inadequately responding to RA treatments. Lacking predictive biomarkers of response or personalised medicine approaches to guide use of targeted therapies in RA patients, EULAR and ACR guidelines [1,2] both recommend to loop over available ts- and bDMARDs as long as the patient’s response is considered as inadequate. Meanwhile, for historical reasons and despite the similar clinical efficacy of these drugs, anti-TNFs have a large dominance in medical practice.

Objectives: Determine in what proportions the different mechanisms targeted by existing DMARDS families are dominant in RA patients synovial tissue.

Methods: Retrospective analysis of 7 private or public datasets of 300 rheumatoid arthritis patients, consisting in all cases of transcriptomic data from synovial biopsies. Three datasets come from the Rheumatikit platform [3,4] (low-density microarrays or qPCR). Four other datasets are publicly available on Gene Expression Omnibus (GSE89408, GSE45667, GSE97165, GSE21537, produced on Illumina, KTH or Affymetrix platforms). Each mechanism of action is associated to a « drug target complex » (DTC), consisting of the genes coding for proteins directly targeted by the DMARDs of interest. For a given dataset, computations are made in four steps: 1) each patient is described by its different DTC values (an average of the expression values of the members of each DTC) 2) each patient is scored for each of its DTC value. Each of these DTCs are scored as a percentile of the corresponding DTC distribution over the full dataset from which a given patient’s data is extracted. This gives, for a single patient, as many percentiles as defined DTCs. 3) for each individual patient, a ranking of DTC values is then operated. This allows to overcome the fact that absolute numerical values of two different DTCs should not be compared. 4) A summary statistic is then computed over each dataset separately, to conclude which DTC is dominant in which proportion of the cases among this dataset.

Results: This analysis exhibits different dominance patterns for RA-related mechanisms of action in individual patients. Statistically, no unique mechanism is shown dominant in a majority of patients; On the four public datasets, where all DTCs of interest are available, averaged dominance proportions across datasets are : IL1 15%, IL6 20%, TNF 11%, B Cells 20%, JAK 17%, T Cells 7%. About 10% of the patients exhibit equivalent dominance patterns between multiple DTCs. On all seven datasets, this analysis also outputs weak or moderate correlations between the dominance levels of multiple DTCs.

Conclusion: These results highlight large variability in metabolic patterns underlying RA; such observation is consistent with the similar efficacy of these drugs. Production of these inflammatory mediators by EC is important contributors to inflammatory activation of EC. Our findings demonstrate that activation of the endothelium and may be a potential novel therapeutic target.

Disclosure of Interests: None declared

RESULTS: A total of 27 studies included 4,678 JIA cases and 7,634 control subjects. There were 23 studies on Caucasians, 3 on Asians, and 1 on Africans. Seven studies were on IL-1β-899 C/T, 5 were on IL-1β-511 C/T, 6 were on IL-1β-174 G/C, 19 were on TNF-α-308 G/A, and 14 were on TNF-α -238 G/A polymorphisms. Meta-analysis of IL-1β-899 C/T, IL-1β-511 C/T, IL-1β-174 G/C, and TNF-α-308 G/A and -238 G/A polymorphisms revealed no significant associations between JIA and minor alleles (OR 0.99, 95% CI 0.87–1.12, P = 0.84; OR 1.10, 95% CI 0.97–1.25, P = 0.57; OR 1.04, 95% CI 0.91–1.19, P = 0.57; OR 1.01, 95% CI 0.87–1.37, P = 0.46; OR 0.85, 95% CI 0.63–1.13, P = 0.26). Subgroup analysis was conducted on the relationship between JIA and proinflammatory cytokines based on ethnicity. In Caucasians, there was no significant association between IL-1β-899 C/T, IL-1β-511 C/T, IL-1β-174 G/C, and TNF-α-308 G/A and -238 G/A polymorphisms and JIA; however, there were significant relationships between JIA and recessive (TT vs. CT + CC) and additive (TT vs. CC) models of IL-1β-511 C/T polymorphisms (OR 1.48, 95% CI 1.09–2.00, P <0.01; OR 1.46, 95% CI 1.05–2.03, P <0.02).

Conclusion: IL-1β-899 C/T, IL-1β-511 C/T, IL-1β-174 G/C, and TNF-α-308 G/A and -238 G/A polymorphisms were not significantly associated with overall JIA susceptibility in all ethnicities. However, differences according to ethnicity were observed, and the TT genotype of IL-1β-511 C/T was associated with a high prevalence of JIA in Caucasians.

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