

A1.6 IDO PATHWAY IN RA PATIENTS RESPONDING TO BIOLOGIC TREATMENTS

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Background and Objectives Indoleamine 2,3-dioxygenase (IDO) is an enzyme involved in immune tolerance, which is thought to be defective in Rheumatoid Arthritis (RA). It is expressed in mononuclear cells including dendritic cells (DC), and could play a role in DC-regulatory T cells crosstalk. Our aim was to study IDO expression in peripheral blood of patients with RA compared to controls. Effect of biotherapies on IDO was also evaluated under anti-rheumatic biotherapies.

Methods Human PBMC were purified by density gradient centrifugation and IDO gene expression was assessed by qRT-PCR. In parallel, the dosage of kynurenine was performed in plasma to evaluate IDO activity. For some patients, PBMC were cultured for 24 hours with LPS, IFN γ or both before IDO assays.

Results We included 40 patients with RA and 30 controls including 15 spondylarthropathies (SpA), 10 osteoarthritis (OA) and 5 osteoporosis (OP). Our results showed that IDO was over-expressed and more active in RA than in non inflammatory diseases. Interestingly, in RA patients, before treatment with biotherapies, kynurenine plasmatic levels were negatively correlated with the DAS28 activity score ($r = -0.552$; $p < 0.016$), and IDO mRNA ratio with ESR ($r = -0.536$; $p < 0.003$). After 3 months of biologics (independently of treatments), kynurenine levels significantly decreased in responders, while they remained unchanged in non responders. In anti-TNF α -treated RA patients ($n = 10$), IDO mRNA was significantly decreased after 3 months whereas in tocilizumab (IL-6 receptor-inhibitor, $n = 17$) or abatacept (CTLA4-Ig; $n = 10$) treated patients, IDO levels did not change significantly.

Conclusions IDO was up-regulated and more functional in patients with RA. It was negatively correlated with systemic inflammation and disease activity. IDO gene expression was also more inducible in this group of patients. So, in RA, IDO could contribute to decrease systemic inflammation and disease activity in a counter-regulation loop (which needs to be confirmed in further experiments). Tocilizumab and abatacept exerted an IDO-independent protection, whereas after an anti-TNF α treatment, IDO expression and inductibility decreased. This could help in treatment strategies in RA.

A1.7 INTERFERON AND B-CELL GENE SIGNATURES CONTRIBUTE TO DIAGNOSIS OF PRE-CLINICAL RHEUMATOID ARTHRITIS

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Background/Objective Early diagnosis of the preclinical phase of rheumatoid arthritis (pre-RA) allows timely start of treatment with the potential to prevent disease progression. It is known that antibodies against citrullinated proteins (ACPA) and rheumatoid factor (RF) have diagnostic value to identify pre-RA. However, since only 20–40% of ACPA⁺/RF⁺ arthralgia patients develop arthritis within 5 years, better prognostic markers are needed. Recently, we demonstrated involvement of interferon (IFN) response and B-cell gene signatures in pre-RA. The objective is to demonstrate the value of these signatures to diagnose pre-RA.

Methods Peripheral blood (Paxgene) was collected from 115 ACPA⁺/RF⁺ arthralgia patients who were clinically followed for arthritis development, one or more swollen joints, with a mean follow-up time of 23 months (IQR 12–30). An IFN and B-cell score was calculated based on 7 Type I IFN response genes and 3 B-cell related genes, respectively, measured by multiplex qPCR. Cox regression analysis and Receiver Operating Characteristic (ROC)-curve analysis were used to demonstrate prognostic and diagnostic significance.

Results Out of 115 arthralgia patients 44 developed arthritis after a median time of 8 months (IQR 5–13). Stratification of these individuals based on the IFN score revealed that 60% of the IFN^{high} patients converted to arthritis compared to 32% in IFN^{low} patients ($P = 0.011$). For the B-cell signature, 58% in B-cell^{low} patients developed arthritis, compared to 33% of B-cell^{high} patients ($P = 0.020$). Combined analysis revealed a significant high risk for arthritis development in IFN^{high}/B-cell^{low} patients (80%, hazard ratio (HR) 6.22, $P = 0.003$) and a low risk for IFN^{low}/B-cell^{high} patients (26%, HR 0.16, $P = 0.003$). To demonstrate clinical utility a ROC-curve was constructed of ACPA⁺/RF⁺ alone and in combination with both signatures. The area under the curve reached 0.619 ($P = 0.032$, CI 0.514–0.724) for ACPA⁺/RF⁺ and increased to 0.803 ($P = 0.0001$, CI 0.718–0.888) with IFN and B-cell signatures included. The sensitivity to diagnose pre-RA increased from 16% to 52% when both signatures are included, with a cut-off of 94% specificity.

Conclusions These findings demonstrate the clinical value of IFN and B-cell gene signatures as biomarkers for the diagnosis of pre-RA.

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A1.8 MAGNETIC RESONANCE IMAGING OF HAND AND FOOT JOINTS OF PATIENTS WITH ACPA POSITIVE ARTHRALGIA WITHOUT CLINICAL ARTHRITIS

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Background Anti-citrullinated-peptide antibodies (ACPA) and acute phase reactants are increased before arthritis becomes clinically detectable, suggesting that the processes underlying rheumatoid arthritis (RA) start preclinical. Whether local inflammation occurs in the preclinical phase is unknown. Therefore we studied small joints of ACPA-positive arthralgia-patients on local subclinical inflammation.

Methods Imaging was performed using 1.5T-extremity-MRI. Painful hand or foot joints of 21 ACPA-positive arthralgia-patients without clinical arthritis were imaged. For comparison, hand and foot joints of 22 ACPA-positive RA-patients and of 19 symptom-free controls were studied. Within the ACPA-positive arthralgia-patients painful and symptom-free joint regions were compared. Scoring was performed according to the OMERACT RAMRIS method. Analyses were performed on joint region level and focused on inflammation (synovitis plus bone marrow edoema).

Results The mean combined inflammation-scores of the MCP/PIP-joints of the controls, the painful joints of ACPA-positive arthralgia-patients and ACPA-positive RA-patients were 0.1, 0.7, 3.7, respectively ($p < 0.001$). Likewise the mean combined inflammation-scores of the wrist were 0.9, 2.3, 10.3, respectively ($p < 0.001$) and that of the MTP-joints 0.5, 0.9, 3.8, respectively ($p = 0.10$). The total RAMRIS-scores of the painful and symptom-free joints within ACPA-positive arthralgia-patients were correlated ($r_s = 0.61$).

Conclusions The present data suggest that local subclinical inflammation occurs in ACPA-positive arthralgia-patients.