Progressive Multifocal Leukoencephalopathy Occurring with Extended Interval Dosing of Natalizumab: Analysis of Cases in the TOUCH® Database

5698

Foley J,[1] Zhovtis Ryerson L,[2] Chang I,[3] Kister I,[2] Cutter G,[4] Metzger R,[1] Goldberg JD,[5] Li X,[5] Riddle E,[3] Kasliwal R,[3] Ren Z,[3] Hotermans C,[3] Ho PR,[3] Campbell N[3]

[1]Rocky Mountain MS Clinic, Salt Lake City, UT; [2]Department of Neurology, NYU Langone Health, New York University, New York, NY; [3]Biogen, Cambridge, MA; [4]University of Alabama School of Public Health, Birmingham, AL; [5]New York University School of Medicine, New York, NY

Conclusions

- While natalizumab extended interval dosing (EID) is associated with a significantly lower risk of progressive multifocal leukoencephalopathy (PML) than standard interval dosing (SID), it does not completely eliminate the risk of PML; 3 of 1988 and 12 of 3331 EID patients had PML in the primary and secondary analyses, respectively.
- EID PML patients had elevated known risk factors for PML,[1,2] including longer natalizumab treatment duration, higher rates of prior immunosuppressant (IS) use, and predominantly higher anti–JC virus (JCV) antibody index values than the overall EID group and SID PML patients.
  - This observation reinforces the importance of the known PML risk factors and suggests that individualized consideration of these risk factors remains important in the context of EID.
- Under both the primary and secondary definitions of EID, dosing intervals for the EID PML cases were shorter than for the overall EID cohorts, suggesting that lower PML risk might be observed in patients with either longer dosing intervals or a higher proportion of EID than SID during their overall treatment period.
- These conclusions are limited by missing anti-JCV antibody index values and a lack of statistical comparisons due to limited numbers of cases.

Introduction

- A recent analysis of multiple sclerosis (MS) patient data in the TOUCH registry and the TYSABRI® Global Safety Database demonstrated that EID is associated with a clinically and statistically significant lower risk of PML than SID in anti-JCV antibody positive patients receiving natalizumab.[3]
- In that analysis, PML risk was assessed under 3 definitions of EID (Figure 1):
  - The *primary definition* assessed the impact of EID versus SID in the previous 18 months of recorded infusion history on PML risk.
  - The *secondary definition* assessed the impact of any prolonged period of EID dosing in the patient's infusion history on PML risk.
  - The *tertiary definition* assessed the impact of an overall dosing history consisting primarily of EID dosing on PML risk.
- EID under the primary and secondary definitions resulted in 94% and 88% reductions in PML risk, respectively (Figure 2).
  - No cases of PML were observed under the tertiary definition.
- In the primary and secondary EID definition cohorts, 13 PML cases were observed.

Objective

- To describe the demographic, infusion history, and risk factor profiles of patients who developed PML on natalizumab EID in comparison with those who did not develop PML.

Methods

- All patients in these analyses were anti-JCV antibody positive.
- Demographics, treatment history, and covariates of interest (sex, age, anti-JCV antibody index, total natalizumab exposure, prior IS use, duration of MS, and average dosing interval [ADI]) in the EID PML cases and in all EID patients were assessed using summary statistics.

Results

EID PML cases

- Overall, 1988 patients met the primary definition and 3331 met the secondary definition of EID.
  - Of the 13 PML cases identified in an EID group in this analysis, 3 met the primary definition and 12 met the secondary definition of EID, with 2 cases meeting both definitions (Figure 3).
  - Of the 12 PML cases that met the secondary definition of EID (EID at any point in treatment history), 8 had switched back to treatment consistent with SID prior to the PML event (Figure 3).

Natalizumab exposure

- The EID PML cases under the primary and secondary definitions had greater natalizumab exposure than the corresponding overall EID cohort (Table 1).
  - For all natalizumab infusions, the median dosing interval was numerically shorter for the EID PML cases than for the overall EID groups (primary definition: 33.7 vs 35.5 days; secondary definition: 31.6 vs 33.5 days).
  - The EID PML cases had numerically longer total natalizumab duration than the overall EID groups (median duration under primary definition: 74 vs 59 months; median duration under secondary definition: 74.5 vs 56 months).
  - The EID PML cases had also received numerically more total natalizumab infusions than the overall EID groups (median doses under primary definition: 68 vs 50; median doses under secondary definition: 68 vs 51).
  - The EID PML cases had numerically more natalizumab infusions than the overall EID groups prior to the defining final 18 months under the primary definition (median infusions: 54 vs 37) and prior to switching from SID to EID under the secondary definition (median infusions: 40.5 vs 25).

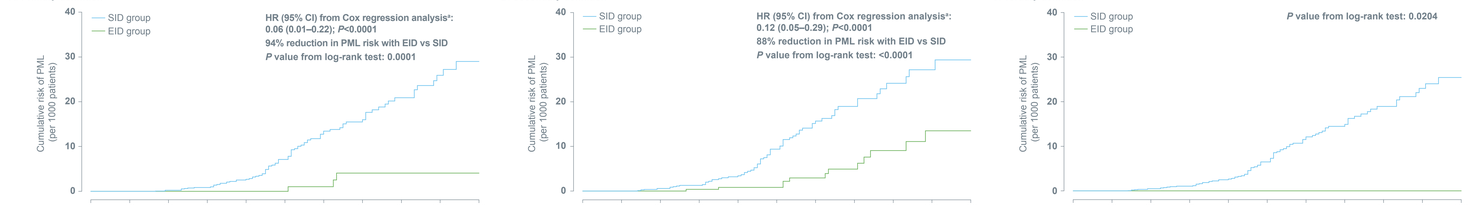
Prior IS use and anti-JCV antibody index*

- Anti-JCV antibody index data from the 6–12 months prior to PML diagnosis were available for 7 cases (mean value: 2.92); all but 1 of these had index values ≥1.5 (Figure 3).
- The proportion of patients with prior IS use was numerically higher in the primary and secondary EID PML cases than in the corresponding overall EID cohorts (33% vs 5% under the primary definition; 17% vs 5% under the secondary definition; Table 1).

Outcomes

- Of the 13 EID PML patients, 5 (30%) were deceased at the time of this analysis (Figure 3).

Figure 2. Kaplan-Meier estimates of the cumulative probabilities of PML in the EID group versus the SID group according to the (A) primary, (B) secondary, and (C) tertiary definitions of EID[3]



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

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

Number of patients at risk[b]

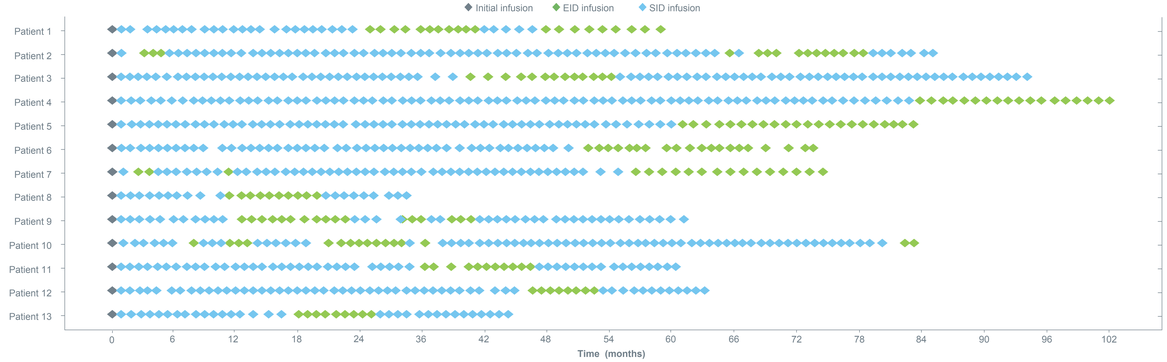
SID group	23,168	17,187	11,836	8898	6844	4920	3277	2201	1486	920	388
EID group	815	749	577	454	370	274	198	137	93	61	21

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

CI=confidence interval; HR=hazard ratio.
[a]EID vs SID. Model includes age, sex, prior IS use, 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.

Figure 3. Dosing and risk factor information for individual EID PML cases



	EID definition(s) met	Anti-JVC antibody index	Prior IS use (y/n)	Outcome
Patient 1	1	2.06	N	Alive
Patient 2	2	4.66	N	Alive
Patient 3	2	3.32	N	Alive
Patient 4	2[a]	3.16	N	Alive
Patient 5	2[a]	2.42	N	Deceased
Patient 6	1, 2	NA	N	Alive
Patient 7	1, 2	NA	Y	Alive
Patient 8	2	3.72	N	Deceased
Patient 9	2	NA	N	Alive
Patient 10	2	1.07	N	Deceased
Patient 11	2	NA	N	Alive
Patient 12	2	NA	N	Deceased
Patient 13	2	NA	Y	Deceased

NA=not available.
[a]Patient did not meet primary definition of EID due to receiving ≥16 doses in the final 18 months.

Figure 1. Primary, secondary, and tertiary definitions of EID employed in the TOUCH analysis[3]

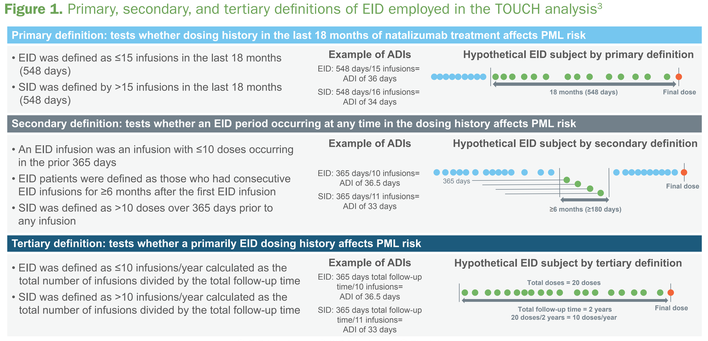


Table 1. Characteristics of patients in EID and SID groups by EID definition

	Primary definition				Secondary definition			
	EID		SID		EID		SID	
Patient characteristic	PML cases (n=3)	All patients (n=1988)	PML cases (n=90)	All patients (n=13,132)	PML cases (n=12)	All patients (n=3331)	PML cases (n=72)	All patients (n=15,424)
Female, %	100	69	66	67	67	69	65	66
Age at first infusion, mean (SD), years	32.3 (4.0)	42.9 (11.3)	44.5 (10.3)	44.0 (11.0)	43.1 (11.0)	43.0 (11.2)	43.4 (10.3)	43.9 (11.4)
Prior IS use, %	33	5	16	5	17	5	15	5
Time between infusions, median (Q1, Q3), days	33.7 (33.3, 35.6)	35.5 (33.3, 38.8)	29.7 (28.7, 30.6)	29.7 (28.8, 30.8)	31.6 (30.9, 32.4)	33.5 (31.7, 36.9)	29.3 (28.6, 30.2)	29.4 (28.7, 30.5)
Total number of infusions, median (Q1, Q3)	68 (50, 68)	50 (31, 75.5)	60 (47, 73)	46 (28, 70)	68 (58, 83)	51 (31, 75)	58 (42, 70)	27 (17, 53)
Total duration of natalizumab treatment, median (Q1, Q3), months	74 (58, 75)	59 (37, 87)	58.5 (47, 71)	44 (27, 68)	74.5 (59.5, 85)	56 (36, 81)	54 (40.5, 66)	26 (16, 51)
Number of natalizumab infusions before the defining EID treatment period, median (Q1, Q3)	54 (37, 55)	37 (18, 63)	NA	NA	40.5 (19, 56.5)	25 (13, 44)	NA	NA

NA=not applicable; Q1=quartile 1; Q3=quartile 3; SD=standard deviation.

*Information on prior IS use was available for all patients; anti-JCV antibody index values were available for 7 of 13 patients.

References 1. Bloomgren G *et al. N Engl J Med.* 2012;366:1870-1880; 2. Ho P-R *et al. Lancet Neurol.* 2017;16:925-933; 3. Zhovtis Ryerson J, *et al.* Presented at ACTRIMS; February 1–3, 2018; San Diego, CA. LB250. **Disclosures** This study was funded by Biogen. JF: personal compensation and compensation for consulting activities from Biogen, Genentech, Genzyme, Teva. LZR: personal compensation from Biogen, Teva for speaker and advisory board activities; research support from Biogen. IC, ER, ZR, CH, P-RH, NC: employees of and own stock and/or stock options in Biogen. IK: has served on advisory boards of Biogen, Genentech. RM: holds stock in Biogen. GC: has served on data and safety monitoring boards for AMO Pharmaceuticals, Apotek, Horizon Pharmaceuticals, Modigenetech/Prolor, Merck, Merck/Pfizer, Opko Biologics, Neurim, Reata, Receptos/Celgene, Sanofi, Teva, NHLBI (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, Medimmune, MedDay, Novartis, Opexa Therapeutics, Roche, Savara, Somahlution, Teva, TG Therapeutics, Transparency Life Sciences; president of Pythagoras, a private consulting company. JDG, XL: nothing to disclose. **Acknowledgments** All named authors meet the International Committee of Medical Journal Editors criteria for authorship for this poster and take responsibility for the integrity of the work as a whole. Biogen provided funding for editorial support in the development of this poster; John Watson, PhD, of Ashfield Healthcare Communications (Middletown, CT) wrote the first draft of the poster based on input from authors, and Joshua Safran of Ashfield Healthcare Communications copyedited and styled the poster per congress requirements. Biogen reviewed and provided feedback on the poster to the authors. The authors had full editorial control of the poster and provided their final approval of all content.