8 CTLA-4-IG (ABATACEPT) THERAPY REDUCES T CELL FUNCTION FOR ALL DEFINED CD4 CELL SUBSETS INCLUDING REGULATORY T CELLS (TREG)

Jessica Herrath,¹ Jennifer Pieper,¹ Ronald van Vollenhoven,² Vivianne Malmström¹ ¹Rheumatology Research Unit, Department of Medicine, Karolinska University Hospital Solna, Karolinska Institutet, Stockholm, Sweden; ²Unit for Clinical Research Therapy, Inflammatory Diseases, Karolinska Institutet, Solna, Stockholm, Sweden

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Background and objectives Rheumatoid arthritis (RA) is a complex autoimmune disorder primarily affecting peripheral joints where CD4+T cells are abundant at the site of inflammation. Regulatory T cells (Treg) are a crucial T cell subset in maintaining immune homeostasis. The authors, and others, have previously shown that Treg are significantly enriched in synovial fluid of patients with inflammatory arthritis such as RA.

CTLA-4-Ig is a T cell co-stimulation modulator and licensed for the treatment of moderate to severe RA, including patients with a history of failing other biological therapies.

Here, the authors aimed to understand the effect of CTLA-4-Ig therapy on different T cell subset function in patients with RA, first by a phenotypic and in vitro analysis approach of peripheral blood mononuclear cells (PBMCs) from patients undergoing CTLA-4-Ig therapy and second by assessing the suppressive capacity of synovial-fluid derived Treg in vitro in co-cultures supplemented with CTLA-4-Ig.

Materials and methods Peripheral blood was collected at baseline and after three or 6 months of CTLA-4-Ig therapy from RA patients (n=22). Phenotyping was done by multiparameter flow cytometry, cytokine production was assessed following polyclonal stimulation and analysed by both intracellular flow cytometry and luminex technology. In addition, CTLA-4-Ig was added to in vitro co-culture assays to assess its influence on synovial-fluid derived Treg and T effector cells from chronic RA patients (n=6).

Results In vitro stimulation of PBMCs from patients at baseline and after 6 months of CTLA-4-Ig therapy resulted in a significant reduced output of IFN- γ , IL-13, TNF and in a modest reduction of IL-17 (n=14). The frequency of Treg was decreased after 3 months of treatment (n=8), and a diminution of the Treg-associated markers FOXP3 ($p \leq 0.01$), CTLA-4 ($p \leq 0.01$), CD39 ($p \leq 0.01$) and CD25 ($p \leq 0.05$) was seen.

Functional studies to determine to what extent abatacept interfered with suppressive capacity of Treg showed no beneficial effect on Treg function in contrast to what the authors have previously demonstrated for tocilizumab (anti-IL6R) and adalimumab (anti-TNF). Still, addition of CTLA-4-Ig to co-cultures reduced the proliferative capacity of T effector cells.

Conclusion CTLA-4-Ig therapy diminishes T cell effector functions in vitro but does not completely abrogate their function. This diminution also included Treg frequency. So far, T cell phenotyping could not predict treatment response, instead more detailed studies are needed such as analysis of antigen-specific T cells relevant for RA initiation and progression.