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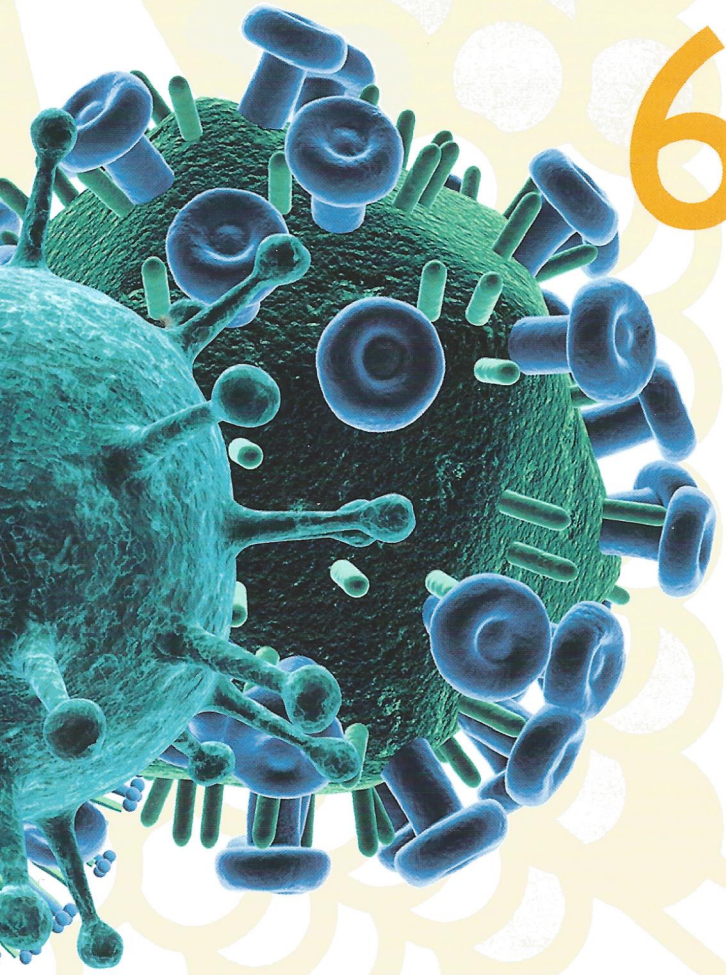

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HUMAN POLYOMAVIRUS JC MONITORING IN A COHORT OF MULTIPLE SCLEROSIS PATIENTS TREATED WITH NATALIZUMAB: AN OBSERVATIONAL STUDY

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Background: The occurrence of Progressive Multifocal Leukoencephalopathy (PML), caused by Human Polyomavirus JC (JCV), in patients affected by Multiple Sclerosis (MS) treated with monoclonal antibody natalizumab, has raised concerns about the safety of this drug. The precise mechanism by which this medication may have facilitated the pathogenesis of PML is a matter of debate. Therefore, the aims of this research have been 1) the evaluation and monitoring of JCV infection, 2) the analysis of the possible rearrangements within the viral noncoding control region (NCCR) and 3) the genotyping analysis of the viral protein 1 (VP1) in dynamic cohorts of MS patients treated with natalizumab.
Materials and methods: JCV-specific quantitative PCR was performed on biological samples collected at the enrollment (t0) and every 4 months (t1, t2, t3) for 1 year and in the second year of treatment (t4, t5). Then, specific PCR products for JCV NCCR and VP1 sequences were analyzed. Moreover, JCV-specific antibodies were assessed by STRATIFY JCV® in serum at t0 and t3.
Results: After 1 year of natalizumab, results showed a significant association between patients with JC viruria and a positive STRATIFY JCV® respect to those patients with no JCV-specific antibodies ($p=0.0006$). Moreover, at t4 the JC viremia was prevalently observed rather than JC viruria ($p=0.04$). Regarding NCCR sequence analysis, in peripheral blood mononuclear cells of patients STRATIFY JCV® positive at t3 and treated with 12 natalizumab infusions, NCCR sequencing revealed the presence of 4 rearranged sequences. In particular, two of them were compatible with the neurotropic variant IIR found in a PML patient. Finally, VP1 sequence analysis showed the prevalence of the genotypes 1A, 1B and 4.
Conclusions: In conclusion, for a more accurate PML risk stratification, testing JC viruria seems to be useful to identify patients who harbor JCV with an undetectable specific humoral immune response. It may also be important to study the JCV NCCR rearrangements since they could generate neuro-invasive viral variants increasing the risk of PML onset.