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Anti-JCV antibody index further defines PML risk in natalizumab-treated MS patients

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INTRODUCTION

- In the phase 3 AFFIRM trial, natalizumab (Tysabri®, Biogen Idec) significantly reduced annualized relapse rate and the risk of sustained disability progression over 2 years compared with placebo.[1]
- The occurrence of progressive multifocal leukoencephalopathy (PML) necessitates an understanding of relative risk for informed benefit-risk evaluation and treatment decisions.
- The presence of anti-JC virus (JCV) antibodies is a risk factor for PML development in natalizumab-treated patients.[2]
  - Detection of anti-JCV antibodies has reliably predicted PML risk and affirmed the low risk of PML in anti-JCV antibody negative patients.[3]
  - As of May 6, 2013, 147 PML cases had ≥1 sample tested at least 6 months prior to PML diagnosis; 145 of 147 (99%) tested anti-JCV antibody positive prior to PML.[3]
- Results from a large prospective study, STRATIFY-2, validated the lower risk of PML in anti-JCV antibody negative patients with an estimate of 1 per 10,000 patients.[4]
- Recently, 3 European studies based on 2–9 natalizumab-treated MS patients who developed PML have reported higher anti-JCV antibody levels in patients who developed PML compared with those who did not develop PML.[5-7]
- We evaluated whether anti-JCV antibody levels may further define PML risk along with other known risk factors in anti-JCV antibody positive patients.

OBJECTIVES

- To examine the association between anti-JCV antibody index and PML risk in anti-JCV antibody positive natalizumab-treated patients.
- To explore PML risk estimates based on different anti-JCV antibody index thresholds in anti-JCV antibody positive patients.
- To explore longitudinal stability of anti-JCV antibody index-based results for patients who maintained or changed serological status over time, including pre-PML analyses performed in patients who developed PML.

METHODS

- Anti-JCV antibody status and anti-JCV antibody index were determined using the second-generation anti-JCV antibody assay STRATIFY JCV DxSelect™ (Focus Diagnostics, Cypress, California).
  - Index is the sample optical density (OD) value normalized to an assay calibrator. Index is a corollary to antibody titer, which is derived by serially diluting the sample.
- Anti-JCV antibody index data were collected from anti-JCV antibody positive patients enrolled in natalizumab clinical studies and from postmarketing data.
- To assess the association of anti-JCV antibody index with PML risk, data from 1039 non-PML patients from 2 natalizumab clinical studies, AFFIRM and STRATIFY-1, and 45 pre-PML patients from clinical trials (excluding STRATIFY-2) and postmarketing sources as of September 2012 were evaluated (test data set).[1,4,8]
  - Findings were validated using anti-JCV antibody index data from 1483 non-PML patients (from baseline) and 26 pre-PML patients from STRATIFY-2 (validation data set).[4]
  - For both data sets, pre-PML samples were collected at least 6 months prior to PML diagnosis.
- The predicted probabilities of PML and non-PML patients above and below index thresholds ranging from 0.7 to 1.5 were calculated using all available longitudinal data (total samples = 5547) from the combined test and validation data sets.
- The probabilities were then applied to the numerators and denominators of anti-JCV antibody positive patients in the current PML risk stratification algorithm (from September 2012) to provide index-based PML risk estimates.

Longitudinal stability of anti-JCV antibody index

- Using combined data from AFFIRM and STRATIFY-1 collected every 6 months over a period of 18 months, the longitudinal stability of index at various thresholds was examined for patients who maintained or changed serostatus from anti-JCV antibody negative at baseline to positive using the following categories:
  - Ever high: ≥1 sample above index threshold;
  - Consistently high: ≥2 consecutive samples above index threshold.

Statistical analysis

Association of index and PML

- For patients with more than 1 available index sample, the lowest index was used.
- *P* values were calculated using a Wilcoxon rank-sum test.
- A cross-sectional analysis was performed to assess potential relationships between anti-JCV antibody index and current PML risk factors (prior immunosuppressant [IS] use and natalizumab treatment duration ≤24 vs >24 months).

Distribution of PML and non-PML by index threshold and PML risk

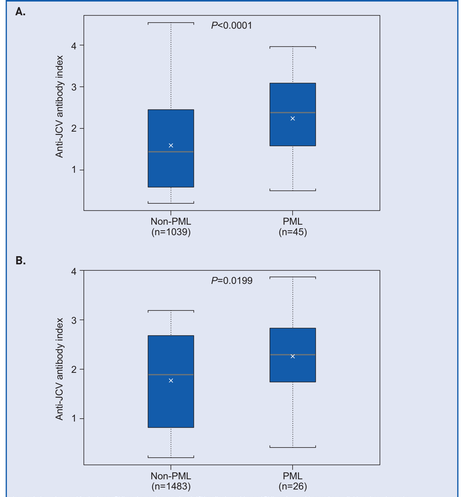
- A repeated measures analysis was used to estimate predicted probabilities, odds ratios (ORs), and *P* values from generalized estimating equations with a logit link. An exchangeable correlation structure was assumed.

RESULTS

Anti-JCV antibody index and PML

- The median anti-JCV antibody index value was significantly higher in PML patients at least 6 months prior to PML diagnosis compared with non-PML patients for the test data set (*P*<0.0001; Figure 1A).
  - Results of the association between anti-JCV antibody index and PML for the validation data set confirmed the findings of the test data set (*P*=0.0199; Figure 1B).

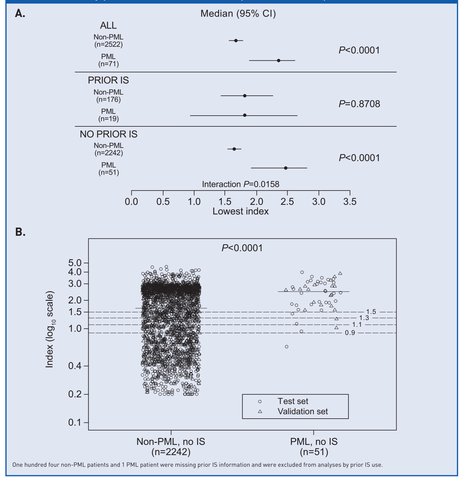
Figure 1: Anti-JCV antibody index in non-PML and PML patients for (A) test data set and (B) validation data set



Lowest index value used for both non-PML patients who tested anti-JCV antibody positive and PML patients with samples available at least 6 months prior to PML diagnosis, as of September 2012.
In the validation data set, optical densities above 3.0 that were used to calculate anti-JCV antibody index were reported as 3.0 by the testing laboratory.
Box represents interquartile range; gray horizontal line=median, horizontal bars=range, x=mean.

- No association was shown between anti-JCV antibody index and duration of natalizumab treatment (*P*=0.39) or prior IS use (*P*=0.51) in the combined population of PML and non-PML patients (data not shown).
- When the test and validation data sets were combined and stratified by prior IS use, a different relationship between anti-JCV antibody index and PML risk was observed (Figure 2A).
  - For patients with no prior IS use, the median anti-JCV antibody index was significantly higher in PML patients compared with non-PML patients (*P*<0.0001).
  - In patients with prior IS use, there was no difference in anti-JCV antibody index distribution between PML and non-PML patients (*P*=0.87).
- Subsequent analyses of anti-JCV antibody index and PML risk were limited to patients with no prior IS use for the following reasons:
  - There was a small number of PML patients with prior IS use and available anti-JCV antibody index data (n=19).
  - Underlying biology that may contribute to a difference in anti-JCV antibody index in patients with prior IS is complex and not well understood.
  - Pooling patient populations might underestimate the risk of PML in patients with prior IS exposure.
- Scatter plot representation of anti-JCV antibody index data for the combined test and validation data sets of patients with no prior IS treatment highlight the significantly higher index distribution (*P*<0.0001) for PML patients compared with non-PML patients, with only 1 of 51 PML cases having index <0.9 and 6 of 51 PML cases having index <1.5 (Figure 2B).
  - Results were consistent after removing 239 patients who were not treated with natalizumab from the non-PML group; thus, natalizumab-treated patients with no prior IS who developed PML (n=51) had significantly higher anti-JCV antibody index distribution compared with non-PML patients (n=2003) (*P*<0.0001; data not shown).

Figure 2: (A) Median anti-JCV antibody index in anti-JCV antibody positive non-PML and PML patients stratified by prior use of IS; (B) anti-JCV antibody index distribution in anti-JCV antibody positive non-PML and PML patients with no prior IS use



One hundred four non-PML patients and 1 PML patient were missing prior IS information and were excluded from analyses by prior IS use.

Anti-JCV antibody index threshold and PML risk

- Table 1 shows the estimated proportions of natalizumab-treated PML (n=51) and non-PML patients (n=2242) without prior IS use from the combined test and validation data sets who fell below a range of anti-JCV antibody index thresholds.

Table 1: Proportions of anti-JCV antibody positive non-PML and PML patients with no prior IS use by index threshold

Index threshold	Percentage non-PML below	95% CI	Percentage PML below	95% CI	OR	*P* value
≤0.7	21.1	19.5–22.7	0.6	0.1–3.9	45.6	<0.001
≤0.9	28.2	26.5–30.1	1.7	0.2–10.9	22.9	0.002
≤1.1	33.6	31.8–35.6	4.4	1.4–12.9	11.1	<0.001
≤1.3	37.9	36.0–39.9	7.5	3.0–17.6	7.5	<0.001
≤1.5	42.9	41.0–44.9	10.1	4.5–21.2	6.7	<0.001

Data for patients with no prior IS use: 2242 non-PML patients and 51 patients using all available anti-JCV antibody index data at least 6 months prior to PML diagnosis. A total of 5547 samples were analyzed by repeated measures with predicted probabilities, ORs, and *P* values estimated from generalized estimating equations with a logit link. An exchangeable correlation structure was assumed.
CI=confidence interval.

- Using the combined test and validation data sets, PML risk estimates for anti-JCV antibody positive patients with no prior IS use were generated for each index threshold over the range of 0.9 to 1.5 (Table 2).
  - For anti-JCV antibody positive patients with no prior IS use and an anti-JCV antibody index at or below each threshold in the range between 0.9 and 1.5, the risk of PML was lower compared with the total population of anti-JCV antibody positive patients with no prior IS use, as per the current algorithm.[2,3]
  - For patients with an anti-JCV antibody index >1.5, the risk of PML was higher compared with the total population of anti-JCV antibody positive patients with no prior IS use, as per the current algorithm.[2,3]

Table 2: PML risk estimates by index threshold in anti-JCV antibody positive patients with no prior IS use

Index result	PML risk estimates per 1000 patients (no prior IS use) 1–24 months (95% CI)	25–48 months (95% CI)	49–72 months (95% CI)
≤0.9	**0.1** (0–0.41)	**0.3** (0.04–1.13)	**0.4** (0.01–2.15)
≤1.1	**0.1** (0–0.34)	**0.7** (0.21–1.53)	**0.7** (0.08–2.34)
≤1.3	**0.1** (0.01–0.39)	**1.0** (0.48–1.98)	**1.2** (0.31–2.94)
≤1.5	**0.1** (0.03–0.42)	**1.2** (0.64–2.15)	**1.3** (0.41–2.96)
>1.5	**1.0** (0.44–1.41)	**8.1** (6.44–9.8)	**8.5** (6.22–11.38)

PML risk estimates for anti-JCV antibody index thresholds were calculated based on the current PML risk stratification algorithm (from September 2012) and predicted probabilities shown in Table 1 for the population at or below that particular index (0.9–1.5) and for the population above an index of 1.5. For index thresholds below 0.9, patient numbers were insufficient to allow for calculation of risk estimates.

Longitudinal stability of anti-JCV antibody index

- Longitudinal data were available every 6 months over a period of 18 months for 553 anti-JCV antibody negative patients at baseline who had no prior IS use.
  - Over a period of 18 months, 87% of patients who tested anti-JCV antibody negative at baseline remained anti-JCV antibody negative at subsequent testing (Table 3).
  - Over a period of 18 months, 96% of patients who tested anti-JCV antibody negative at baseline remained below the anti-JCV antibody index threshold of 0.9.
  - Over a period of 18 months, 69% (51 of 74) patients who changed serostatus from negative at baseline to having ≥1 positive sample remained consistently below the anti-JCV antibody index threshold of 0.9.
    - Approximately 4% of patients who tested anti-JCV antibody negative at baseline had ≥1 sample above the anti-JCV antibody index threshold of 0.9 over a period of 18 months.
    - Approximately 2% of patients who tested anti-JCV antibody negative at baseline had ≥2 consecutive samples above the anti-JCV antibody index threshold of 0.9 over a period of 18 months.
- Longitudinal data were relatively similar for index thresholds of 0.9, 1.2, and 1.5 (Table 3).

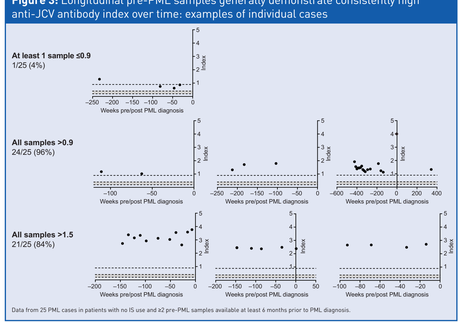
Table 3: Anti-JCV antibody index over a period of 18 months for patients who were anti-JCV antibody negative at baseline (n=553)

	Index threshold 0.9	1.2	1.5
Percentage at consistently lower risk	**95.8%**	**96.0%**	**96.6%**
• Consistently negative	86.6%	86.6%	86.6%
• ≥1 positive sample but low anti-JCV antibody index (consistently below threshold)	9.2%	9.4%	9.9%
Percentage at higher risk			
Ever high (≥1 sample above index threshold)	**4.2%**	**4.0%**	**3.4%**
• Consistently high (≥2 consecutive samples above index threshold)	2.2%	2.0%	1.6%

Includes longitudinal samples collected every 6 months from 553 anti-JCV antibody negative patients at baseline who had no prior IS use and were followed over a period of 18 months in AFFIRM and STRATIFY-1.

- Twenty-five natalizumab-treated MS patients who developed PML had no prior IS use and ≥2 pre-PML samples at least 6 months prior to PML diagnosis.
- One patient (4%) had 3 samples with an anti-JCV antibody index <0.9, 2 of which were collected within 12 months of PML diagnosis (Figure 3). For the remaining 24 patients (96%), all samples had an anti-JCV antibody index >0.9, and for 21 of 25 (84%) patients, all samples had an anti-JCV antibody index >1.5.

Figure 3: Longitudinal pre-PML samples generally demonstrate consistently high anti-JCV antibody index over time: examples of individual cases



Data from 25 PML cases in patients with no IS use and ≥2 pre-PML samples available at least 6 months prior to PML diagnosis.

CONCLUSIONS

- **Anti-JCV antibody index may further differentiate PML risk for anti-JCV antibody positive MS patients.**
  - In natalizumab-treated patients with no prior IS use, a higher anti-JCV antibody index correlates with an increased PML risk.
- **Most patients who are anti-JCV antibody negative at baseline remain consistently negative or change to lower index anti-JCV antibody positive status.**
  - In the combined AFFIRM and STRATIFY-1 cohorts, of those patients who tested anti-JCV antibody negative at baseline, 87% remained consistently negative and 96% remained consistently at lower risk (anti-JCV antibody index ≤0.9, ≤1.2 or ≤1.5) over a period of 18 months.
  - These analyses may potentially better inform PML risk in patients who seroconvert or test intermittently positive.
- **Longitudinal pre-PML samples demonstrate consistently positive anti-JCV antibody status and a high anti-JCV antibody index over time.**
  - Ninety-six percent (24/25) of natalizumab-treated MS patients who developed PML and had 2 or more samples available had all pre-PML samples with an index above 0.9.
- **Further data collection and evaluation of this new hypothesis of anti-JCV antibody index and PML risk assessment are ongoing.**

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