

Therapy with natalizumab is associated with high JCV seroconversion and rising JCV index values

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ABSTRACT

Objective: The aim of the study was to analyze John Cunningham virus (JCV) serology in natalizumab-treated patients over time and assess whether they are influenced by natalizumab treatment.

Methods: German (n = 1,921; 525 longitudinally) and French (n = 1,259; 711 longitudinally) patients were assessed for JCV serology alongside their therapy with natalizumab.

Results: JCV serostatus changed in 69 of 525 longitudinally followed German patients (13.1%) over 14.8 months. Seroconversion according to serostatus was seen in 43 of 339 initially JCV– German patients (12.7% in 14.8 months; 10.3% per year) and 41 of 243 initially JCV– French patients (16.9% in 24 months; 8.5% per year). JCV index values could be reproduced ($R^2 = 0.89$) with the caveat of 8 of 50 samples (16%) being set into different risk categories between 2 assessments. Index values of JCV+ patients rose over time ($p = 0.009$) but not because of aging. Treatment with natalizumab was associated with a 15.9% increase of value in JCV+ patients in 14.8 months (12.9% per year).

Conclusions: JCV seroconversion and index values may be influenced by treatment with natalizumab. It is therefore important to monitor patients' JCV serology but also to incorporate additional risk factors into the progressive multifocal leukoencephalopathy risk stratification. *Neuroimmunol Neuroinflamm* 2016;3:e195; doi: 10.1212/NXI.000000000000195

GLOSSARY

JCV = John Cunningham virus; **MS** = multiple sclerosis; **PML** = progressive multifocal leukoencephalopathy; **RRMS** = relapsing-remitting multiple sclerosis.

Natalizumab was approved for the treatment of active relapsing-remitting multiple sclerosis (RRMS) starting in 2006.^{1,2} The development of 566 cases of progressive multifocal leukoencephalopathy (PML) (June 2015³) has been a significant problem of an otherwise successful treatment regimen. Patients are currently stratified using 3 measures: prior immunosuppressant use, duration of natalizumab treatment, and presence of antibodies against the PML-inducing John Cunningham virus (JCV).⁴ Recently, the JCV serology biomarker has been extended to include the level of anti-JCV antibody titers represented as a JCV index value.⁵ In April 2015, the European Medicines Agency initiated a re-review of the drug after data from an interim report of the STRATIFY-2 trial suggested that the JCV seroconversion during natalizumab therapy might be higher than previously assumed. We have been assessing JCV serostatus and index values in 2 large cohorts of German and French patients with multiple sclerosis (MS) treated with natalizumab. This study shows how JCV serology (status and index) is influenced by treatment with natalizumab in addition to the known JCV serostatus change by aging⁶ from a

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study in which patients were not treated with natalizumab but with many other disease-modifying treatments.

METHODS Patients and biomaterials. Serum samples of 1,921 patients (Germany) and 1,259 patients (France; BioNAT) with RRMS alongside natalizumab therapy were processed as published previously.⁷ The patient cohorts and their seroprevalence are shown in a flow diagram in figure e-1 at Neurology.org/nn.

Standard protocol approvals, registrations, and patient consents. The study was approved by the local ethics committee (University of Muenster: Ethik-Kommission der Ärztekammer Westfalen-Lippe und der Medizinischen Fakultät der Westfälischen Wilhelms-Universität, registration number 2010-245-f-S; Comité éthique du sud ouest et outre mer II: 2-09-02), and informed written consent was obtained from all participants. This study was performed according to the Declaration of Helsinki.

Anti-JCV antibody status and index value. Sera samples were processed and analyzed by Unilabs (Copenhagen, Denmark) with the second-generation ELISA kit STRATIFY JCV DxSelect[®] (EL1950; Focus Diagnostics, Cypress, CA) according to the manufacturer's instructions.⁵

Statistics. Continuous variables such as JCV index are characterized by means. Categorical variables such as JCV serostatus are described by absolute and relative frequencies. Univariate correlations are estimated by Spearman correlation coefficient. Data are visualized as scatterplots and supplemented by linear regression lines. Significance of longitudinal JCV index value changes was calculated using Wilcoxon matched-pairs signed rank test. The *p* values were considered significant at ≤ 0.05 . No adjustment for multiplicity was performed. Statistical analyses were conducted using Prism (version 5; GraphPad, San Diego, CA).

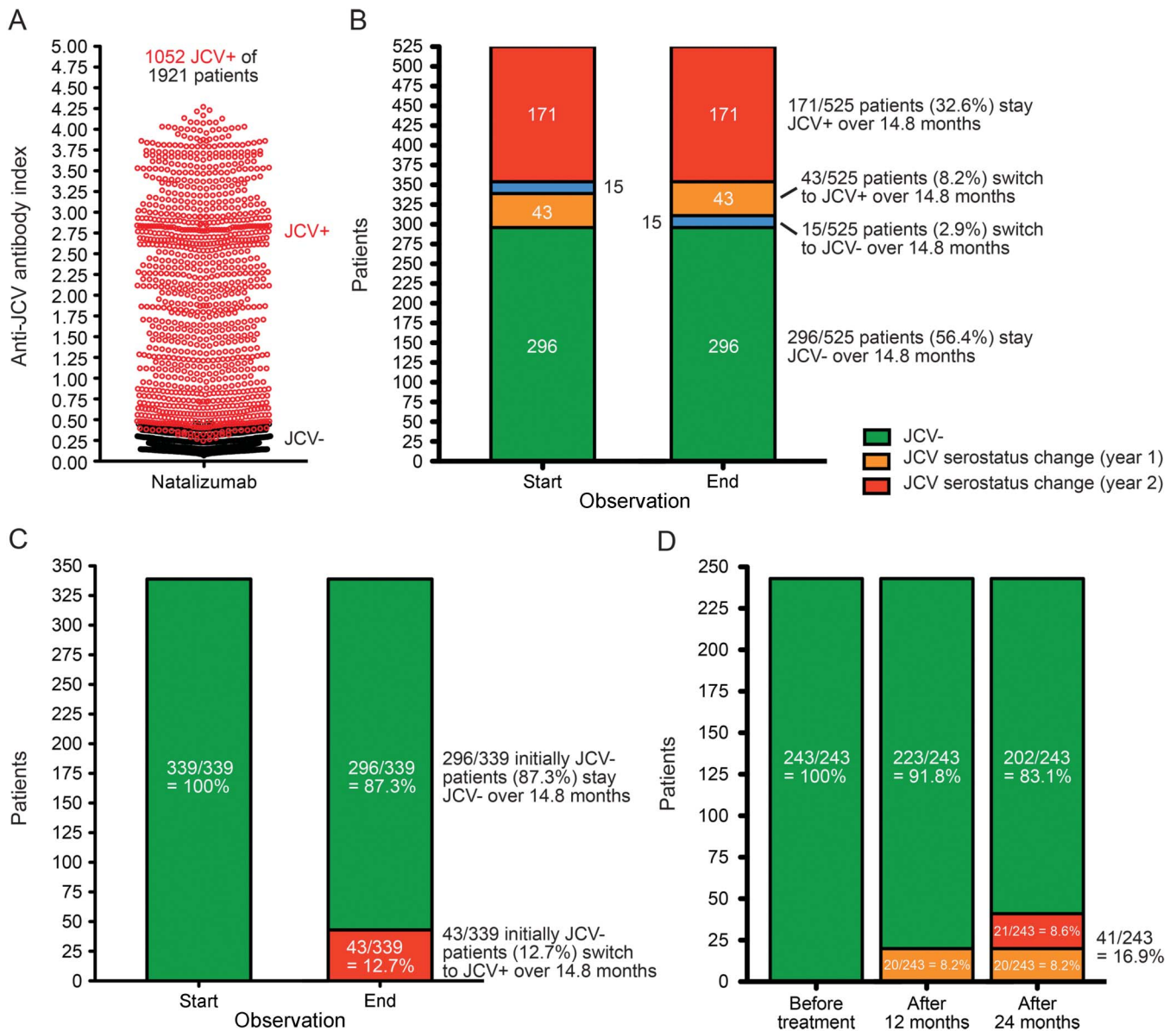
RESULTS JCV serostatus. Overall JCV serostatus assessment set 1,052 of 1,921 German patients (54.7%) under treatment with natalizumab as JCV+ (figure 1A). Longitudinally, 525 of these patients were accompanied for a mean period of observation of $14.8 \pm$ (SD) 8.2 months. Two hundred ninety-six of these 525 patients (56.4%) were JCV- during the complete period of observation and 171 were JCV+ (32.6%). Forty-three patients changed from being JCV- to JCV+ (8.2%) and 15 patients changed from being JCV+ to JCV- (2.9%). Overall, there were 11 patients (2.1%) who transiently changed serostatus during the period of observation but ended up with their initial serostatus (figure 1B). If JCV serostatus was used to determine seroconversion, the longitudinal assessment started out with 339 initially JCV- patients (initial seroprevalence of the longitudinal cohort 35.4%). The serostatus of 43 of these initially JCV- patients changed to JCV+, which is 12.7% in 14.8 months (10.30% per year or 0.86% per month; ultimate seroprevalence of the longitudinal cohort 40.8%) (figure 1C). In the French BioNAT cohort of 1,259 patients (seroprevalence of the whole cohort before start of treatment was 604 of 1,020 patients = 59% and of the longitudinally followed

cohort 468 of 711 patients = 65.8%), of the initially 243 JCV- patients of 711 patients, where all 3 longitudinal time points were available, the serostatus of 20 changed to JCV+ in their first year of treatment (8.2%) and 21 in their second year of treatment (8.6% of 243 initially JCV- patients or 9.4% of the 223 patients, who were still JCV- after 1 year of treatment). Taken together, the serostatus of 41 of 243 patients (16.9%) changed to JCV+ in the first 2 years of natalizumab treatment (8.5% per year or 0.70% per month; ultimate seroprevalence of the French longitudinal cohort after 2 years 71.6%) (figure 1D).

JCV index value. The JCV serostatus was recently extended to incorporate the level of anti-JCV antibodies in serum, normalized to a "JCV index" value. To assess the reproducibility of this value, 50 patient serum samples were measured twice by Unilabs. Overall reproducibility was very good with an R^2 of 0.89. However, 8 of these 50 patients (16%) would have been set in different risk categories between the 2 measurements (thresholds from Plavina et al.,⁵ 2014: JCV-/+ , 0.9, 1.2, 1.5) with one sample actually being set as JCV+ in the first and JCV- in the second measurement and 2 samples being either measured at very high PML risk (JCV index >1.5) or very low risk (JCV index <0.9) (figure 2A) in the 2 measurements. The index values changed in 525 patients in the observation period. The proportion of patients with an index value <0.4 was reduced by 20 patients (from 65.1% to 61.3%), and the group of patients with low risk (between 0.4 and 0.9) was reduced by one patient to 7.8%. The patient groups with medium (0.9–1.5) and high risk (>1.5) grew by 7 patients from 4.6% to 5.9% and by 14 patients from 22.3% to 25%, respectively (figure 2B). Overall, this was a reflection of the change in serostatus (figure 1C) but also suggested that patients who changed serostatus directly presented with high anti-JCV antibody titers afterward, as the groups of low and medium risk did not grow substantially over time. This trend was also clearly visible in the complete cohort of patients (figure 2C), where up to 7 longitudinal samples were assessed from each patient and the seroconversion mostly led to JCV index values of >1.5 (figure 2D).

Change in JCV index values in JCV+ patients. While most of the changes in JCV index values could be attributed to the seroconversion of initially JCV- patients, it was also important to see whether patients presented with stable index values once they converted to JCV seropositivity. Two hundred one JCV+ patients were therefore followed over time and it became clear that the biomarker showed changes over time with higher values after the period

Figure 1 JCV serostatus



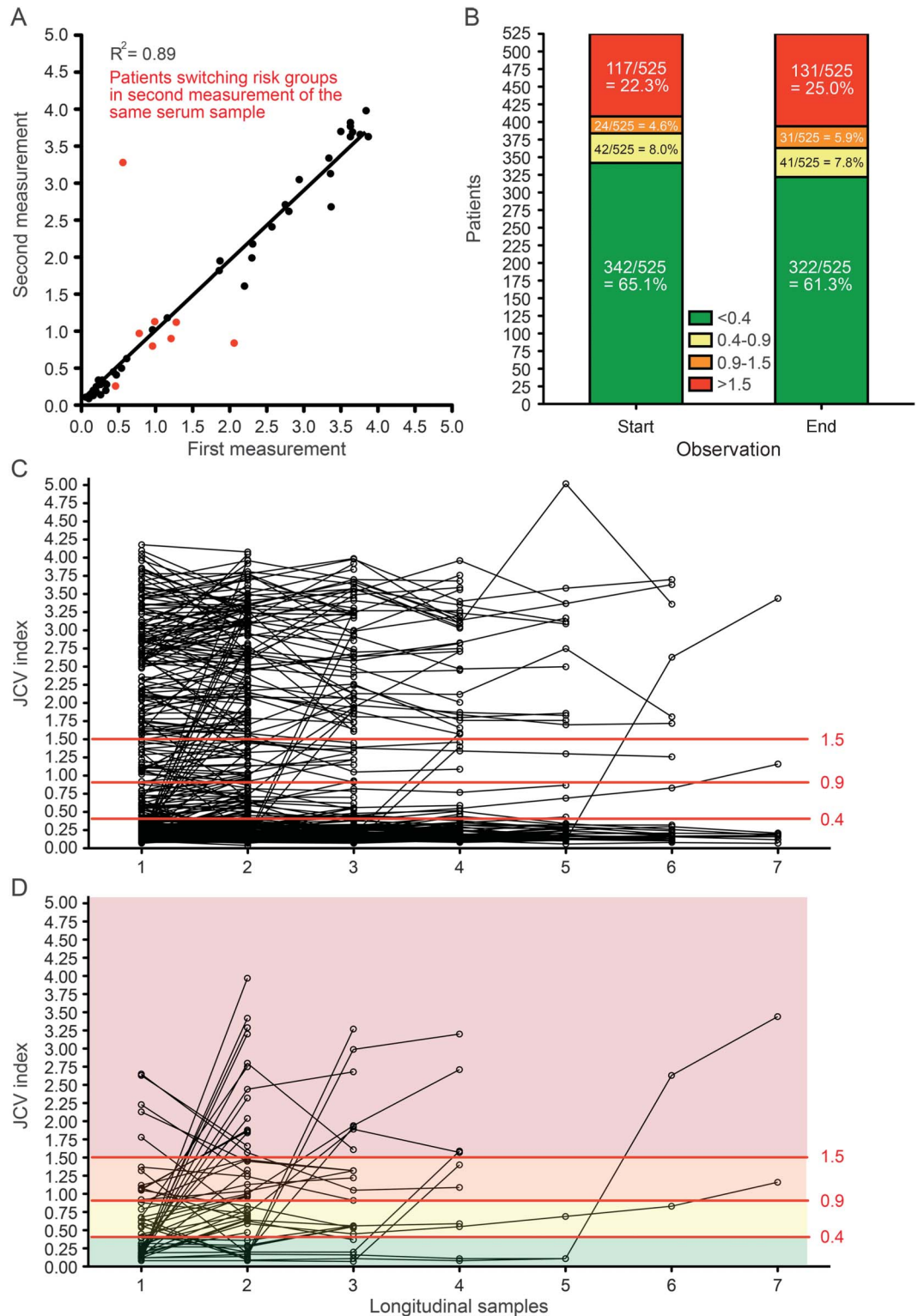
(A) Serostatus of 1,921 natalizumab-treated patients with multiple sclerosis, with JCV- patients shown in black and JCV+ patients in red. A total of 1,052 of these 1,921 patients were set as JCV+ (54.76%). (B) Serostatus of a longitudinally assessed cohort of 525 patients during 14.8 months of natalizumab treatment. (C) Serostatus of the German cohort of 339 initially JCV- patients (of 525 patients) before and after the period of observation (14.8 months of natalizumab treatment). Forty-three of these 339 patients (12.7%) were set as JCV+ after the period of observation. (D) Serostatus of the French cohort ($n = 1,259$; 711 longitudinally; BioNAT) of the 243 initially JCV- patients of 711, where all 3 time points were available, during their first 2 years of treatment. Twenty of these patients (8.2%) were set as JCV+ after the first year and an additional 21 (8.6%) after the second year of treatment, resulting in 41 of 243 patients (16.9%) changing their serostatus to JCV+ in the first 2 years of treatment. JCV = John Cunningham virus.

of observation (mean: 2.046 vs 2.158; $p = 0.009$) (figure 3A). That age had a role in these fluctuations was ruled out because the age of patients contributed to the overall rise in index values (Spearman $r: -0.113$; $p < 0.0001$) due to seroconversion, but the index values of JCV+ patients did not change with age (Spearman $r: 0.0001$; $p = 0.996$) (figure 3B); this was also true for patients who seroconverted during therapy with natalizumab. The index correlation with age in the whole population (JCV- and JCV+) is attributable to seroconversion, but if only

JCV+ patients are considered, their index values do not differ with age; they only differ with prolonged treatment duration.

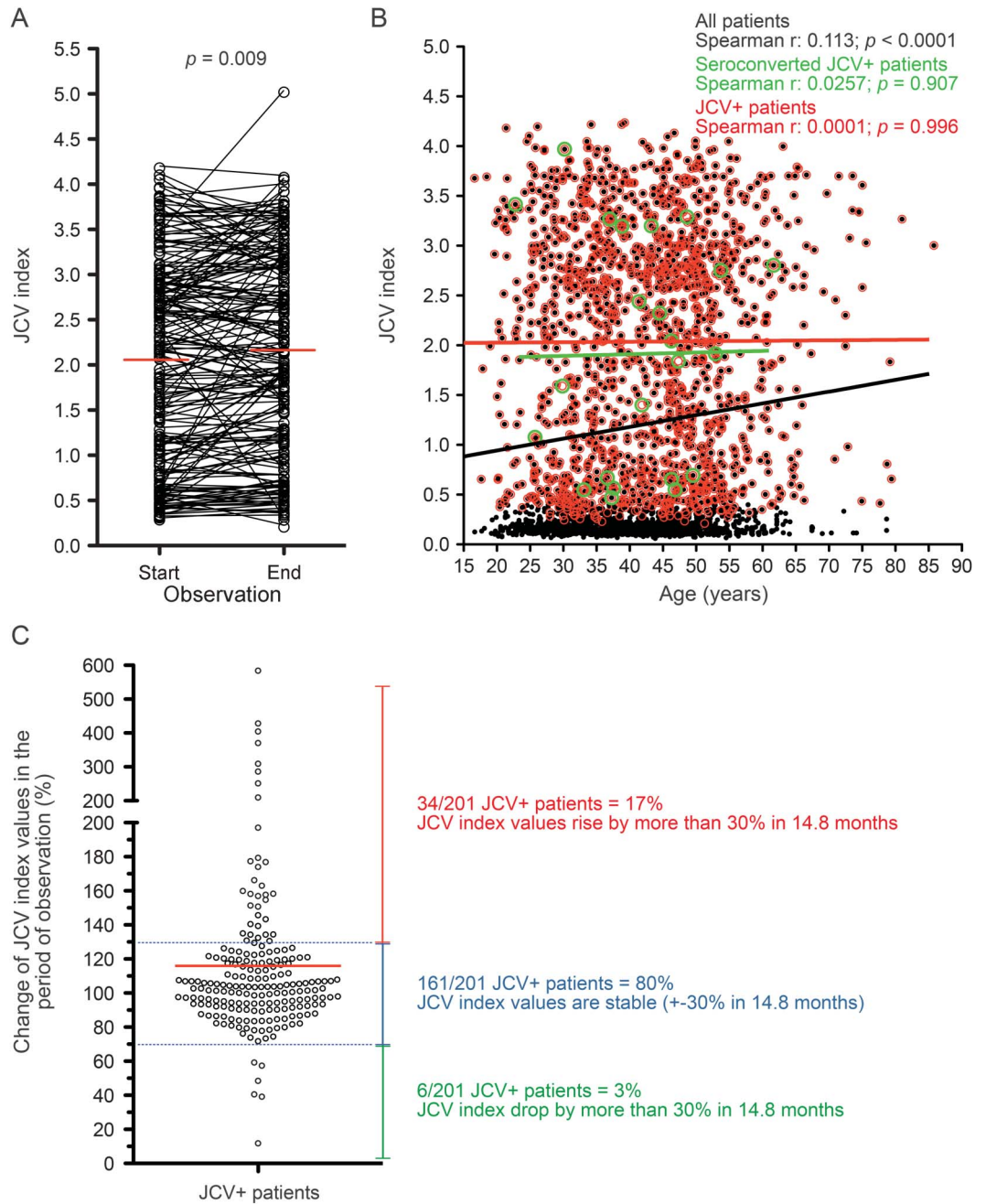
One hundred sixty-one of 201 JCV+ patients (80%) presented with stable JCV index values over time ($\pm 30\%$ in the period of observation). However, the remaining 40 patients (20%) presented with fluctuations of more than 30% in 14.8 months. Only 6 of these patients (3%) presented with decreasing index values, but 34 (17%) presented with increasing index values (mean: 200.8%). Taken together, the

Figure 2 JCV index



(A) Fifty samples of natalizumab-treated patients with multiple sclerosis were assessed twice for their anti-JCV antibody index (JCV index) with an R^2 of 0.89. Eight of these 50 samples (16%) showed 2 different risk associations with the thresholds JCV-/, JCV index 0.4, 0.9, 1.2, and 1.5 in the 2 assessments. (B) JCV index value distributions of a longitudinal cohort of 525 patients at the start and end of the period of observation of 14.8 months. (C) Serial assessment of JCV index values of 525 patients alongside their natalizumab therapy (2-7 JCV serology assessments). Red lines indicate the thresholds 0.4, 0.9, and 1.5. (D) Serial assessment of JCV index values. Only patients whose index values changed by more than 30% over time and whose PML risk group changed are shown (0-0.4 [green], 0.4-0.9 [yellow], 0.9-1.5 [orange], >1.5 [red]). JCV = John Cunningham virus.

Figure 3 JCV index changes in JCV+ patients



(A) Increasing JCV index values of 201 JCV+ natalizumab-treated patients with multiple sclerosis at the beginning and end of a period of observation of 14.8 months (mean: 2.046 vs 2.158; $p = 0.009$). (B) Age (in years) and JCV index value of 1,921 natalizumab-treated patients with multiple sclerosis. Overall, there is a strong rise in index values by age (Spearman $r: 0.113$; $p < 0.0001$) but no rise in the index values of JCV+ patients (Spearman $r: 0.0001$; $p = 0.996$) or patients who converted to JCV seropositivity during treatment with natalizumab (Spearman $r: 0.0257$; $p = 0.907$). (C) Change of JCV index values of 201 JCV+ patients during natalizumab treatment in % (index value at the end of the period of observation/index value at the beginning of the period of observation $\times 100$). Mean rise in index values was 15.9% in 14.8 months. One hundred sixty-one of 201 patients (80%) presented with stable index values ($\pm 30\%$), 34 patients (17%) presented with increasing index values, and 6 patients (3%) with decreasing index values. JCV = John Cunningham virus.

index value of all JCV+ patients increased by 15.9% on average in 14.8 months (12.9% per year or 0.11% per month) (figure 3C).

DISCUSSION There has been strong debate about whether the underlying JCV seroconversion rate by

aging is influenced by treatment with natalizumab.^{9–11} The high seroconversion, which has already been suggested (Plavina et al.,⁵ 2014; $n = 553$; 0.45%–0.72% per month depending on the definition of seroconversion), and the data of seroconversion rates in longitudinally monitored JCV– patients

in our study (10.3% and 8.5% per year) clearly support the facilitation by treatment with natalizumab. It is important to distinguish between seroconversion (a JCV⁻ patient converting to JCV⁺) and an increase in seroprevalence (the percentage of JCV⁺ patients within a cohort). The published rise in seroprevalence by age is 0.5% per year,^{6,12} which translates into a JCV seroconversion of approximately 1% per year in the 40% to 45% of JCV⁻ patients within these cohorts. However, in both calculations, our observed seroconversion of 8% to 10% per year and the rise in seroprevalence of 5% to 6% in 15 to 24 months is at least 8 to 10 times as much as would be expected by age. This dataset suggests that not every patient with MS is susceptible to JCV seroconversion by treatment, but natalizumab might facilitate it in patients who are susceptible. There has recently been an extensive study of 7,724 patients and their JCV serostatus in a group of control patients.⁶ The authors clearly show that when adjusted for age, sex, and country of origin, the duration of MS treatment has no influence on JCV seroprevalence, leaving treatment with natalizumab as the only factor in our study, as sex and country of origin do not change in longitudinal cohorts. Because as yet there are no studies on the influence of other treatments on JCV index values, and despite a very recent study also supporting this hypothesis,¹³ we cannot be certain that it was the treatment with natalizumab that led to the rising index values in our study. However, because there was no correlation with age in JCV⁺ patients and these patients have certainly been treated longer with disease-modifying drugs the older they are, it can be speculated that it is specifically the treatment with natalizumab that induces rising JCV index values (and, therefore, anti-JCV titers). The high seroconversion (putatively induced by higher JCV activity) is also in agreement with the published lower CD62L values induced by natalizumab treatment,⁷ as both are associated with higher PML risk. Because previous hypotheses concerning JCV titers suggested that higher titers are the result of a higher replication rate of the virus,^{14–16} it is conceivable that a higher replication rate is attributable to the fact that the compromised immune cells of natalizumab-treated patients are less capable of suppressing the viral activity of JCV. As long as these biological backgrounds are not fully elucidated, it seems prudent to include the theory of (re)infection with JCV as a source for seroconversion. However, since there are patients who shed the virus in their urine without being antibody seropositive,¹⁷ it seems unlikely that the process leading to seropositivity is solely linked to (re)exposure to JCV.

One drawback of our study is the fact that JCV⁻ patients naturally tend to reassess their JCV serology more often than JCV⁺ patients for a potential seroconversion. Therefore, our prospective longitudinal German cohort, in which patients could decide for themselves how often to assess their serostatus, has a much lower seroprevalence than the overall patient population. This might overexaggerate the percentage of seroconverters in the entire natalizumab-treated MS collective, which is why it is important to calculate the seroprevalence in addition to the seroconversion. Apart from this, it was recently shown that IV immunoglobulin treatment may cause transiently high anti-JCV antibody titers and thereby transient false-positive JCV serostatus results. However, we can rule this out for our seroconverting patients, as well as for the complete cohort, because IV immunoglobulins are usually not applied during natalizumab treatment in Europe.¹⁸

Both observations of this study—the high seroconversion and the rising index values in JCV⁺ patients—have implications for PML risk stratification using JCV serology. It is important to regularly check patients' JCV serology (status and index) for an accurate assessment of their PML risk according to this biomarker. Unfortunately, with a JCV index value mean of more than 2, most JCV⁺ patients are set into the highest PML risk category, with very few of these patients ultimately developing PML. JCV serology should not be the only PML risk biomarker used in the stratification of patients treated with natalizumab. The exploration and potential application of additional biomarkers such as CD62L in peripheral blood^{7,19} or IgM bands in CSF²⁰ is needed to accurately inform patients of their PML risk and ultimately help in reducing PML incidences.

If the hypothesis that treatment with natalizumab is associated with enhanced JCV seroconversion and higher index values is proven, it would also be important to determine whether cessation of natalizumab therapy (or perhaps prolonged infusion intervals) could lead to lower JCV index values as well. This remains to be seen in the studies currently under way regarding switching to other therapies or prolonged infusion intervals. However, from a risk stratification point of view, this would not influence patients because they should always assume the highest measured risk to be on the safe side, and even lowered JCV index values should not suggest that a patient's risk has diminished. These further and larger clinical studies with a strict study protocol should be performed to assess in which capacity natalizumab influences JCV seroconversion and whether this is influenced by treatment dosage/intervals.

Taken together, JCV serology is a sensitive biomarker for PML risk, but it is very dynamic and should be regarded as such. JCV⁻ patients should reassess their status regularly and JCV⁺ patients should check their JCV index values until they have reached the highest risk category, after which JCV serology loses some of its usefulness. The fact that treatment with natalizumab is associated with a very high rate of seroconversion and rising index values does not diminish its clinical efficacy, but calls for more elaborate strategies for PML risk stratification according to current scientific developments, also regarding patients with prior use of immunosuppressants, where the JCV index is not helpful.⁵

AUTHOR CONTRIBUTIONS

N.S. designed and performed research, collected data, analyzed data, and generated funding. T.S.-H. designed and performed research, collected and analyzed data. B.P. performed research, collected and analyzed data. J.B., K.G., and C.C.G. performed research, collected and analyzed data. D.B. performed research, collected and analyzed data, and generated funding. H.W. designed research, analyzed data, and generated funding. All authors wrote the manuscript. H.W. and N.S. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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