

# What is the optimal timing of corticosteroids in the management of PML-IRIS?

## Study of the effects of corticosteroids on viral-specific T cell response

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### INTRODUCTION:

Progressive multifocal leukoencephalopathy (PML) is a severe demyelinating disease of the central nervous system (CNS) caused by the reactivation of the polyomavirus JC (JCV) [1].

Approximately 50 to 90% of adults have been exposed to JCV, and its reactivation in the setting of immunosuppression leads to a lytic infection of oligodendrocytes [1]. The incidence of PML in natalizumab-treated patients is estimated to be 1 case per 1,000 but it increases with longer treatment duration (peak at 24 months) [2], JCV seropositivity and previous use of immunosuppressants (incidence of 1.46/1000 patients). When these three conditions are present, the risk of PML is 8/1000 [3].

In PML caused by natalizumab, the treatment consists in plasma exchange (PLEX), which lead, in almost all cases to an immune reconstitution inflammatory syndrome (IRIS) after a mean delay of 35.3 days. Of note, IRIS can occur even when PLEX is not used [2-4].

IRIS is a paradoxical subacute worsening of clinical and neuroradiological conditions after an initial clinical improvement. IRIS corresponds to an inflammatory response to pathogen(s) associated with recovery of the immune system after a period of immunosuppression [5]. This phenomenon corresponds to CD4+ and CD8+ T cells trafficking into the CNS. The major role of CD8+ T cells in the management of PML has been widely described [6].

The optimal timing when corticosteroids (CS) have to be administered after natalizumab removal in a PML patient remains controversial. Some authors advocate that CS should be given early, at the time of PLEX, to prevent IRIS [7], but others are in favor of delayed CS, in order not to impede the action of JCV-specific cytotoxic T lymphocytes (CTL) on infected oligodendrocytes [4]. Yet, the effect of CS on JCV-specific T cell response is unknown.

### Aim of the study:

In this study, we aimed at examining to which extent CS affect the viral-specific T cell immune response. Indeed, we thought that this information could help in determining whether CS should be given before - or at the time of - IRIS in affected PML patients.

### Material and Methods:

22 relapsing MS patients treated with high doses of intravenous CS (methylprednisolone 1g/day x 3 days), usually followed by tapering oral prednisone for 10 days, were enrolled from January to May 2010.

None of the enrolled MS patients had received CS within 3 months prior to enrollment. Four were on IFN-β treatment, 3 on glatiramer acetate, 1 on fingolimod, and 1 stopped Natalizumab 3 months prior to enrollment.

To elicit a JCV-specific CD4+ and/or CD8+ T cell response, we used 15-mer overlapping by 10 aa and covering the entire major capsid protein VP1; and for EBV and FLU, viral lysate (CD4+>>CD8) and pool of immunodominant peptide epitopes (CD8+).

#### Assays performed:

- To measure the proliferation of viral-specific T cells: thymidine-incorporation proliferation assay
- To assess viral-specific effector T cells: Intra Cellular Cytokine Staining assay (ICS) measuring the secretion of IFN-γ and TNF-α
- To evaluate the impact of CS on the phenotypic pattern of T cells: FACS analysis measuring the expression of CCR7 and CD45RA
- To determine the prevalence of JCV-infection in our cohort: two-step serological assay kindly performed by Biogen Idec (Stratify®), UNILABS, Copenhagen, Denmark)

### DISCUSSION:

- We showed that, on CS, there was a significant decrease of :
  - viral-specific T cell proliferative responses, in particular the JCV-specific ones.
  - INF-γ release by JCV-specific CD8+ T cells, but not by CD8+ T cells specific for FLU or EBV.
- This decrease in INF-γ secreting JCV-specific CD8+ T cells paralleled a strong decrease in effector memory CD8+ T cells [8]. We also found that CS induced a decrease in central memory CD8+ T cells and had an impact on terminally differentiated CD4+ T cells.
- CS treatment impairs significantly JCV-specific T cell responses, in particular the CD8+ T cell one
- Prophylactic CS, i.e. CS given before any sign of clinical or neuroradiological IRIS, may delay or even jeopardize the containment of PML

### REFERENCES:

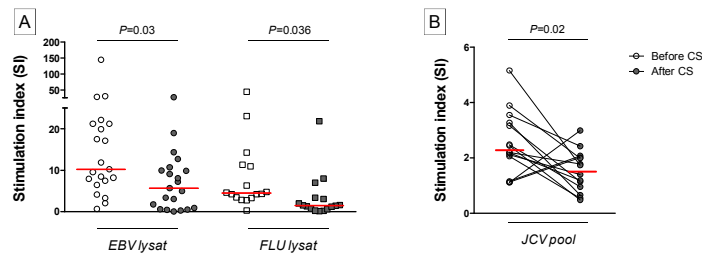
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### DISCLOSURE:

Have nothing to disclose: C. Antonioli, S. Jilek, N. Mercier, G. Le Goff, C. Campiche, M. Canales, and G. Pantaleo.  
 M. Schlupe has served as a consultant for Merck-Serono, has received honoraria, payment for development of educational presentations and travel support from Merck-Serono, Biogen Dompe, Novartis, Sanofi-Aventis and Bayer Schering.  
 R. Du Pasquier serves on scientific advisory boards for Biogen Idec, Merck Serono, Teva, and Novartis, has received funding for travel or speaker honoraria from Biogen Idec, Teva, Merck Serono, and Bayer Schering Pharma.

### RESULTS

#### 1. Decrease of EBV- and FLU-specific CD4+ and JCV-specific CD4+ and CD8+ T cell proliferative responses after CS

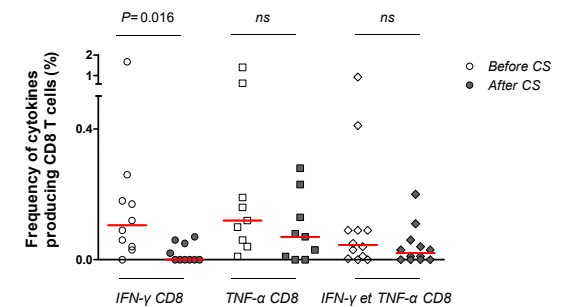


A) Proliferation assay in the 22 patients before and after CS

B) Proliferation assay in 9 JCV-infected patients harboring a JCV-specific T-cell response

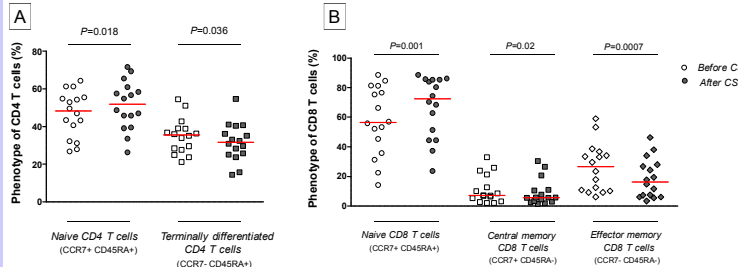
Each pool which elicited a positive response (SI>2), either before, after, or at both time points is represented. Thus, there can be more than one pool per patient. Of note, in few cases, a pool elicited a stronger T-cell response after CS than before, which explains why some dots before CS are situated under the SI of 2. SI= Stimulation Index. Horizontal bars indicate median values of each group.

#### 2. Decreased frequency of IFN-γ producing JCV specific CD8+ T cells after CS



Frequency of cytokine producing JCV-specific T-cells before and after CS in 9 JCV-infected MS patients

#### 3. Changes in the phenotypic T cell population on CS



Horizontal bars indicate median values of each group.

#### 4. Good correlation between JCV serology and detection of JCV DNA in urine by quantitative PCR in 15 MS patients

	JCV Serology +	JCV Serology -
qPCR JCV +	6 patients	0 patients
qPCR JCV -	3 patients	6 patients

JCV DNA was detected by quantitative PCR (qPCR) in the urine of 6/9 patients who were exhibited JCV-specific antibodies in the blood. However, JCV DNA was not detected in the urine of any of the six MS patients who were seronegative for JCV.

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