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Background: Giant cell arteritis (GCA) represents the most prevalent form of systemic vasculitis in elderly, characterized by a remarkable heterogeneity in terms of clinical and histological phenotype, the pathogenetic mechanisms and treatment selection (1). An interplay between cells of both innate and adaptive immunity, appear to govern the pathophysiologic mechanisms (2). Among the different cellular populations, neutrophils may hold a central role in GCA pathogenesis, since they are present in abundance in tissue injury (3,4). Most importantly, they are a source of neutrophil extracellular traps (NETs) that may deliver immunocompetent substances, necessary for the perpetuation of the inflammatory response (5). The detection and function of NETs have not been studied in GCA. **Objectives:** To explore the presence and clinical significance of NETs in temporal artery biopsies (TABs) of patients with GCA.

Methods: Ten patients with GCA [5 with limited cranial vasculitis (CV) and 5 with associated generalized large vessel vasculitis (LVV), as defined by ¹⁸F-fluorodeoxyglucose (FDG) positron-emission tomography with computed tomography (PET/CT)] and 8 patients with polymyalgia rheumatica (PMR) were studied. GCA and PMR patients fulfilled the 1990 ACR and 2012 EULAR/ACR provisional classification criteria, respectively. The presence, location, quantitation and decoration of NETs with IL-6, IL-1 β , and IL-17A were assessed in TABs at the time of disease diagnosis by tissue immunofluorescence and confocal microscopy. Quantification of NETs in tissue sections was performed using the Imaris v.9.3 software that counts the total measure volume instead of only the projection area (6). Serum levels of IL-6 and IL-17A around the time of tissue biopsy were also evaluated in all patients.

Results: All temporal artery biopsies from GCA patients had NETs located mainly in the adventitia, adjacent to the vasa vasorum, whereas TABs from PMR patients had no NET structures. LVV was associated with a higher NETs to total tissue volume ratio, compared to CV-GCA [$p=0.0317$]. NETs decorated with IL-6 were present in TABs of all LVV and 3 of 5 CV-GCA patients, while IL-17A positive NETs were observed in all GCA patients. IL-1 β -positive NETs were not detected in any GCA patient. No relation was found between serum IL-6 and IL17A levels and NETs containing IL-6 and/or IL-17A.

Conclusion: NETs bearing IL-6 and IL-17A cytokines are present in inflamed GCA-TABs. IL-6 positive NETs are associated with the LVV phenotype and might be useful as a tissue biomarker for disease severity and extent.

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Of mice and man: insights into pathophysiology of rheumatoid arthritis and spondyloarthritis

OP0030

TREATMENT OF NON-BIOLOGIC-DMARD-IR PSA PATIENTS WITH UPADACITINIB OR ADALIMUMAB RESULTS IN THE MODULATION OF DISTINCT FUNCTIONAL PATHWAYS: PROTEOMICS ANALYSIS OF THE SELECT-PSA 1 PHASE 3 STUDY

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Background: Treatment of non-biologic-DMARD-IR (DMARD-IR) PsA patients with upadacitinib (UPA) at 15 mg QD, an oral JAK1 selective inhibitor, resulted in improvement in musculoskeletal symptoms, psoriasis, physical function, fatigue, quality of life, and inhibited radiographic progression; improvements were

observed as early as Week 2 (ACR20 and ACR50). UPA 15 mg QD was non-inferior to adalimumab (ADA) 40 mg EOW for ACR20¹

Objectives: To determine the relative biological pathway modulation of UPA compared with ADA in patients with PsA via the evaluation of a pre-defined set of plasma proteins associated with inflammation.

Methods: Patients from the SELECT-PSA1 study (DMARD-IR PsA patients) were randomly selected (PBO, n=100; UPA 15 mg QD, n=100; ADA 40 mg EOW, n = 100). The levels of 92 inflammation related protein biomarkers (pBM) were analyzed using a multiplexed Proximity Extension Assay platform in plasma samples collected at baseline, week 2, and 12; change from baseline in protein levels were expressed as Log₂ Fold Change; a Repeated Measure Mixed Linear Model identified proteins modulated by UPA and ADA compared to Baseline. Functional pathway prediction was performed in silico with a commercially distributed software where 52 significantly modulated pBM (mean ILog₂ FCI ≥ 0.1 AND FDR ≤ 0.05) were selected; results were summarized based on 3 core biological groups: 1) adaptive immune system, 2) innate immune system, and 3) non-immune connective and vascular systems.

Results: At the single pBM-level, at the week 2 and 12 time points, treatment with UPA 15 mg QD resulted in distinct down modulation of T cell-associated (CD5, CD8a, IL15Ra, SLAMF1, TRANCE) and myeloid cell-associated pBM (CSF-1, CCL7, CCL13) that was not observed in the ADA treated group. Reciprocally, treatment with ADA 40 mg EOW resulted in a specific down modulation of a subset of neutrophil associated pBM (CCL3, CCL4, and S100A12). Both treatments resulted in the down modulation of IFN-, IL6-, and TNF-related pBM (CXCL9, CXCL10, CXCL11, IL6, TNFRSF19, and TNFSF14) suggesting a common node of activity related to these pivotal cytokine-signaling pathways.

Functional pathway prediction based on the pBM data revealed that treatment with UPA is preferentially associated with the inhibition of T cells, but also NK cells and lymphocytes, compared to the predicted effects of treatment with ADA. Treatment with UPA also preferentially inhibited pathways related to bone damage and angiogenesis, as compared to the predicted effect of treatment with ADA. Finally, both treatments were predicted to inhibit multiple pathways associated with the activity of myeloid cells and phagocytes.

Conclusion: Consistent with previous observations in RA², UPA is predicted to inhibit multiple functional pathways associated the pathobiology of PsA belonging to the general categories of adaptive and innate immunity but also non-immune vascular and connective tissue biology. In contrast, treatment with ADA appears to affect more specifically functional pathways associated with the innate immune system.

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