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JCV Seroconversion in a Group of Iraqi Patients with Multiple Sclerosis Receiving Natalizumab

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ABSTRACT

Background: Natalizumab is a well-established therapy for multiple sclerosis (MS) that carries a risk of progressive multifocal leukoencephalopathy (PML) linked to John Cunningham virus (JCV). While JCV seroconversion has been well studied in the western hemisphere, data from the Middle east, including Iraq, are limited.
Objectives: To assess JCV seroconversion rates and associated risk factors among Iraqi MS patients treated with Natalizumab.
Materials and methods: A retrospective cohort study included patients with MS who were followed at the MS Clinic of Baghdad Medical City between January 2015 and December 2023. Data were collected from 290 patients and included demographics, treatment duration, prior exposure to other disease-modifying therapies (DMTs), and JCV antibody index values. The JCV antibody status was assessed every six months using a two-step enzyme-linked immunosorbent assay (ELISA).
Results: In this sample, 18% (n = 52) exhibited persistent JCV seroconversion, corresponding to an annual conversion rate of 5.2%. The seroconversion rate was 25.4% in males and 15.5% in females; which was just short of reaching statistical significance (P-value = 0.06). No significant association was observed between seroconversion and age, treatment duration, or prior exposure to DMTs (P-value > 0.05). Notably, the highest seroconversion rate (20%) was observed in patients who had previously received treatment with interferon-β derivatives. Importantly, no cases of PML were identified during the study period.
Conclusion: JCV seroconversion in Iraqi patients on natalizumab was 18% (annual 5.2%), with no significant risk factors identified. JCV monitoring remains crucial, and no cases of PML were detected.
Keywords: JCV seroconversion; Multiple sclerosis; Natalizumab; Progressive multifocal leukoencephalopathy.

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INTRODUCTION

Natalizumab, an effective monoclonal antibody for reducing relapses and disability progression in multiple sclerosis (MS), carries a risk of PML, a serious JCV-mediated disease. Monitoring JCV seroconversion is essential for guiding treatment decisions and identifying patients at higher PML risk [1, 2].

Recent research has primarily investigated JCV seroconversion rates and the associated risk of PML in Western countries. Reported annual seroconversion rates ranged from 7.3% to 10.8% [3]. But specific data to Iraqi patients remain scarce, despite the possibility of cultural, environmental, and healthcare system factors influencing immunological responses.

Additionally, although global trends can be determined from previous studies, a limited number of studies exist at a local level, notably in Iraqi health care facilities. Limiting the clinicians' ability to construct therapeutic plans tailored to the demographic and background disease of Iraqi MS patients [4].

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The proposed study addresses a gap in the literature, providing relevant data on JCV seroconversion rates and associated risk factors within the Iraqi patient population. These rates will also help establishing local thresholds for monitoring and preventative strategies against PML, tailored to the demographics of MS patients in Iraq [5].

While no significant difference in the quality of life (QoL) among Iraqi MS patients treated with interferon β-1b, fingolimod, or natalizumab was detected [6]; it remains essential to monitor JCV status, particularly in those on natalizumab to optimize care and patient safety; and Predictors such as Expanded Disability Status Scale (EDSS) scores were found to be negatively associated with QoL across all treatments.

additionally, the findings from this study may provide a basis for further development of guidelines and policies for prospective monitoring of JCV serostatus among MS patients in the community treated with natalizumab. considering the devastating effects of PML, the clinical impact of this research is includes the management of patients with MS as well as general public health efforts to maintain education and awareness among healthcare providers and patients [7].

This study aims to investigate the JCV seroconversion in natalizumab-treated patients with MS, determine the average time to seroconversion from start of therapy, study the trends of the JCV index in sero-converters, and assess for potential risk factors associated with increased JCV conversion rates (specifically age at start of treatment, sex, duration of treatment, and previous disease modifying therapy for MS (DMTs).

MATERIALS AND METHODS

A single-center, retrospective cohort study conducted in Baghdad/Iraq, at the MS clinic in Baghdad Medical City, included documents from January 2015 to December 2023. All required prior authorizations and approvals were acquired from the Iraqi Board of Medical Specializations and the director of the MS clinic before the commencement of this study (Reference number 1102, dated February 2nd, 2024). Due to the retrospective design of the study, the requirement for informed consent was waived.

The data were obtained through a record-based survey, specifically by extracting data from the MS clinic's files. Convenience sampling was used to collect all available cases from January 2015 to December 2023. As a retrospective record-based study, the sample size was determined by available files rather than a formal sample size calculation. Instead, all files that met the eligibility requirements within the study period (January 2015-December 2023) was reviewed, yielding a total of 290 patients after exclusions. To confirm suitability for statistical analysis, a post-hoc estimation of power was calculated assuming a significance threshold of 5% and a moderate effect size (equivalent to Cohen's d $\approx$ 0.5 for continuous data or an odds ratio around 2.0 for categorical variables), and the cohort size provided more than 80% power of detecting statistical significance. Indicating the final sample was adequate to address the research question with precision.

The study inclusion criteria were based on: (1) Diagnosis of MS according to the 2017 revised McDonald criteria [8]. (2) Natalizumab treatment administered, (3) At least two available JCV indices at 6-month intervals, and (4) A negative JCV-index at the start of treatment with Natalizumab. Patient age, sex, length of time on natalizumab, age of onset of therapy, most recent JCV index value by the last observation point, and history of use of other DMTs for MS before natalizumab were obtained.

Patients were excluded if they had a positive JCV serostatus at the start of natalizumab therapy or if fewer than two JCV index results were available. Incomplete follow-up, missing data, or concurrent immunosuppressive conditions were also excluded from the study. Based on these criteria, a total of 337 patient records were initially screened. Of these, 47 patients were excluded, and the remaining 290 patients met all criteria and were included in the study.

Routine JCV index testing was conducted at six-month intervals, as recommended by the manufacturer of the drug. All testing was performed centrally by Unilabs A/S (Copenhagen, Denmark) using the second-generation two-step (Indirect) JCV antibody enzyme-linked immunosorbent assay (ELISA) method. Since the ELISA results were taken from the patients' files, we cannot interpret the steps.

Data were organized using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) and analyzed with IBM SPSS Statistics version 29.0.0.0 (Statistical Package for the Social Sciences; IBM Corporation, Armonk, NY, USA). Categorical variables were summarized as frequencies and percentages, while continuous variables were expressed as means with standard deviations (SDs) and ranges. The Shapiro-Wilk test was used to assess the normality of constant data. For normally distributed data, independent t-tests were used; for non-normally distributed data, the Mann–Whitney test was employed. Associations between categorical variables and JCV seropositivity were evaluated using the chi-squared test. The risk of JCV seroconversion, along with 95% confidence intervals (CIs), was calculated for patients who were initially JCV-negative but seroconverted during follow-up. Relationships between demographic and clinical variables and the risk of seroconversion were analyzed using independent t-tests, chi-squared tests, or Mann–Whitney tests, as appropriate. A P-value of less than 0.05 was considered statistically significant.

RESULTS

A total of 290 patients were included, with a male-to-female ratio of 1:3. The mean age at natalizumab initiation was 31 years, and the mean treatment duration was 47 months. The mean time to JCV seroconversion was 45 months. Regarding prior disease-modifying therapies, 29 patients had no previous treatment, 221 had received interferon-β derivatives, 34 had been treated with both interferon-β and fingolimod, and six had received fingolimod alone. At baseline, 238 patients were JCV-negative, while 30 had a JCV index value of 1.5 or higher (Figure 1).

After a mean treatment duration of 4 years and a mean duration of seroconversion of 3 years, most MS patients (82%) had remained JCV-seronegative. Durable positive seroconversions were observed in 18% (52/290) of individuals who were initially JCV-negative. Given the mean observation period of approximately 3 years (35 months) among these 290 patients, the annual rate of durable positive seroconversions is approximately 5.2%. This corresponds to an estimated monthly seroconversion rate of 0.43%. The Mann-Whitney test revealed no statistically significant difference in the average duration of natalizumab treatment and the time to seroconversion among different seroconversion statuses, with a P-value of 0.948 (Table 1).

When comparing age at the start of natalizumab treatment according to JCV seroconversion status, 238 patients

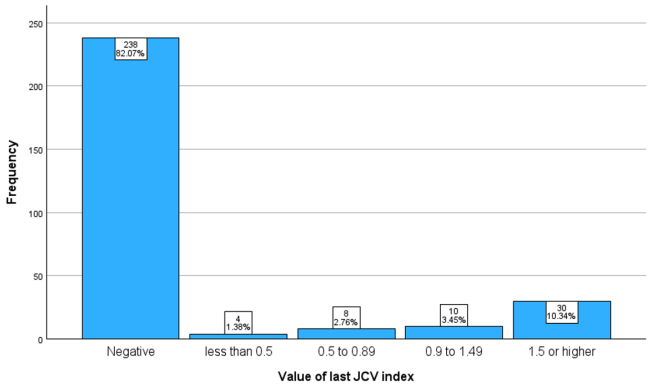

Figure 1. Frequency of the last John Cunningham virus (JCV) index value.

did not seroconversion during the study period, with a mean age of 31 years (SD = 9.91, SE = 0.64). In contrast, 52 patients who developed JCV seroconversion had a slightly higher mean age of 32 years (SD = 9.02, SE = 1.25). The independent t-test revealed no statistically significant difference in the mean ages across various seroconversion statuses, as evidenced by a P-value of 0.424. JCV seroconversion was more frequent among male patients, with a rate of 25.4%, compared to 15.5% among female patients. Although females represented the larger proportion of the study population, but seroconversion was relatively higher in males. Still, there was no statistically significant difference in JCV seroconversion between the sexes. This is supported by the chi-square test that yielded a P-value of 0.06 (Table 2). Most patients who previously received interferon-β derivatives showed JCV seroconversion (20%), representing the highest seroconversion rate among the treatment groups. Patients without prior MS treatments had the lowest seroconversion rate (6.9%). Interestingly, no cases of seroconversion were observed among those who had previously received fingolimod alone. Overall, JCV seroconversion occurred in 17.9% of the cohort. A chi-square test showed no statistically significant difference in seroconversion status among individuals who got different types of treatment earlier, with a P-value of 0.19 (Table 2).

DISCUSSION

Among patients who seroconverted, JCV index values gradually increased over time, with 30 patients (57.6% of converters) reaching values $\geq$1.5 by the end of follow-up, this impacts the ability to keep the patients on long term natalizumab infusion due to increasing risks of PML with higher titers, keeping in mind that higher titers correlate with higher viral replicative activity manifesting as both viremia and viriuria in otherwise asymptomatic patients [9].

The seroconversion rate of 5.2% in our study, although higher than the reported rate in post-marketing studies for natalizumab (approximately 4%), remains significantly lower than the rates reported in several studies conducted worldwide. Rates from similar work yielded percentages ranging from 7.3% from a combined Australian/Brazilian cohort [10], 9.08% at the Royal Melbourne Hospital [11], and 16.5% (19 of 115) seroconverted to a positive JCV antibody status during treatment at the MS Centre of Catania University Hospital [12]. These results further support geographical factors potentially favoring higher JCV seroconversion rates in European countries compared to Asian countries, and in a meta-analysis of JCV seroconversion status performed by Azimi et.al. a subgroup analysis was performed by considering the country of the origin, which showed that the pooled incidence of seroconversion during the studies was 6% in Asian countries and 21% in European/American countries [13]. In all cases, it remains higher than background annual seroconversion rates estimated to be in the range of 0.5 to 1% in normal populations; no cases of PML were detected throughout the observation period. Although the difference did not reach statistical significance, a higher rate of seroconversion was observed in males compared to females, which is consistent with the results obtained in several similar trials conducted in different countries. This trend may reflect differences in adaptive immune responses between males and females [14]. Research indicates that women typically mount more robust humoral and cellular immune responses, characterized by higher antibody production and more effective T-cell activation. These sex-specific responses may account for the observed trend, where males, despite having higher seroconversion rates in specific contexts, could represent a lower overall measure of immune efficiency compared to their female counterparts [14].

Although it is well established that the risk of PML is increased proportionately with the number of infusions and the duration of natalizumab therapy [15], no association was detected between the duration of treatment (measured in months) and JCV seroconversion in our study. This result was recorded consistently in other studies investigating the same parameter [16]. Previous studies suggest that risk factors for PML may not be directly correlated with JCV seroconversion rates. In an open-label, multinational, multicenter, prospective observational study, PML risk is multifactorial, rising mainly after three years of natalizumab, with higher rates in those with prior immunosuppressant use, and almost all cases occurring in JCV-positive patients [17]. The duration of monitoring or the characteristics of the patient population might influence these observations, as JCV seroconversion often requires extended periods to manifest [18].

The mean age of non-converters was 31 $\pm$ 9.9 years, while the sero-converters had a mean age of 32 $\pm$ 9 years. these findings suggest that JCV seroconversion rates do not vary significantly by age among MS patients on natalizumab, in concordance with prior literature, suggesting that age does not have a strong influence on JCV seroconversion rates in MS patients treated with natalizumab [19]. This finding aligns with broader research, including that of Branco et al. [20]. JCV antibody status showed no significant association with natalizumab use, aligning with previous studies and emphasizing the need to consider individual risk factors for JCV infection. Seroconversion occurred across age groups, including younger patients, highlighting the importance of routine JCV antibody monitoring to reduce PML risk.

This study found no significant association between JCV seroconversion and prior DMT use before starting natalizumab. The cohort included a narrow range of previous therapies, only one patient had received mitoxantrone, while the others had been treated mainly with interferon-β, fingolimod, or fampridine, limiting generalizability. The absence of an association is consistent with international findings showing that, although prior immunosuppression contributes to PML risk, JCV seroconversion is largely independent and influenced primarily by treatment duration and rising antibody titers [18]. These results reinforce the need

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Table 1. Mean duration of natalizumab (NZB) exposure and time to John Cunningham virus (JCV) seroconversion.

	NZB exposure duration (In months)	NZB exposure duration (In years)	JCV seroconversion duration (In months)	JCV seroconversion duration(In years)
Mean	47	4	35	3
Standard Deviation	28.88	2.39	29.08	2.41
Minimum	4	< 1	4	< 1
Maximum	105	9	103	8

Table 2. Factors associated with John Cunningham virus (JCV) seroconversion*.

		The last JCV index			
		Negative N(%)	Positive N(%)	Total N(%)	P-value
Sex	Male	53 (74.65%)	18 (25.35%)	71 (100.0%)	0.06
	Female	185 (84.47%)	34 (15.53%)	219 (100.0%)	
Any previous treatments for MS	None	27 (93.10%)	2 (6.90%)	29 (100.0%)	0.19
	Interferon-β derivative	170 (80.19%)	42 (19.81%)	212 (100.0%)	
	Interferon-β derivative, Fingolimod	27 (87.10%)	4 (12.90%)	31 (100.0%)	
	Interferon-β derivative, Fampridine	5 (55.56%)	4 (44.44%)	9 (100.0%)	
	Fingolimod	6 (100.00%)	0 (0.00%)	6 (100.0%)	
	Interferon-β derivative, Fingolimod, Fampridine	3 (100.00%)	0 (0.00%)	3 (100.0%)	

* MS: Multiple sclerosis, N: number, %: percentage. Negative JVC index = 0 or undetected. The significance of a JCV index ≥ 1.5 is that the risk of progressive multifocal leukoencephalopathy increases with higher levels of the JCV index.

for individualized monitoring and risk-management strategies, with consideration of patients' treatment history when assessing natalizumab-related risk [21, 22]. About 5.2% of Iraqi patients on natalizumab develop JCV antibodies each year, highlighting the need for structured follow-up. Anti-JCV antibody testing should be done at least twice yearly, with closer monitoring for rising index values. Patients with an index > 1.5 require careful risk–benefit evaluation. Male patients and those with prior immunosuppressive therapy may need stricter surveillance. National protocols led by neurological societies could improve early seroconversion detection and reduce PML risk, especially in resource-limited settings.

This study has limitations. Its single-center retrospective design limits generalizability, and the lack of detailed immunological data restricted identification of predictors of JCV seroconversion. The lack of logistic regression analysis limited the adjustment for potential confounders, and confidence intervals were not consistently reported, thereby reducing the precision of the effect estimates.

CONCLUSION

This is the first study on JCV seroconversion among Iraqi patients with MS treated with natalizumab. An annual durable seroconversion rate was estimated at 5.2% (0.43% per month), which was lower than western countries. No significant associations were observed with demographic or clinical variables. These findings highlight the importance of routine JCV antibody monitoring for all natalizumab-treated patients to enable early identification and management of PML risk.

ETHICAL DECLARATIONS

Acknowledgments

None.

Ethics Approval and Consent to Participate

All prior authorizations were acquired from the Iraqi Board of Medical Specializations and the director of the MS clinic before the commencement of this study (Reference No. 1102, dated February 2nd, 2024). Due to the retrospective design of the study, informed consent was waived.

Consent for Publication

Not applicable as no need for participants photos or personal information.

Availability of Data and Material

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request, subject to obtaining ethical approval and entering into data sharing agreements.

Competing Interests

The authors declare that there is no conflict of interest.

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Use of Artificial Intelligence

The authors used artificial intelligence for minor language editing; all scientific content and interpretation were done by the author.

Authors' Contributions

Both authors were responsible for conceptualization, design, and writing the manuscript. Both authors read and approved the final version of the manuscript.

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