Six year prospective immunological study of alemtuzumab treated patients: identification of markers of the clinical response

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Background: Alemtuzumab is a highly effective treatment for relapsing remitting multiple sclerosis (RRMS) that selectively targets the CD52 antigen, with consequent profound T and B lymphocyte depletion. In particular alemtuzumab induced a CD4+ T cells lymphopenia, a decrease of Th17 and Th1 cells and pro-inflammatory molecules and a restored Treg suppressor function that long last for years. 25-30% MS patients, however, relapse after alemtuzumab treatment.
Aims: Long-term immunological study of RRMS patients after alemtuzumab treatment to identify markers that could help to predict the clinical response to the drug.
Methods: Multicenter follow-up of 29 alemtuzumab-treated RRMS patients from 6 European sites in the CARE-MS I and CARE-MS II trials. Patients received two courses of alemtuzumab at Month 0 and 12. Further courses have been repeated in non responders. Clinical and immunological evaluation were performed at Months 0, 6, 12, 18, 24, 36, 48, 60 and 72. CD4+ T cells, Treg, Th1 and Th17 cells were evaluated in the peripheral blood mononuclear cells by FACS analysis. mRNA levels of cytokines, chemokines, chemokine receptors and transcriptional factors with pro-inflammatory (IL-1β, IL-2, IL-6, IL-12, IL-17A, IL-17F, IL-21, IL-22, IL-23, IL-26, IFN-γ, T-bet, RORC, TNF-α, CCR3, CCR4, CCR5, CCR6, CXCR3, CXCL10, CCL20, VLA4) or anti-inflammatory function (IL-10, IL-27, TGF-β, FoxP3) were quantified by TaqMan® low density array real-time polymerase chain reaction in whole blood.
Results: Nine patients had a clinical or MRI disease activity resumption between Month 20 and 32. At Month 18 they had a higher Th17/Treg ratio and increased IL-1β mRNA levels compared to patients that remained stable. Two patients continued to present evidence of disease activity despite repeated alemtuzumab courses. They display an atypical CD4+ T population behaviour different from the other patients. Despite that lymphocyte count strongly decreased after the first administration of alemtuzumab and then fluctuated accordingly to alemtuzumab administration, the percentage of CD4+ cells was not or just mildly affected.
Conclusions: An increase of Th17/Treg ratio and of the pro-inflammatory cytokine IL-1β mRNA level after alemtuzumab could be an early marker of MS disease activity resumption suggesting alemtuzumab retreatment. Furthermore, the evaluation of the CD4+ cell percentage could represent a helpful tool to address the individual clinical response to the drug.
Disclosure:
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SD had travel expenses for congresses paid by Merck, Biogen, Novartis and Sanofi-Genzyme;VB: nothing to disclose;
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