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Risk Stratification for Progressive Multifocal Leukoencephalopathy (PML) in MS Patients: Role of Prior Immunosuppressant Use, Natalizumab-Treatment Duration, and Anti-JCV Antibody Status

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INTRODUCTION

- Natalizumab (TYSABRI®), indicated to treat relapsing remitting multiple sclerosis (MS) and moderate-to-severe Crohn's disease, has been administered to more than 78,800 patients worldwide as of December 2010, corresponding to more than 135,200 patient-years of experience.
- Natalizumab has demonstrated efficacy in relapsing MS in both clinical trial and practice settings.
  - Independent of baseline disease activity, natalizumab decreased sustained disability progression by 42%–64% and annualized relapse rates by 68%–81%.[1,2]
  - Thirty-seven percent of natalizumab patients compared with 7% of placebo patients were free of disease activity (clinical relapses, 12-week sustained disability progression, and new radiological lesions) at 2 years, respectively ($P<0.0001$).[3]
- Natalizumab is also associated with an increased risk of progressive multifocal leukoencephalopathy (PML), an opportunistic brain infection resulting from exposure to JC virus (JCV) and a complex interaction between other host immune and genetic factors.[4,5]
  - As of March 4, 2011, 102 cases of PML have been confirmed worldwide, and the overall incidence of PML in the postmarketing setting remains generally consistent with the original estimate from clinical trials: 1 case in 1000 treated patients (95% confidence interval [CI]: 0.2, 2.8).[6]
- Established risk factors for PML include natalizumab treatment duration (especially >2 years) and immunosuppressant (IS) therapy prior to initiation of natalizumab treatment.[7,8]
- Anti-JCV antibody serostatus, which is a marker of exposure to JCV, is currently being investigated as a potential additional, independent PML risk factor.
  - Recently, a unique, 2-step, JC virus-like particle (VLP)-based enzyme-linked immunosorbent assay (ELISA) detected anti-JCV antibodies in approximately 50%–60% of natalizumab-treated MS patients across different geographies, and in 100% of PML patients in whom pre-PML serum samples were available prior to clinical diagnosis of PML.[9–12]

OBJECTIVE

- This analysis was conducted to quantify, for the first time, PML risk in natalizumab-treated MS patients using a combination of 2 established risk factors, duration of natalizumab exposure and prior IS therapy, in addition to anti-JCV antibody serostatus.

METHODS

Patients, Samples, and Data Collection

- Because of the infrequent occurrence of PML, data on natalizumab-treated PML patients were collected from several sources including postmarketing and clinical trial data. The analysis was conducted using currently available data as of March 4, 2011.
  - Prior IS data were not available for all patients exposed to natalizumab; therefore, the proportion of patients with prior IS use in the TYSABRI® Global Observational Program in Safety (as of November 23, 2010) was used for analyses.
  - Anti-JCV antibody prevalence in the general MS population was based on baseline data from patients in ongoing or completed clinical studies (AFFIRM[2], STRATIFY-1, TYGRIS-US, and an independent MS registry in Sweden[13]).
  - Available serum and plasma samples collected prior to PML diagnosis were used for anti-JCV antibody testing to assess the clinical utility of the assay as a risk stratification tool.

Identification of Natalizumab Treatment Duration and Prior IS Use as Independent Risk Factors for PML

- PML incidence was calculated as a function of both the cumulative and 12-month intervals of natalizumab exposure on the basis of 102 confirmed PML cases (as of March 4, 2011).
- IS treatment history of natalizumab-treated MS patients who developed PML in the postmarketing setting was obtained from the natalizumab global safety database and compared with the data obtained from TYGRIS as of November 23, 2010.

Identification of Anti-JCV Antibody Status as a Potential Tool for PML Risk Stratification

- The overall prevalence of anti-JCV antibodies in the general MS population was determined using the analytically validated ELISA as previously described.[12]
- The prevalence of anti-JCV antibodies in MS patients with PML from whom pre-PML serum or plasma samples were available prior to diagnosis was also determined using this assay and compared with the overall prevalence in the general MS population.

Estimation of PML Incidence by Anti-JCV Antibody Status

- The incidence of PML in anti-JCV antibody positive and negative patients was estimated using the overall natalizumab-associated PML incidence, the anti-JCV antibody prevalence in the general MS population, and the number of MS patients that developed PML with pre-PML samples that were tested for anti-JCV antibody status.
- A sensitivity analysis was performed to estimate the incidence of PML in anti-JCV antibody negative patients and to show the relative risk between anti-JCV antibody negative and anti-JCV antibody positive patients.

Quantification of PML Risk: Natalizumab Treatment Duration, Prior IS Use, and Anti-JCV Antibody Status

- Risk-factor algorithms were developed to quantify the estimated risk of PML in patients with and without established risk factors for natalizumab-associated PML (>2 years [yes or no] of natalizumab treatment duration and prior IS use [yes or no]) and anti-JCV antibody serostatus.

RESULTS

Identification of Natalizumab Treatment Duration as a Risk Factor for PML

- Natalizumab-associated PML risk based on 102 postmarketing PML cases is presented by treatment duration (Figure 1A) and 12-month treatment interval (Figure 1B).
- Overall, the greatest PML incidence occurred after 2 years of therapy, with 2.41 per 1000 patients treated according to cumulative duration (Figure 1A) and in the third year of treatment (25–36 natalizumab infusions) with 1.68 cases per 1000 patients (Figure 1B) according to 12-month treatment intervals.
- Assessment of risk at 4 years or beyond of natalizumab treatment duration is limited, as the numbers of patients in this cohort are too small to draw clinically meaningful conclusions at this time.

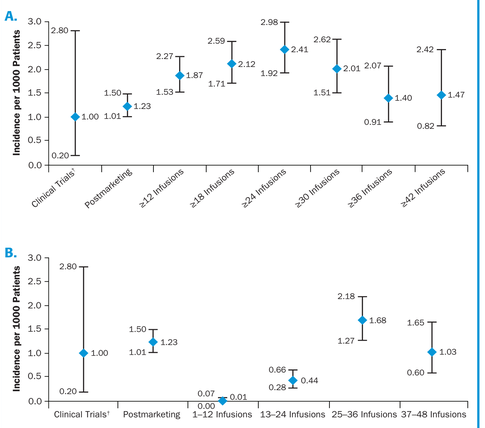
Identification of Prior IS Use as a Risk Factor for PML

- Prior IS use in PML patients was more common compared with prior IS use observed in the overall MS patient population receiving natalizumab.
  - Forty-five percent of natalizumab-treated PML patients had received one or more IS therapies prior to initiating treatment with natalizumab, compared with 20.3% in natalizumab-treated MS patients from the TYGRIS cohort.
  - The most common IS therapies previously used by patients from the TYGRIS cohort and natalizumab-treated patients who developed PML were mitoxantrone, methotrexate, cyclophosphamide, azathioprine, and mycophenolate.
  - There was no specific pattern evident in the type of IS used, duration of use, or washout period between discontinuation of IS use and start of natalizumab treatment.
- On the basis of these data, patients who have previously been treated with an IS have an approximately 4-fold higher risk of PML compared with patients who have never been treated with an IS.

Two-Factor Algorithm Using Established PML Risk Factors

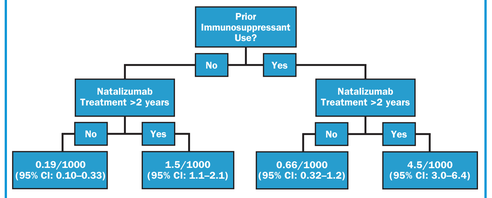
- A 2-factor algorithm estimating the PML incidence associated with the presence of prior IS use and duration of natalizumab use (≤2 or >2 years) was generated using the above data and identified 4 patient subgroups (Figure 2) including:
  - One subgroup with a lower risk (0.19 per 1000 patients);
  - Two subgroups with an incidence similar to that observed across the overall population;
  - One subgroup at greater risk (4.5 per 1000 patients) with both established risk factors.
- Patients at greatest risk for developing PML were those who received IS therapy prior to initiating natalizumab (irrespective of the type and duration of IS) and who were treated with natalizumab >2 years.

FIGURE 1. Natalizumab-Associated PML Incidence* by (A) Cumulative Treatment Duration and (B) 12-month Interval Treatment Duration



For (A) and (B): the clinical trial rate is based on patients who received a mean of 17.9 monthly doses of natalizumab.
*The incidence for each time period was calculated as the number of PML cases divided by the number of patients exposed to natalizumab.
†Reference 6.

FIGURE 2. Approximate Incidence of PML Stratified by Prior Immunosuppressant Use and Natalizumab Treatment Duration



As of November 2, 2010, 32 of 71 confirmed postmarketing PML cases had previous IS exposure (IS status was unknown in 4 patients).

Anti-JCV Antibody Status

- A total of 5896 patients were tested at baseline from AFFIRM (N=823), TYGRIS-US (N=1480), STRATIFY-1 (N=1096), and the Swedish MS Registry (N=2497).
- Anti-JCV antibody prevalence was 54.6% (95% CI: 51.1%–58.0%) in AFFIRM, 47.6% (95% CI: 45.0%–50.1%) in TYGRIS-US, 56.0% (95% CI: 53.0%–59.0%) in STRATIFY-1, and 59.0% (95% CI: 57.0%–60.9%) in the Swedish MS Registry with an overall prevalence of approximately 55% (95% CI: 54%–56%).
- Anti-JCV antibody status was determined in 25 natalizumab-treated MS patients who developed PML, where serum samples were available 6.5–187 months prior to PML diagnosis.
  - The characteristics of these 25 PML patients were comparable to the overall global population of natalizumab-treated PML patients, suggesting that there was no sampling bias (data not shown).
  - All pre-PML samples from the 25 (100%) PML patients tested positive for anti-JCV antibodies.
- Based on current overall PML incidence of 1.23 cases per 1000 patients, it was estimated that these 25 patients came from an overall population of approximately 20,276 patients receiving natalizumab (Table 1).
  - Assuming that 55% of these 20,276 patients were anti-JCV antibody positive (ie, 11,152 patients), the incidence of PML in patients who were anti-JCV antibody positive was estimated to be 2.24 cases per 1000 patients treated.
  - The incidence of PML in anti-JCV antibody negative patients could not be fully ascertained since no PML case has tested anti-JCV antibody negative; however, a sensitivity analysis, conservatively assuming 1 hypothetical PML case in an anti-JCV antibody negative patient, demonstrated at least a 20-fold lower PML incidence (0.11 per 1000 patients) in anti-JCV antibody negative patients compared with anti-JCV antibody positive patients.
- The estimated incidence of PML was significantly lower in natalizumab-treated patients who were anti-JCV antibody negative versus natalizumab-treated patients who were anti-JCV antibody positive ($P<0.0001$).

TABLE 1. Estimated Incidence of PML by Anti-JCV Antibody Status on the Basis of 25 Cases of PML That Were Anti-JCV Antibody Positive Prior to the Diagnosis of PML

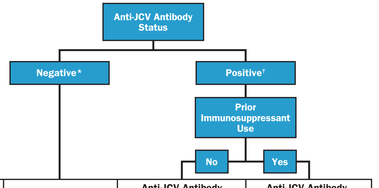
	Number of PML Patients	Total Patients Treated	Incidence per 1000 Patients (95% CI)
Analysis Based Upon Current Data with No Anti-JCV Antibody Negative PML Patients			
Anti-JCV antibody positive	25	11,152	2.24 (1.45, 3.31)
Anti-JCV antibody negative	0	9,124	0 (0, 0.40)
Total	25	20,276	1.23 (0.80, 1.82)
P value[a]		<0.0001	
RR (95% CI[b])		∞ (6.44, ∞)	
Sensitivity Analysis Based Upon Hypothetical Assumption of 1 Anti-JCV Antibody Negative PML Patient			
Anti-JCV antibody positive	25	11,598	2.16 (1.40, 3.18)
Anti-JCV antibody negative	1	9,489	0.11 (0.00, 0.59)
Total	26	21,087	1.23 (0.81, 1.81)
P value[a]		<0.0001	
RR (95% CI[b])		20.5 (3.35, 842)	

[a]1-sided Fisher's exact *P* value comparing estimated incidence of PML in patients tested anti-JCV antibody positive to the incidence in antibody negative patients.
[b]2-sided exact 95% CI of estimated relative risk (RR) based on binomial distribution.

Quantification of PML Risk: Natalizumab Treatment Duration, Prior IS Use, and Anti-JCV Antibody Status

- Patients who were anti-JCV antibody negative represented the lowest risk subgroup in the PML risk stratification algorithm, with an estimated risk of ≤0.11 per 1000 (95% CI: 0–0.59), as determined by the sensitivity analysis (Figure 3).
- Patients at greatest risk of developing PML were those who were treated with natalizumab for >2 years, who received IS therapy prior to natalizumab, and who were anti-JCV antibody positive (8.1 per 1000, 95% CI: 5.4–11.6).
- For patients who were anti-JCV antibody positive and had no prior IS use, irrespective of natalizumab treatment duration, PML risk was consistent with risk in the overall natalizumab-treated population (Figure 1A and 1B).

FIGURE 3. Approximate Incidence of PML Stratified by Natalizumab Treatment Duration, Prior Immunosuppressant Use, and Serum Anti-JCV Antibody Status



Natalizumab Exposure	Anti-JCV Antibody Negative	Anti-JCV Antibody Positive with No Prior Immunosuppressant Use	Anti-JCV Antibody Positive with Prior Immunosuppressant Use
0–2 Years	≤0.11/1000 (95% CI: 0–0.59)	0.35/1000 (95% CI: 0.19–0.60)	1.2/1000 (95% CI: 0.58–2.2)
>2 Years		2.8/1000 (95% CI: 2.0–3.8)	8.1/1000 (95% CI: 5.4–11.6)

*Estimate based on all anti-JCV antibody negative patients receiving at least 1 dose of natalizumab and 1 hypothetical PML case that was anti-JCV antibody negative at the time of PML diagnosis.
†PML incidence in anti-JCV antibody positive patients was calculated on the basis of the following assumptions: 55% of natalizumab-treated MS patients were anti-JCV antibody positive, the proportion of natalizumab-treated patients with prior IS use was 20% based on TYGRIS data, and 100% of confirmed cases of PML were anti-JCV antibody positive prior to the onset and diagnosis of PML.

CONCLUSIONS

- PML risk in natalizumab-treated MS patients can be quantified and stratified by natalizumab treatment duration and prior IS use.
- These results suggest that PML risk may also be stratified by anti-JCV antibody status.
- The clinical utility of anti-JCV antibody testing is currently being evaluated in the STRATIFY clinical trials.
  - According to current data, patients with all 3 risk factors (ie, anti-JCV antibody positive AND prior IS use AND >2 years of natalizumab treatment) are at the greatest risk for developing PML. Assessment of benefit-risk may be most important in this subgroup of patients.
  - Patients who are anti-JCV antibody negative may be at significantly lower risk for developing PML.
- Further research to identify additional host and viral factors that contribute to or predict PML development will build upon the current risk stratification algorithms to help enable clinicians and patients in making more well-informed benefit-risk therapy decisions.

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Disclosures

AS, CH, SR, AN, SL, TP, GB, MS, CB: employees of Biogen Idec.

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