Natalizumab Extended Interval Dosing Is Associated with a Reduction in Progressive Multifocal Leukoencephalopathy Risk in the TOUCH® Registry

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Conclusions

- This study demonstrates that extended interval dosing (EID), as defined here, is associated with a clinically and statistically significant lower risk of progressive multifocal leukoencephalopathy (PML) than standard interval dosing (SID) in anti–JC virus (JCV) antibody positive patients.
- Most EID patients switched from SID to EID after >2 years of treatment, the average dosing interval (ADI) was 35–43 days for EID versus 30–31 days for SID, and patients with any gap in treatment of >12 weeks were excluded.
- As the TOUCH® Prescribing Program does not collect effectiveness data, additional prospective studies are needed to establish whether the effectiveness of natalizumab is maintained with EID.

Introduction

- Natalizumab, which is approved for the treatment of relapsing forms of multiple sclerosis at the dose of 300 mg given intravenously every 4 weeks, is associated with a risk of PML.[1]
- Infusion of natalizumab every 5–8 weeks (EID) has been explored with the aim of reducing PML risk while maintaining efficacy. However, prior studies on the impact of this practice on PML risk have been inconclusive.[2]
- The TOUCH Prescribing Program, a mandatory US Risk Evaluation and Mitigation Strategy (REMS),[1] represents the largest potential data source on PML risk in patients on EID.

Objective

- To determine whether EID was associated with reduced PML risk compared with SID in the TOUCH registry.

Methods

Patients

- TOUCH Prescribing Program data as of June 1, 2017, were used for this analysis.
- This analysis included only patients who were anti–JCV antibody positive.
- Patients with any dosing interval >12 weeks or <3 weeks were excluded.

Dosing interval definitions

- SID and EID were defined and the statistical analysis plan was finalized under conditions blinded to PML events.
- Analyses used 3 definitions of SID and EID (Figure 1) based on average dosing intervals (ADIs) of ≥3 to <5 weeks for SID and >5 to ≤12 weeks for EID.

Statistical analysis

- PML risk in the EID and SID groups was estimated using the life-table method and Kaplan-Meier (KM) estimates.
- Hazards of PML in the EID and SID cohorts were compared using Cox regression models (adjusted for age, sex, prior immunosuppressant use, initiation calendar year, and number of infusions).

Results

Patients

- The numbers of patients included in each analysis population are shown in Figure 2.
- Baseline demographics were well balanced across dosing groups (Table 1).

Natalizumab exposure

- The number of natalizumab infusions and total duration of natalizumab treatment were higher in the EID groups than in the SID groups with all 3 definitions (Table 1).
- Prior to meeting EID criteria, most EID patients received SID treatment for >2 years. (As assessed by the secondary definition, in which each infusion was defined as SID or EID, patients received a mean of 32.0 infusions and a median [range] of 25 [1–121] infusions before starting EID.)

PML risk

- In the first 4 years of treatment, only 1 PML case was observed for EID (with the secondary definition). In years 5 and 6, PML risk was substantially lower for EID than for SID across all 3 definitions (Table 2; data for the tertiary definition are not shown, as no EID PML cases were observed).
- Cox regression analysis revealed a 94% reduction in PML risk with EID versus SID in the primary analysis and an 88% reduction in risk in the secondary analysis (both $P<0.0001$; Figure 3A–B).
  - Regression analyses could not be performed for the tertiary definition, as there were no EID PML cases observed.
- This finding is supported by KM analyses, which demonstrate significantly lower cumulative risk of PML for EID patients than for SID patients with each definition (Figure 3A–C).

Limitations

- Data on anti-JCV antibody index are not captured in TOUCH and therefore could not be included as a covariate in the Cox regression analysis.
- The definitions of EID may have potential biases:
  - Bias that could lead to more PML cases in the EID cohorts: EID patients had in general received more doses than SID patients.
  - Bias that could lead to fewer PML cases in the EID cohorts: there may have been a selection bias, as these might be patients treated longer without developing PML before subsequently being placed on EID.
- TOUCH does not include effectiveness data; therefore, the relative effectiveness of EID and SID were not compared.

Figure 1. Definitions utilized in EID analysis

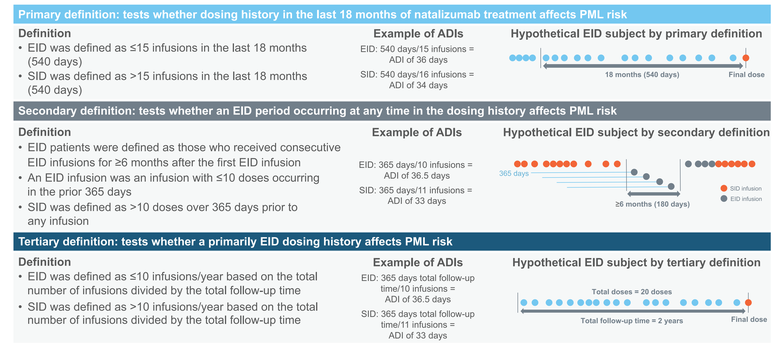
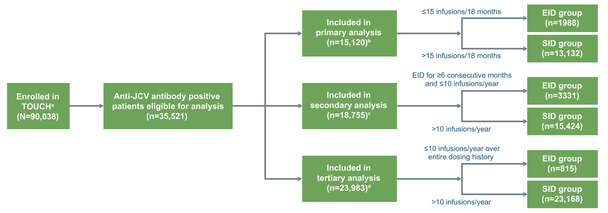


Figure 2. Patient flow diagram for primary, secondary, and tertiary definitions



[a]Patients enrolled as of June 1, 2017.
[b]A total of 20,401 patients were excluded from the primary analysis because they had <18 months of data available (n=9540) or ≥1 dosing gap (defined as an interval >12 weeks between 2 consecutive infusions) or overdose (defined as an interval <3 weeks between 2 consecutive infusions) (n=10,861).
[c]A total of 16,766 patients were excluded from the secondary analysis because they did not meet the EID or SID definitions (n=4320), they had ≥1 dosing gap or overdose (n=11,051), or they had switched between SID and EID more than once (n=1395).
[d]A total of 11,538 patients were excluded from the tertiary analysis because they had ≥1 dosing gap or overdose.

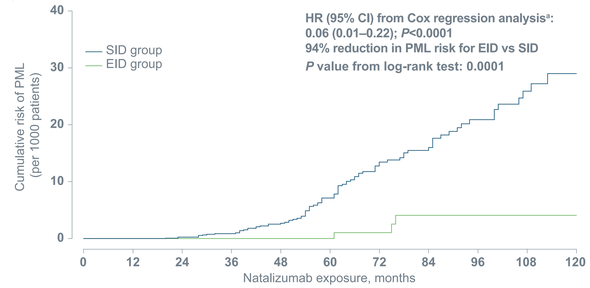
Table 2. PML incidence rate per 1000 patients (no. of PML cases per adjusted number of patients at risk) in anti-JCV antibody positive patients without prior IS use for the primary and secondary definitions[a]

Natalizumab exposure (no. of doses)[b]	Primary definition		Secondary definition	
	EID group	SID group	EID group	SID group
1–12	0.00 (0/1806)	0.00 (0/11,890)	0.00 (0/2980)	0.00 (0/13,049)
13–24	0.00 (0/1659)	0.28 (3/10,907)	0.00 (0/2722)	0.60 (6/9921)
25–36	0.00 (0/1366)	0.46 (4/8608)	0.44 (1/2292)	0.46 (3/6514)
37–48	0.00 (0/1080)	2.02 (13/6439)	0.00 (0/1841)	2.58 (12/4650)
49–60	1.23 (1/810)	3.96 (19/4801)	1.45 (2/1380)	4.14 (14/3385)
61–72	1.70 (1/589)	4.46 (15/3363)	2.04 (2/980)	4.74 (11/2323)

[a]Based on the life-table method. The sample size for patients with prior IS use was insufficient for interpretation; the adjusted number of patients at risk was 95 for the EID group and 689 in the SID group for the primary definition and 171 for the EID group and 747 for the SID group for the secondary definition. The tertiary definition is not shown, as no PML cases were observed with EID using this definition.
[b]Data beyond 6 years are not shown.

Figure 3. KM estimates of the cumulative probabilities of PML in EID versus SID groups according to primary, secondary, and tertiary definitions

A. Primary definition



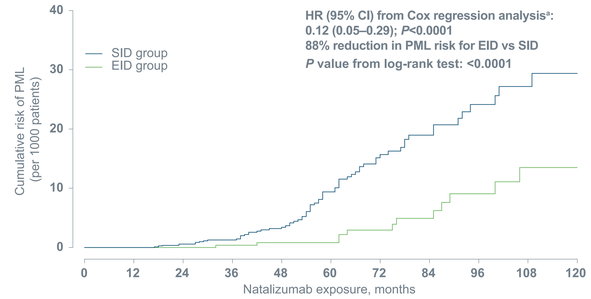
Number of patients at risk[b]

SID group	13,132	13,132	10,596	7850	5989	4236	2775	1823	1205	734	296
EID group	1988	1988	1817	1502	1225	958	700	515	374	247	113

Cumulative number of PML cases[c]

SID group	0	0	3	9	22	45	68	74	82	87	89
EID group	0	0	0	0	0	0	1	3	3	3	3

B. Secondary definition



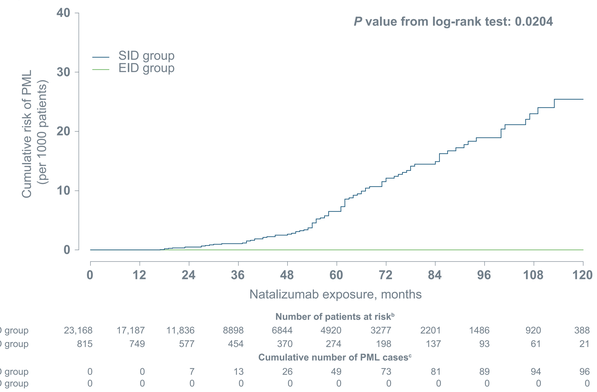
Number of patients at risk[b]

SID group	15,424	13,104	8083	5629	4134	2829	1756	1117	718	440	172
EID group	3331	3285	2949	2463	1990	1494	1063	756	535	342	145

Cumulative number of PML cases[c]

SID group	0	0	6	11	22	43	58	63	68	70	71
EID group	0	0	0	1	2	2	5	7	10	12	12

C. Tertiary definition[d]



Number of patients at risk[b]

SID group	23,168	17,187	11,836	8898	6844	4920	3277	2201	1486	920	388
EID group	815	749	577	454	370	274	198	137	93	61	21

Cumulative number of PML cases[c]

SID group	0	0	7	13	26	49	73	81	89	94	96
EID group	0	0	0	0	0	0	0	0	0	0	0

[a]EID vs SID. Model includes age, gender, prior use of immunosuppressants, EID/SID group, and calendar year at the start of natalizumab treatment as covariates. [b]Number of patients who were still in the study and did not have PML at the end of the specified time. [c]Cumulative number of PML cases at the end of the specified time. [d]Because no PML events were observed in the EID group for the tertiary definition, the Cox regression analysis cannot be performed.

Table 1. Baseline characteristics, natalizumab exposure, and ADIs across the 3 definitions

Characteristic	Primary definition		Secondary definition		Tertiary definition	
	EID group (N=1988)	SID group (N=13,132)	EID group (N=3331)	SID group (N=15,424)	EID group (N=815)	SID group (N=23,168)
Females, n (%)[a]	1376 (69)	8846 (67)	2293 (69)	10,239 (66)	539 (66)	15,636 (67)
Mean age at first infusion (SD), years	42.9 (11.3)	44.0 (11.0)	43.0 (11.2)	43.9 (11.4)	42.0 (11.4)	43.9 (11.6)
Prior immunosuppressant therapy, n (%)[b]	95 (5)	689 (5)	175 (5)	799 (5)	49 (6)	1310 (6)
Median number of natalizumab infusions (min, max)	50.0 (11, 132)	46.0 (17, 142)	51.0 (6, 137)	27.0 (7, 142)	32.0 (2, 103)	26.0 (1, 142)
Median duration of natalizumab treatment (min, max), months	59.0 (19, 130)	44.0 (19, 131)	56.0 (8, 131)	26.0 (7, 130)	43.0 (3, 129)	25.0 (1, 131)
ADI, days						
Mean (SD)	36.7 (4.9)	30.0 (1.6)	35.0 (4.9)	29.8 (1.7)	43.0 (5.4)	30.5 (2.6)
Q1, Q3	33, 39	29, 31	32, 37	29, 31	39, 45	29, 31

Q1=25th quartile; Q3=75th quartile; SD=standard deviation. [a]Information on patient sex was missing for <1% patients in each group. [b]Information on prior immunosuppressant (IS) therapy was missing for 4%–5% patients in each group.

References 1. TYSABRI® (natalizumab) [prescribing information]. Cambridge, MA: Biogen; 2017; 2. Zhovtis Ryerson L, et al. *J Neurol Neurosurg Psychiatry*. 2016;87:885-889. **Disclosures** These analyses were funded by Biogen. LZR: personal compensation from Biogen, Teva for speaker and advisory board activities; research support from Biogen; JF: personal compensation and compensation for consulting activities from Biogen, Genentech, Genzyme, Teva; NC, IC, ER, ZR, BY, CH, P-RH: employees of and own stock and/or stock options in Biogen; IK: has served on advisory boards of Biogen, Genentech; RM: stock in Biogen; GC: has served on data and safety monitoring boards for AMO Pharmaceuticals, Apotek, Horizon Pharmaceuticals, Modigenetech/Protor, Merck, Merck/Pfizer, Opko Biologics, Neurim, Reata Pharmaceuticals, Receptos/Celgene, Sanofi, Teva Pharmaceuticals, NRLBI (Protocol Review Committee), NICHD (OPRU oversight committee); compensation for consulting or advisory boards from Argenix, Atara Biotherapeutics, Bioeq GmBH, Consortium of MS Centers (grant), Genzyme, Genentech, Innate Therapeutics, Klein-Buendel Inc., Medimmune, MedDay, Novartis, Opexa Therapeutics, Roche, Savara Inc., Somahlution, Teva Pharmaceuticals, TG Therapeutics, Transparency Life Sciences; president of Pythagoras, Inc., a private consulting company; XL, JG: nothing to disclose. **Acknowledgments** All named authors meet the International Committee of Medical Journal Editors criteria for authorship for this presentation and take responsibility for the integrity of the work as a whole. Biogen provided funding for editorial support in the development of this presentation; Mary Goodsell and Alison Adams, PhD, of Ashfield Healthcare Communications (Middletown, CT, USA) wrote the first draft of the presentation based on input from authors and revised subsequent drafts, and Joshua Safran of Ashfield Healthcare Communications copyedited and styled the presentation per congress requirements. Biogen reviewed and provided feedback on the presentation to the authors. The authors had full editorial control of the presentation and provided their final approval of all content.