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May baseline JCV status influence the MS clinical evolution during Natalizumab treatment? Evidence from a multicenter-2 years-prospective study

E. D'Amico[1], A. Zanghì[1], A. Signori[2], LME Grimaldi[3] and F. Patti[1*]

Abstract

Background: We prospectively assessed the influence of JCV- status on disability's accrual in RRMS patients treated with Natalizumab at two tertiary MS centres, settled in Italy.

Methods: Negative binomial model was used to assess the influence of baseline JCV status (positive or negative) treatment on clinical and radiological disease activity during the 24 months' follow-up.

Results: One hundred eighty four patients treated with Natalizumab were enrolled (83 JCV +, whilst 101 JCV-). Over the two years of follow-up there was not significant clinical and radiological differences between the two groups.

Conclusion: JCV + RRMS did not showed a severe clinical course than JCV – RRMS.

Keywords: JCV, RRMS, MRI, EDSS, Clinical course, Natalizumab

Background

The cause of Multiple Sclerosis (MS) is not known, but several factors have been shown to be associated with the risk of developing this disease including virus infections [1]. JC virus (JCV) is a human polyomavirus that, after reactivation in immunocompromised individuals, can cause progressive multifocal leukoencephalopathy (PML) [2]. PML is a fatal demyelinating disease of the white matter of the brain, due to the lytic destruction of oligodendrocytes infected by JCV [3].

The possible involvement of JCV in MS pathogenesis was first postulated by Stoner [4]. A study excluded this possibility [5], whereas others reported the presence of JCV DNA in the cerebrospinal fluid and plasma of MS patients, but not of controls [6, 7]. Overall, evidence does not support the hypothesis that persons with MS would be at increased risk to develop PML.

We questioned whether relapsing remitting (RR) MS patients with a JCV baseline positive (+) status may experience a more severe clinical course than persons with RRMS and JCV baseline negative (-) status.

Methods

We performed a retrospective multicenter study of longitudinal, prospectively collected data at the tertiary MS centers of Catania and Cefalù, both settled in South Italy. The study took place between January 2013 and January 2014 (index window). Inclusion criteria were: i) persons older than 18 years and able to understand the purpose of the study, providing informed consent; ii) clinical definite RRMS according to revised McDonald 2010 criteria [8]; iii) RRMS who started Natalizumab treatment within one month after the anti-JCV antibody serum test during the index window.

The enrolled persons were followed up for 24 months from the inclusion date. As date of study inclusion, we considered the time in which they signed the informed consent and performed the anti-JCV antibody test. RRMS who seroconverted during the observation period were excluded.

Anti-JCV antibody status was analyzed in fresh samples using the Stratify JCV TM DxSelectTM test as described elsewhere (www.focusdx.com). All analyses were

* Correspondence: patti@unict.it
[1]MS center, University of Catania, Via Santa Sofia, 78, 95123 Catania, Italy
Full list of author information is available at the end of the article

performed at Unilabs a.s., Nygårdsvej 32, 2100 København, Denmark.

RRMS attended the MS centers every 28 days for Natalizumab administration. They performed a clinical visit after one month from the inclusion and every six months until the last follow up visit (at 24 months). In every clinical visit, any exacerbation, level of disability assessed by Expanded Disability Status Scale (EDSS) value and the number of new T2, new T1 and T1 Gadolinium (Gd) lesions were collected. EDSS progression was defined as increase of 1 point from baseline when EDSS < 5.5 or 0.5 point for EDSS ≥ 5.5. Study approval was obtained from the local ethics committee of the coordinator center.

Statistical methods

Baseline continuous characteristics were compared between the two groups (JCV + vs JCV-) by mean of independent samples Student's *t*-test (age, age at onset, disease duration) while non-parametric Mann-Whitney test was used for EDSS, relapses and T2 lesions and Fisher's exact test for gender.

Negative binomial model was used to statistically test differences between the two groups on number of relapses, number of new T2 and new T1-Gd lesions developed at 24 months from stratify.

For relapses the annualized relapse rate (ARR) was reported.

Multivariable models were built to adjust for baseline differences between the two groups on characteristics as age and EDSS. Only variables significantly associated with the investigated outcome were considered into the model. The two groups were compared on progression frequency using fisher's exact test. A *p*-value lower than 0.05 was considered statistically significant. Stata (v.13; Stata Corp.) was used for the computation.

Results

A total of 184 patients treated with Natalizumab were considered in the study. Demographic and clinical characteristics at baseline were reported in Table 1.

Based on JCV status at baseline, patients were classified as JCV + ($n = 83$; 45.1%) and JCV - ($n = 101$; 54.9%). Positive patients were older ($p = 0.07$) and with a higher EDSS ($p = 0.017$) as compared with negative patients.

Relapses

Over 24 months of follow up the JCV- showed a mean number of relapses of 0.20 (ARR: 0.10) while for JCV+ was 0.166 (ARR = 0.083) with not significant differences between the two groups ($p = 0.82$; Table 2).

T2 lesions

Over 24 months of follow up number of new T2 lesions from baseline was slightly higher in JCV+ patients (9.5 ± 14.9) as compared with JCV- (5.6 ± 9.1) but without significant differences between the two groups ($p = 0.23$).

Gd lesions

Over 24 months of follow up all persons with RRMS in both groups had zero new Gd lesions.

EDSS progression

At 24 months, 6 on 68 (8.8%) RRMS patients in JCV+ and 3 on 73 (4.1%) in JCV- were progressed; without significant difference between the two groups ($p = 0.31$).

Discussion

Baseline JCV status did not influence the short clinical course in terms of disease activity in our cohort of RRMS patients, showing similar results on the most important outcomes: ARR, Gd lesions and EDSS progression.

Recently, in a German pediatric population, it was found no evidence that seropositivity for anti-JCV antibodies could influence the clinical course [9].

The detection of latent viral agents could be a challenge in MS scenario [4]; JCV could infect naïve B cells, immortalized cell lines, and B cells; and JCV infected B cells can be found in the brain [10]. Virions released from infected B cells can be taken up by primary human fetal glial cells, suggesting that B cells can carry associated JCV into the brain. It is recognizing the role of B

Table 1 Baseline demographic and clinical characteristics

Characteristics	NTZ-JCV positive ($n = 83$)	NTZ-JCV negative ($n = 101$)	*P*-value
Age at disease onset (years), mean (SD)	29 (10)	26.5 (8.4)	0.07
Age at stratify (years), mean (SD)	39.6 (10.4)	38 (10.5)	0.29
Female (%)	53 (63.9)	74 (73.3)	0.20
Disease duration (years), mean (SD)	11.3 (8.1)	11.4 (8.6)	0.94
EDSS pre-stratify, median [IQR]; mean (SD)	3.5 (2–5); 3.1 (1.9)	3 (2–4); 3 (1.6)	0.017
Relapses year before stratify, median [IQR]; mean (SD)	1 (1–2); 1.34 (0.86)	1nn; 1.39 (0.80)	0.62
T2 lesions pre–stratify, mean (SD; IQR)	51.2 (38.5; 21–65)	51.6 (37.4; 20–70)	0.82

IQR interquartile range, *SD* standard deviation
NTZ Natalizumab, *JCV* John Cunningham virus

Table 2 Relationship between JCV positivity and MRI and clinical outcomes

Endpoint	JCV-	JCV+	*p*-value
ARR on 24 months	0.10 ± 0.25	0.083 ± 0.24	0.82
New T2 lesions at 24 months	5.6 ± 9.1	9.5 ± 14.9	0.23
Disability progression, n (%)	3/73 (4.1)	6/68 (8.8)	0.31

Results are reported as mean ± SD except where differently stated

cell in driving inflammation and neurodegeneration in MS [10]. Still, treatments targeting B cells represent the most promising potential target for next future in MS [11]. Then, according to this pathogenetic model we have to investigate if the JCV reactivation could act as possible triggering factor for onset or disease activity in MS patients [12, 13].

However, our study has a short follow up and data on new T2 lesions results statistically underpowered.

Therefore, more studies with long term follow up and large sample size are needed to clarify the role of seropositivity of anti-JCV antibodies in MS population.

Conclusion

No definitive data can exclude the role of JCV in modulating the MS activity in terms of disability and radiological activity accrual. We are aimed to asses any correlation between change of JCV status and clinical course in our cohorts. This topic also opens new perspectives on current matters of debate in MS field, such as the pathogenetic role of viral agents and the introduction of immunomodulant drugs with specific targets.

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Availability of data and materials
The data that support the findings of this study are available from the corresponding author (F. Patti) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the corresponding author (F. Patti).

Authors' contributions
DE, ZA, SA, GMLE, PF contributed to designing and revising the article; AS performed the statistical analysis of collected data. All authors read and approved the final manuscript.

Competing interests
DE reports personal fees from Merck Serono, Bayer-Schering, outside the submitted work. ZA received travel foundings from Bayer-Schering outside of the submitted work. SA reports personal fees from Novartis for teaching activity outside of the submitted work. GLME reports personal fees from Merck Serono, Biogen, Teva, Novartis, Genzyme, Roche, Bayer-Schering, outside the submitted work. PF reports personal fees from Merck Serono, Biogen, Teva, Novartis, Genzyme, Roche, Bayer-Schering, outside the submitted work.

Consent for publication
Manuscript has been approved by ethics committee and has, therefore, been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Ethics approval and consent to participate
Manuscript complains with ethical standards; all the patients have given their informed consent prior to their inclusion in the study. Details that might disclose their identity have been omitted.

Publisher's Note

Author details
[1]MS center, University of Catania, Via Santa Sofia, 78, 95123 Catania, Italy. [2]Dipartimento di Scienze della salute (DISSAL), University of Genoa, Via Antonio Pastore, 1, 16132 Genoa, Italy. [3]U.O.C. Neurologia, Fondazione Istituto San Raffaele "G. Giglio", Cefalù, Italy.

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