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Reply to Letter to the Editor

Reply to letter to the editor: "JC viremia and multiple sclerosis" by Focosi *et al*

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First of all, we would like to thank the authors for the interest and the opportunity to go into depth of our results concerning the possible role of beta interferon treatment on frequency of JC virus (JCV) DNA detection in peripheral blood mononuclear cells (PBMCs) of multiple sclerosis (MS) patients.

The authors are concerned because in their opinion DNA of JCV could not be found also in the peripheral blood of healthy people and, to this regard, they quote several scientific papers reporting negative results. However, the analysis of the literature performed by them is restricted because it ignores a large body of evidences reported by several authors, in more recent years, and showing the presence at a variable range of JCV DNA in the peripheral blood of both healthy subjects and patients with MS (Dorries *et al*, 1994, 2003; Azzi *et al*, 1996; Gu *et al*, 2003; Pietropaolo *et al*, 2005).

At the end of the paragraph regarding this topic, the authors suspect that polymerase chain reaction (PCR) we used could be flawed by methodological errors. The only possible answer to these comments is that our experience in the field of JCV dates from a long time and, more important, we participated to the recently settled European Quality Control for JCV/BKV PCR methods validation with excellent results (www.qcmd.org, 2007).

The authors also hypothesize that the presence of JCV in PBMCs of relapsing-remitting MS (RRMS) patients could be due to a misdiagnosis of progressive multifocal leukoencephalopathy (PML). We underline again that our MS patients were diagnosed according to the Poser *et al* (1983) criteria. Moreover, we believe that only inexpert neurologists could confuse PML with MS, mostly if we consider that our patients had MS diagnosed many years before the samples' collection.

We would also like to inform the authors and to highlight that the first scientist suggesting a possible etiological relation between MS and JCV was the late lamented Gerald Stoner (1991).

On these themes Focosi and colleagues recall also that Du Pasquier *et al* showed a strong cytotoxic lymphocyte (CTL) response against JCV VP1 in MS patients (Du Pasquier *et al*, 2006). In our opinion, this is an indirect evidence of the fact that JCV circulates in the blood of MS patients, stimulating immune competent cells against viral antigens. Regarding our previous data (Ferrante *et al*, 1998) showing the presence of JCV DNA in cerebrospinal fluid (CSF), Focosi *et al* stated that other authors did not confirm this report. Recently, we confirmed these results (Mancuso *et al*, 2007) and we would like to point out again that MS is a disease that can last for more than 20 years and its diagnosis is usually made from 5 to 15 years after the real onset of the disease. In addition, MS is characterized by very high cellular trafficking from periphery to central nervous system (CNS), an aspect that, in our opinion, supports the transport of viruses, and not only JCV, to the CNS and to the CSF of MS patients. We could also speculate about the preanalytical phase of the study of viruses' research in CSF (time of collection, length and methods of storage, etc.), but due to space restriction, we will not discuss this issue further.

Again regarding the possible relation between JCV and MS, Focosi *et al* quoted, without any apparent reason, the paper of Agostini *et al* (2000), showing the high frequency of JCV genotype 2b in PML patients, a finding that was also shown by our group (Ferrante *et al*, 2001).

Finally the authors underlined the differences between our data and those by Alvarez-Lafuente *et al* (2007) who did not find any statistically significant differences between treated and untreated MS

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patients. We would like to suggest that not only methodological aspects could be different but also the geographical provenience, clinical history, and perhaps genetic background of our patients and Alvarez-Lafuente's patients could be different.

However, this is only the beginning of a new era of interest in JCV and MS relationship and we believe that we must be open to different possible results during the coming years each time a new aspect of a very complex disease, such as MS, is studied.

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