Reduced LAG-3$^+$ T cells are restored by TNF inhibitors in PBMCs derived from active PsA patients in vitro

Smadar Gertel*, Ari Polachek*, Victoria Furer, David Levartovsky and Ori Elkayam.
Department of Rheumatology, Tel Aviv Sourasky Medical Center and the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.

Background: PsA disease is characterized by aberrant T cell regulation, one of the regulatory receptors expressed on T cells is lymphocyte-activation gene (LAG)-3.

Aim: To assess surface levels of LAG-3 on CD4$^+$ T cells derived from PsA patients with low and high disease activity in comparison with healthy controls and determine the effect of biologics on the LAG-3$^+$ T cell population in vitro.

Methods: PsA patients recruited to this study were clinically assessed and classified as having minimal disease activity (MDA) or non-MDA, healthy donors were included as controls. Peripheral blood mononuclear cells (PBMCs) were co-cultured with medium alone or with TNF inhibitors (i) or IL-17Ai and their effect on %CD4$^+$LAG-3$^+$ T cells was determined.

Results: In PBMCs derived from healthy controls (n=15) and from MDA PsA patients (n=14) the %CD4$^+$LAG-3$^+$ T cells after 5 days in culture with medium alone was 7.7±0.6 and 7.5±0.9, respectively. Supplementation of either TNFi or IL-17Ai to the culture had no effect on the %CD4$^+$LAG-3$^+$ T cells (8.5±0.6, 7.0±0.6 and 7.6±0.9, 7.7±0.9, respectively) (Figure 1). In contrast, significantly lower %CD4$^+$LAG-3$^+$ T cells were found in non-MDA (n=13) (3.1±0.3, $p< 0.0001$) as compared to MDA PsA patients and healthy controls. In non-MDA PsA patients, incubation with TNFi restored the %CD4$^+$LAG-3$^+$ T cells compared to medium control (7.9±0.9, $p< 0.0001$), to an equivalent levels as determined after incubation with medium in healthy and MDA PsA patients. On the other hand, after supplementation of IL-17Ai the %CD4$^+$LAG-3$^+$T cells remain low (3.2±0.4). Moreover, there was a significant inverse correlation between percentages of CD4$^+$LAG-3$^+$T cells after in vitro culture with medium alone and the clinical disease activity of the PsA patients in the cohort (CPDAI, r=-0.47, $p < 0.02$ and PASDAS, r=-0.51, $p < 0.008$).

Conclusions: Lower surface LAG-3 expression levels on CD4$^+$ T cells may reflect active PsA disease state. TNF inhibitors have potency to up-regulate this population. Larger studies are needed to verify this observation.

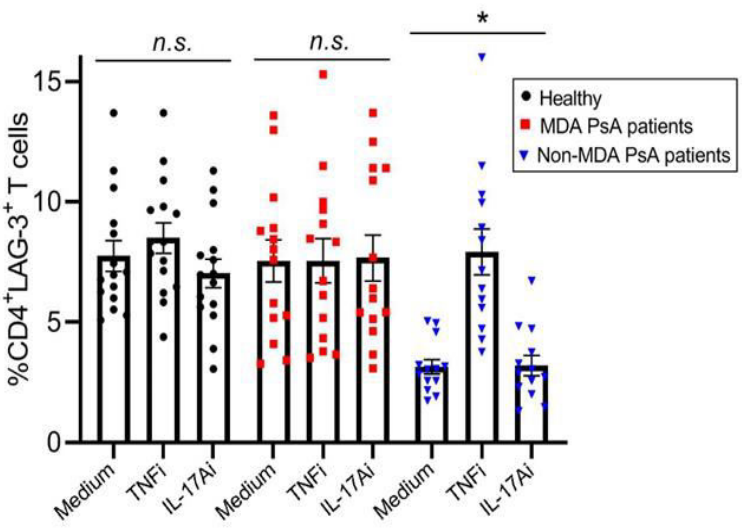

Figure 1. *Levels of CD4$^+$LAG-3$^+$ T cells derived from healthy, MDA and non-MDA PsA patients and different biologics ability to modulate the CD4$^+$LAG-3$^+$ T cells in vitro.* PBMCs from healthy donors (n=15), MDA (n=14) and non-MDA (n=13) PsA patients were co-cultured medium or with TNFi (Adalimumab) or IL-17Ai (Ixekizumab). Analysis of CD4 and LAG-3 expression was determined by flow cytometry. Graphs represent the mean percentages ± SEM of CD4$^+$LAG-3$^+$ T cells. Significance between groups was determined by Mann-Whitney U test, * $p < 0.001$.