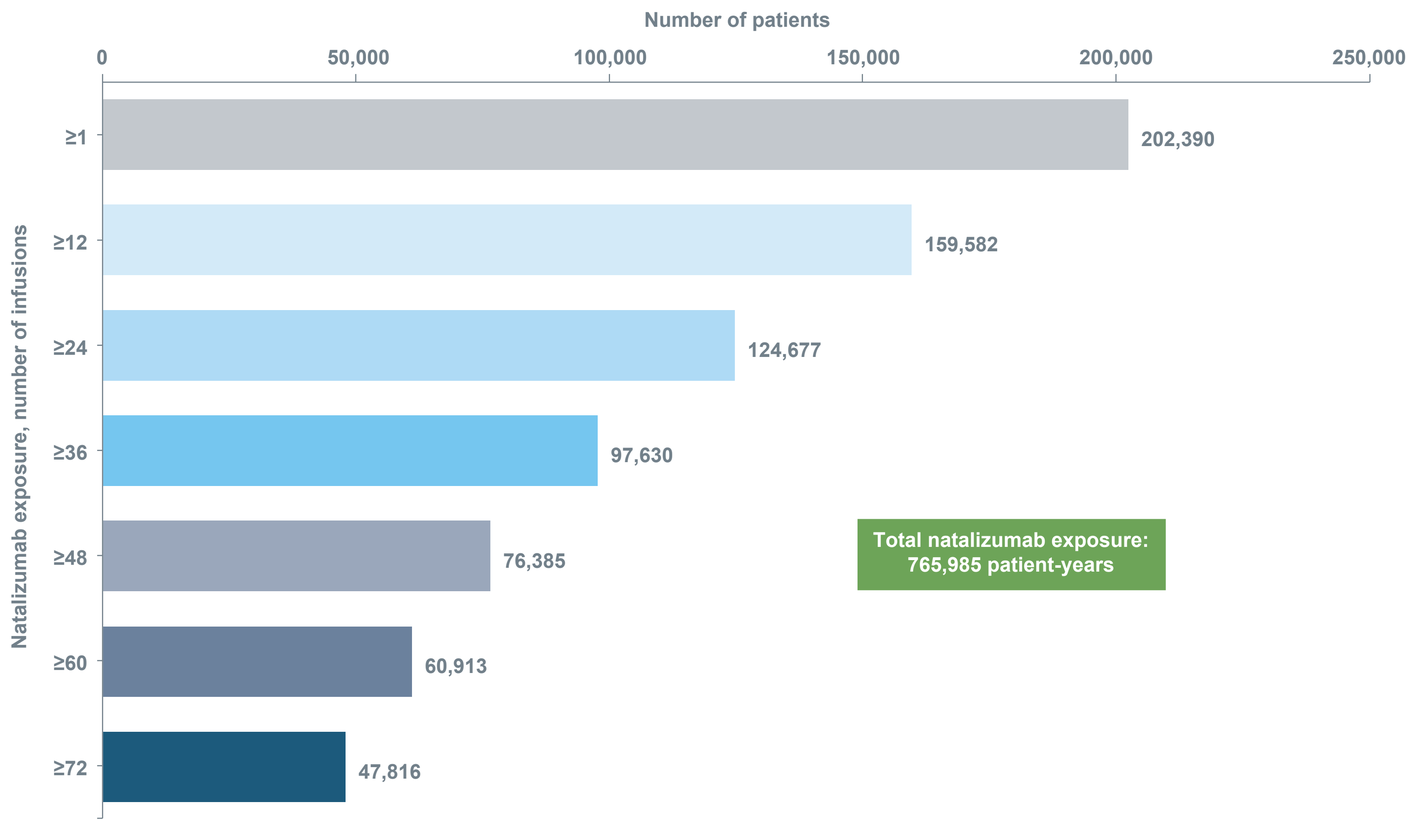
Results

- Between November 2004 and August 2019, 202,390 patients worldwide received ≥1 natalizumab dose (total exposure: 765,985 patient-years) (Figure 1).
- As of September 2019, the overall incidence of natalizumab-associated PML was 4.08 per 1000 patients.
- The increase in the global incidence of PML levelled off in April 2016, remaining between 4.08 and 4.24 per 1000 patients since that time (Figure 2).
- PML incidence was greatest in patients in the higher-risk exposure epochs (37–48, 49–60, and 61–72 infusions) (Figure 3).
  - Incidence in these higher-risk exposure epochs was highest in 2012–2014 and has been decreasing since 2015.

Literature

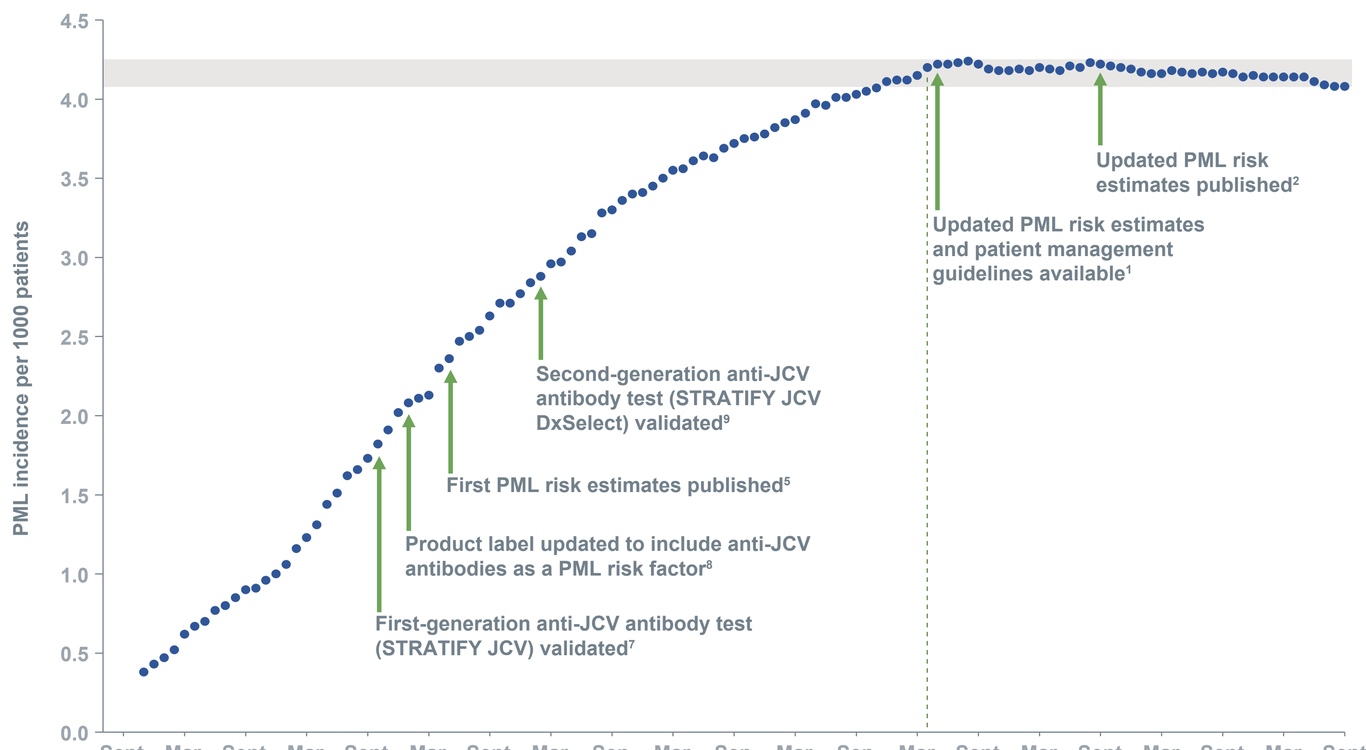
- The results of this analysis extend previous work showing that the greatest increase in PML incidence occurred between 2009 and 2013.[10]
- Previous analyses of PML incidence data demonstrated greater increases in the numbers of patients in higher-risk exposure epochs (37–48, 49–60, and 61–72 infusions) from December 2011 to December 2013 than in later time periods (December 2013–December 2015 and December 2015–December 2017).[3] This relative increase may have been a key contributor to the increasing PML incidence seen during that time.

Figure 1. Worldwide cumulative natalizumab exposure in the postmarketing setting and in postapproval MS clinical trials of natalizumab (through 31 August 2019)



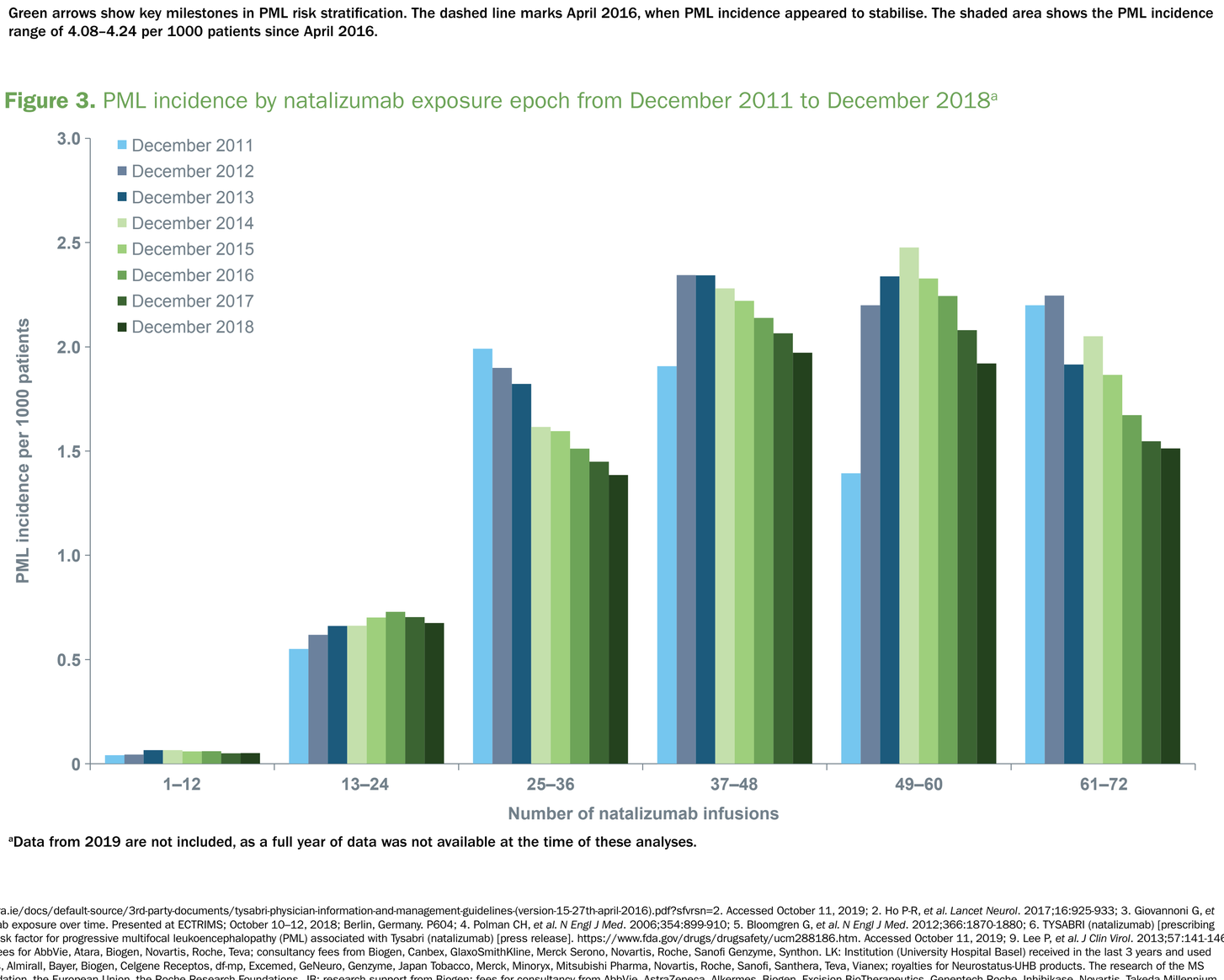
Less than 2% of patients exposed in the postapproval setting were treated in a clinical trial setting. Exposures are estimates and may not fully reflect treatment interruptions that occurred in certain patients.

Figure 2. PML incidence among natalizumab-treated patients from November 2009 to September 2019



Green arrows show key milestones in PML risk stratification. The dashed line marks April 2016, when PML incidence appeared to stabilise. The shaded area shows the PML incidence range of 4.08–4.24 per 1000 patients since April 2016.

Figure 3. PML incidence by natalizumab exposure epoch from December 2011 to December 2018[a]



[a]Data from 2019 are not included, as a full year of data was not available at the time of these analyses.

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