Proceedings Paper:
Ouboussad, L, Hunt, L, Wong, C et al. (4 more authors) (2018) Investigating IL-6 intracellular signalling in peripheral blood cell subsets in patients at early and later stages of rheumatoid arthritis (RA). In: Annals of the Rheumatic Diseases. 38th European Workshop for Rheumatology Research, 22-24 Feb 2018, Geneva, Switzerland. BMJ Publishing Group , A31-A32.

https://doi.org/10.1136/annrheumdis-2018-EWRR2018.65

EWRR 2018 - Abstract submission

Topic: Cell signaling

Submission N°: EWRR18-1154

INVESTIGATING IL-6 INTRACELLULAR SIGNALLING IN PERIPHERAL BLOOD CELL SUBSETS IN PATIENTS AT EARLY AND LATER STAGES OF RHEUMATOID ARTHRITIS (RA).

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Registration status: I still need to register to EWRR

Introduction: Rheumatoid arthritis (RA) is a chronic, inflammatory arthritis that evolves along an immunological and inflammatory disease continuum. The era of targeted biological therapies has been transformative; however, a significant unmet need is the effective tailoring of therapy to deliver optimal treatment responses. In addition, the concept of a window of opportunity is well-recognised whereby early commencement of treatment confers improved outcomes compared to delayed treatment. The importance of pro-inflammatory cytokines TNF and IL-6 in particular, is well recognised; but high, homogeneous response in early RA (ERA) compared to later RA remains unexplained.

Objectives: The present project focuses on measuring the phosphorylation of STAT3 (p-STAT3) levels as an indication of the activation of IL-6/JAK-STAT signalling pathway at different disease stages (early and established/later). The main aim is to evaluate the variation in cell-subset IL-6 signalling and its association with response to treatment which included IL-6 targeted therapy (Tocilizumab-TCZ) as well as other bDMARD.

Methods: Phosphorylation of IL-6/JAK-STAT key transcription factor STAT3 (p-STAT3) was measured using multiparameter phosphoflow cytometry (phosflow) in T-, B- cells and monocytes isolated from peripheral blood of RA patients. Patients cohorts represented groups at different stages of RA: Treatment-naïve Early RA (ERA group) n=20. Later RA group (LRA n=20) refractory RA patients failing to respond to one or more biologics. Healthy control group (HC n=20) and additional comparable group of 20 early RA patients treated with methotrexate (MTX).

Results: Our previous data evaluating IL-6 pathway (JAK-STAT and also, PI3K/Akt and MAPK/ERK) in T-, B- and monocyte cells showed that p-STAT3 is predominantly affected in CD4+ T cells (1). Constitutively, p-STAT3 levels in CD4+ T cells were higher in later RA group (MFI:316±33.3) compared to ERA (MFI:296±40.96; p=0.057) and healthy individuals (285±21.6; p=0.01). Upon stimulation of the pathway using cis and trans Il-6 activation, there was little induction in the later RA patient cohort. Whereas early RA group showed a capacity for further activation of p-STAT3. Further analysis is currently being undertaken to understand the kinetics of this variability including response to treatment and biopsies of synovial tissue for phosphoprotein verification.

Conclusions: Our results are in line with previous findings (2,3), there was a difference in p-STAT3 levels at baseline between early and later RA, and differential response to stimulus with IL-6. Investigation of early vs later RA biologic response profiles will enable us to better understand the multiple cytokine networks, their interaction, and how disease duration and therapy alters this.

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Disclosure of Interest: None declared