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T REGULATORY CELLS AS BIOMARKER OF DISEASE ACTIVITY AND RESPONSE IN PSORIATIC ARTHRITIS PATIENTS: RESULTS FROM APREMILAST-TREATED COHORT

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Background: The PDE4-inhibitor apremilast has been recently introduced in the treatment of Psoriatic Arthritis (PsA). It acts by down-regulating intracellular inflammatory mediators synthesis by elevating cAMP levels. Tregs, a subset of FOXP3+ CD4 T cells, play a key role in preventing immune responses and could exert their suppressive function via cAMP (1). Reduced frequencies of circulating Tregs have been observed in inflammatory disorders, nonetheless very few data are available on PsA patients.

Objectives: We evaluated peripheral Tregs in a cohort of PsA patients treated by apremilast.

Methods: Seventeen PsA patients (M/F 3/14; median age 56.0 years, IQR 20.0; median disease duration 15.0 years, IQR 11.0) with polyarticular subset treated by apremilast, were evaluated at baseline (T0) and after 6 (T1) and 12 weeks (T1). Clinimetric evaluation included DAS28, DAPSA, CDAI, and SDAI. Moreover, US assessment was performed at wrists, metacarpophalangeal (MCP), and proximal interphalangeal (PIP) joints: synovial effusion/hypertrophy and power Doppler were scored by a semi-quantitative scale (0-3), obtaining a total score (0-198). Treg frequency was assessed in peripheral blood mononuclear cells by flow cytometry, as the percentage of CD127low FOXP3+ in live CD4+ T cells (%Treg).

Figure 1: Correlation between %Treg and disease activity indices (DAS28, CDAI, SDAI, DAPSA, US inflammatory score).

Results: At baseline we identified a median %Tregs of 4.6 (IQR 1.1), inversely correlating with DAS28 ($r=-0.5$, $p=0.02$), DAPSA ($r=-0.7$, $p=0.003$), CDAI ($r=-0.6$, $p=0.01$), SDAI ($r=-0.6$, $p=0.003$) and US inflammatory score ($r=-0.6$, $p=0.01$) (Figure 1). Treatment with apremilast was able to induce a significant improvement in all activity indices at T1 (DAS28, $P=0.009$; DAPSA, $P=0.01$; CDAI, $P=0.005$; SDAI, $P=0.006$; US score, $P<0.0001$) and T2 (DAS28, $P<0.0001$; DAPSA, $P=0.007$; CDAI, $P=0.008$; SDAI, $P=0.006$; US score, $P=0.0005$). Furthermore, responding patients according with EULAR criteria at T2 showed significantly higher %Treg at

baseline in comparison with non-responder patients (median 4.8, IQR 1.2 versus median 2.9, IQR 1.1; $P=0.02$).

Conclusion: The results of our study demonstrate that %Treg is a marker of disease activity in PsA patients. Moreover, the baseline value of Tregs could predict the response to apremilast after 12 weeks of treatment.

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PDE4 TARGETING SELECTIVELY INHIBITS INFLAMMATORY-DRIVEN OSTEOCLASTOGENESIS

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Background: Patients suffering from Psoriatic arthritis (PsA) commonly develop bone erosions and inflammatory-induced bone loss. This process is mediated by osteoclasts derived from monocytic precursors, and modulated by inflammatory cytokines (i.e. TNF, IL-1, IL-6, IL-17, IL-10 and GM-CSF) from immune and stromal cells. In immune cells (including CD14⁺ osteoclast pre-cursors), PDE4, an enzyme responsible for hydrolysing cyclic AMP to inactive AMP, drives inflammatory effects [1]. Importantly, Apremilast (APR; a selective PDE4 inhibitor) has known efficacy in PsA [2], and decreases pro-inflammatory mediators whilst increasing anti-inflammatory mediators (IL-10) [3]. Although published data indirectly suggest a positive impact of APR on bone in PsA, data is lacking with regard to the impact on bone resorption.

Objectives: To evaluate the impact of a selective inhibition of PDE4 by APR on osteoclastogenesis from human CD14⁺ precursors.

Methods: Osteoclasts were differentiated from primary human CD14⁺ blood monocytes (healthy controls) with RANKL and MCSF, in the presence or absence of APR. To specifically study the impact of APR on osteoclastogenesis in an inflammatory context, osteoclastogenesis was also undertaken in the presence of: (i) TNF, (ii) Supernatants from activated Peripheral Blood Mononuclear Cells (PBMC) or activated CD3 cells, treated with or without APR, (iii) Co-culture with activated PBMC or activated CD3 cells, treated with or without APR. TRAP⁺ multinucleated cells (mature osteoclasts) were enumerated via microscopy.

Results: In a non-inflammatory context, PDE4 inhibition by APR did not affect the differentiation of CD14⁺ precursors into mature osteoclasts. However, TNF-enhanced osteoclastogenesis was significantly decreased by APR (-30.0% +/- 14.9; $p=0.0279$). The treatment of either activated PBMCs or purified CD3⁺ T cells with APR substantially reduced cellular activation. In PBMCs this decrease in cellular activation resulted in a decrease in conditioned media-driven osteoclastogenesis (-49.7% +/- 13.2; $p=0.0385$). In comparison, APR treatment of purified CD3⁺ T cells did not reduce their osteoclastogenic potential.

Conclusion: The results of this study reveal that PDE4 targeting potentially inhibits inflammatory-driven osteoclastogenesis. Moreover, these data also suggest that CD3⁺ T cells are not the main target of PDE4 inhibition in this context. In summation, our study supports the hypothesis that APR can modulate bone integrity in inflammatory condition such as PsA.

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