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. High-risk exposure epochs are defined as periods of 12 infusions or greater treatment duration (37–48, 49–60, and 61–72 infusions). The number of patients with high-risk exposure epochs (37–48, 49–60, and 61–72 infusions) has increased over time, and the number of patients with longer exposures is expected to continue to increase. This increase may have been a key contributor to the increase in the number of patients with longer exposures is expected to over time, corresponding to the time natalizumab has been available as a treatment option.

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 when a sufficient number of patients were available for analysis. As individual-level data for anti-JCV antibody status and history of prior JCV use are 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 leveled off in April 2016, remaining between 4.08 and 4.24 per 1000 patients since that time (Figure 2). The increase in the number of patients with higher-risk exposure epochs (37–49, 40–60, and 61–72 infusions) has increased over time, and has been decreasing since 2015. The update of the natalizumab product label to include an anti-JCV antibody test (STRATIFY JCV assay) in October 2013 has coincided with a stabilisation of overall PML incidence. The introduction of risk estimates for PML stratification in the global postmarketing setting since the introduction of the first-generation anti-JCV antibody test, followed by the introduction of a second-generation test in 2016, has coincided with a stabilisation of overall PML incidence since 2015.

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, 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 with an additional 25 months of data.
• Over the past 4 years, the number of patients treated for longer durations (>36 infusions) has increased, while PML incidence in higher-exposure epochs (37–49, 49–60, and 61–72 infusions) has decreased.
• The number of patients with longer exposures is expected to increase 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-JCV virus [JCV] antibodies and prior immunosuppressant use) may be decreasing in the natalizumab-exposed population, which is consistent with physicians’ management 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.

Literature

The results of this analysis extend previous work showing that the greatest increase in PML incidence occurred between 2009 and 2013.3,4 Previous analyses of PML incidence data demonstrated greater increases in the numbers of patients in higher-risk exposure epochs (37–49, 40–60, and 61–72 infusions) from December 2011 to December 2013 than in later time periods (December 2013–December 2015 and December 2015–December 2017). This relative increase may have been a key contributor to the increasing PML incidence seen during that time.