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FRI0364

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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FRI0366 **SUBSTANTIAL CHANGES IN BONE FORMATION REGULATORS BIOMARKERS IN EARLY AXIAL SPONDYLOARTHRITIS – ROLE OF TNF INHIBITORS**

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Background: The hallmark of advanced axial spondyloarthritis (SpA) is spine ankylosis, due to an excess of bone formation. Our hypothesis was that pathways of bone formation regulators changed over time and that their changes were related to inflammation or use of “anti-inflammatory” drugs (like non-steroidal anti-inflammatory drugs (NSAIDs) and/or Tumor Necrosis Factor inhibitors (TNFi)).

Objectives: This prospective study aimed to describe the 5-year serum changes of bone formation regulators markers (sclerostin, bone morphogenetic protein 7 (BMP-7) and Dickkopf-1 (DKK-1)) in early axial SpA and to assess determinants of their changes.

Methods: The DESIR cohort is a prospective, multicentre French study of 708 patients (34 ± 9 years, 58% HLA B27 positive, BASDAI 45 ± 20) with early (> 3 months and < 3 years) inflammatory back pain suggestive of axial SpA. Sclerostin, BMP-7 and DKK-1 serum levels were assessed at baseline, two and five years. Change in bone formation regulators over time was analysed using mixed linear models, first in complete-cases and then in available-cases analysis. Determinants of serum biomarkers change were analysed using mixed linear models and we searched for an interaction between time and determinants of serum biomarkers.

Results: Serum levels of each biomarkers at baseline, two and five years are reported in Table 1. Serum BMP-7 significantly increased over time, with a mean of 0.17 pg/mL per month (Figure 1A). Median relative change of BMP-7 at five years was 53.0% [IQR -31.6%, 286.8%]. Serum BMP-7 levels was undetectable in 337 patients (59.6%) at baseline, in 111 patients (48.0%) at two years and in 59 patients (20.2%) at five years. At baseline, serum sclerostin was significantly correlated with age (r = 0.28, p < 0.001), weight (kg) (r = 0.10, p = 0.007), CRP level (mg/mL) (rS = -0.14, p < 0.001), mSASSS (r = 0.08, p = 0.03), number of syndesmophytes (r = 0.15, p < 0.001), bone mineral density in hip and lumbar spine (r = 0.19, p < 0.001 and r = 0.18, p = 0.001 respectively). Serum sclerostin significantly increased over time, with a mean of 0.001 ng/mL per month (Figure 1B). Median relative change of sclerostin at five years was 14.8% [-7.9%, 41.4%]. Serum DKK-1 did not significantly vary over time. In multivariate analysis, serum BMP-7 increased with moderate or high disease activity (ASDAS-CRP) (0.19 pg/mL per month, p = 0.01), in men (5.3 pg/mL, p = 0.004) and decreased with the duration of TNFi use (-0.04 per month of TNFi use, p < 0.001). Unlike in serum BMP-7, there was not a significant interaction between time and determinants of serum sclerostin. In multivariate analysis, serum sclerostin increased with time (0.001 ng/mL per month, p < 0.001), age (0.007 ng/mL per year, p < 0.001) and in men (0.05 ng/mL, p = 0.001) but decreased with the use of TNFi (-0.037 ng/mL, p < 0.001), in patients with a Z score ≤ -2 at at least one site (-0.036 ng/mL, p = 0.005) and with serum BMP-7 levels (-0.0006 ng/mL per unit of serum BMP-7, p = 0.03).

Conclusion: Serum BMP-7 levels significantly increased over time with a rapid and substantial change. Serum sclerostin levels significantly increased over time but to a lesser degree than serum BMP-7. Serum BMP-7 changes were related to the use of TNFi.

Table 1. Serum levels of bone biomarkers over time

	SOST (ng/mL)	DKK-1 (pg/mL)	BMP-7 (pg/mL)
Baseline	0.45 ± 0.18	5413.0 ± 2370.0	11.0 ± 27.5 2.1 [0 – 15.7]
Two years	0.46 ± 0.15	5621.3 ± 2571.0	20.3 ± 19.2 16.2 [5.2 – 27.7]
Five years	0.51 ± 0.19	4998.2 ± 2889.3	20.9 ± 17.6 19.5 [7.2 – 30.6]

Results are expressed by mean ± standard deviation and median [IQR]

Figure 1:

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FRI0367 **INFLAMMATORY PROCESSES IN EXPERIMENTAL SPONDYLOARTHRITIS ARE ACCOMPANIED BY FORMATION OF ECTOPIC LYMPHOID STRUCTURES IN THE BONE MARROW AND ALTERATIONS IN THE B CELL LINEAGE**

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Background: Tumour necrosis factor (TNF) is important in immune-mediated inflammatory diseases such as spondyloarthritis (SpA). SpA patients have extensive angiogenesis in inflammatory and bone forming regions. Transmembrane (tm)TNF-transgenic (tg) mice (1) that overexpress tmTNF develop SpA symptoms, including inflammation, bone destruction and bone formation. Interestingly, these mice also develop lymphoid aggregates in the bone marrow (BM) of the axial and peripheral skeleton.

Objectives: Characterization of lymphoid aggregates in tmTNF tg mouse BM in the context of angiogenesis and bone formation.

Methods: Ankles, femora, tibiae, vertebrae and spleens from tmTNF tg mice and wild-type (WT) littermates (6 weeks, 12 weeks, and 8 months old; n=5 per age per group) were dissected and analyzed by confocal microscopy. In addition, 12 week old mice (n=5 per group) were analyzed by flow cytometry. To study the importance of TNF-R signaling in these processes, tmTNF tg mice lacking TNF-RI (tmTNF tgTNF-RI^{-/-}) or TNF-RII (tmTNF tgTNF-RII^{-/-}) (n=4 per group) were investigated.

Results: Immunofluorescent (IF) evaluation demonstrated that BM of tmTNF tg mice contained extensive lymphoid aggregates, both in the vertebrae and the ankles, but not in the femurs or spleen. IF microscopy demonstrated that the aggregates in the BM contain characteristics of ectopic lymphoid structures (ELS) and consisted of B220⁺ B cells and FDC-M1⁺ follicular dendritic cells that are in close proximity of MECA79⁺ high endothelial venules (HEVs). Flow cytometric analysis revealed that most B220⁺ B cells are IgD⁺ naive B cells and that tmTNF tg vertebrae