14 ANTI-IL6R TREATMENT ACTS ON CD4⁺ FOXP3⁺ REGULATORY T CELLS IN A MODEL OF RHEUMATOID ARTHRITIS

A Thiolat,¹ J Biton,¹ L Semerano,^{1,2} D Lemeiter,¹ M C Boissier,^{1,2} N Bessis¹ ¹EA4222, Li2P, Paris 13 University, 74 rue Marcel Cachin, Bobigny, France; ²Rheumatology Department, Avicenne Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), 125 rue de Stalingrad, Bobigny, France

10.1136/annrheumdis-2011-201230.14

Background and objectives Studies have demonstrated the clinical efficacy of tocilizumab, a humanised anti-IL-6 receptor (R) antibody (Ab), in patients with rheumatoid arthritis (RA). The rationale for blocking IL-6 in this disease mainly lays on the pro-inflammatory role of this cytokine in the disease. Moreover, IL-6 acts as a 'pivot', determining whether an immune response is dominated by regulatory CD4⁺Foxp3⁺ T cells or Th17 effector T cells. However, only few works have studied the consequences of anti-IL-6R treatment on Tregs cells and only focuses on their frequency. In this study, the authors hypothesised that IL-6 inhibition leads to Tregs modifications in RA models given that (i) anti-IL6R is therapeutic in RA and its models by inhibiting Th17 cells, and (ii) IL-6 plays a determining role in inducing Th17 when present, or Tregs when it is absent.

Our objective was thus to elucidate anti-IL-6R mode of action in RA models by studying the consequences of this treatment on Tregs phenotype and biological activity.

Methods Mice with collagen-induced arthritis were treated by MR16-1 (a rat antimouse IL-6 receptor monoclonal Ab provided by Chugai Pharmaceutical Co LTD, Japan) and the evolution of Tregs (defined as CD4⁺ FoxP3⁺) during arthritis course was assessed at key time points (day 9–17–28 and 43 after CIA induction) by studying their number, frequency and phenotype (expression of GITR, ICOS, Helios, CD62L, CTLA-4 and CD39) in lymph nodes (LN) and spleen by flow cytometry. Finally, the immunosuppressive activity of the Treg cells on CFSE-labeled CD4⁺ CD25⁻ T effector (Teff) cells proliferation

was also studied. Numerical analysis of Th17 and Th1 cells was also performed at the same times by flow cytometry.

Results Clinical evaluation of arthritides in mice treated with anti-mouse IL-6R mAb showed, as expected, a less severe disease as compared to control Ig treated mice. A decreased Teff/Tregs ratio overtime were observed in the LN of MR16-1 treated mice. Tregs phenotype was modified in treated mice mostly at day 17, with a decreased frequency of Tregs expressing CD62L or Helios (spleen) but an enhanced intensity of CD39 expression on Tregs (spleen and LN) and increased frequency of CD39+ Tregs (LN). No modification in ICOS, GITR and CTLA-4 were observed on Tregs at any time in any compartments. Lastly, the immunosuppressive activity of the Treg cells on Teff cells proliferation was not modified, suggesting that Tregs immunosuppression activity was probably due to another mechanism..

Conclusion Tregs are modified by anti-IL-6R treatment in CIA, that could result in an enhanced peripheral generation of Tregs (Helios down regulation), an increased Tregs activation (CD39+ upregulation) and a better capacity to leave the secondary lymphoid organs and to migrate within the inflammatory joint (decreased CD62L down regulation). Altogether, this study shows that inhibition of IL-6 in CIA also acts by modifying Tregs state.