FULL-LENGTH ARTICLE NPub.org/r3qvxm

Risk of natalizumab-associated PML in patients with MS is reduced with extended interval dosing

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Study objective and summary result

This study compared natalizumab extended-interval dosing (EID) and natalizumab standard-interval dosing (SID) in terms of the risk of progressive multifocal leukoencephalopathy (PML) in patients with multiple sclerosis (MS), and found that EID is associated with a lower risk of PML.

Classification of evidence

Class III.

What is known and what this paper adds

PML is a potential adverse event in patients with MS who receive natalizumab, and past investigations have identified relevant variables, including treatment duration, prior use of immunosuppressants, and presence of anti–JC virus (JCV) antibodies. This investigation suggests that the dosing schedule is also relevant to the risk of PML.

Participants and setting

The investigators analyzed data from 35,521 anti-JCV antibody-positive patients. Data through June 1, 2017, were obtained from the Tysabri Outreach: Unified Commitment to Health (TOUCH) database and the Tysabri Global Safety Database.

Design, size, and duration

The investigators accessed the TOUCH database to obtain data concerning demographics, the dates and doses of natalizumab injections, and histories of treatment with immunomodulatory/immunosuppressant therapies. The study analysis plan was prespecified prior to accessing PML event data from the Tysabri Global Safety Database. Since the specific practice of EID varies, the investigators conducted 3 separate analyses involving different definitions of EID and SID: the primary analysis assessed the PML risk associated with the last 18 months of infusion history; the secondary analysis assessed the PML risk associated with any prolonged period of EID in the patient's infusion history; and the tertiary analysis assessed the effect of a dosing history consisting primarily of EID on PML risk. Cox regression models were used to compare EID and SID in terms of PML risk, adjusting for age, sex, prior immunosuppressants, time since natalizumab initiation, and cumulative number of infusions.

Table PML risk in EID cohort vs SID cohort in the primary and secondary analyses

Analysis	Covariate-adjusted hazard ratio (95% confidence interval) for PML in the EID group vs the SID group
Primary	0.06 (0.01–0.22)
Secondary	0.12 (0.05–0.29)

Primary outcome measure

Difference in PML risk between EID and SID.

Main results and the role of chance

The mean average dosing periods were 36.7, 35.0, and 43.0 days for the primary, secondary, and tertiary analyses, respectively, for the EID cohorts and 30.0, 29.8, and 30.5 days for the primary, secondary, and tertiary analyses, respectively, for the SID cohorts. EID was associated with reduced likelihood of PML in the primary (94% relative risk reduction) and secondary (88% relative risk reduction) analyses ($p < 0.001$) when compared with SID. No PML cases were identified in the EID group in the tertiary analysis, and the Cox regression model 95% confidence interval was nonestimable.

Bias, confounding, and other reasons for caution

This investigation may have been subject to selection bias.

Generalizability to other populations

This investigation's large sample size favors the generalizability of the results.

Study funding/potential competing interests

This study was funded by Biogen. Some authors report receiving lecture honoraria, consulting fees, committee appointments, and funding from various healthcare companies, including Biogen; being employees of Biogen and Sanofi; owning Biogen stock; serving on NIH committees; and receiving funding from the Consortium of MS Centers. Dr. Cutter is the president of Pythagoras, a private consulting firm. Go to Neurology.org/N for full disclosures.

A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.