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TRANSCRIPT-PROTEIN ASSOCIATIONS IN EARLY RA PATIENTS ACHIEVING SUSTAINED DRUG-FREE REMISSION AFTER TREATMENT WITH TOCILIZUMAB

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Background: In disease modifying anti-rheumatic drug (DMARD)-naïve early rheumatoid arthritis (RA) patients, we previously identified networks of differentially co-expressed genes associated with achieving sustained drug-free remission (sDFR).¹ A better understanding of processes involved with translation of mRNA into proteins might be used to develop personalised treatment for early RA patients.

Objectives: To identify inflammatory proteins associated with achieving sDFR by performing multi-analyte profiling in pre-treatment serum and subsequently to study significantly enriched biological pathways and compare these with the pathways previously found in the transcriptomic analyses.

Methods: In this exploratory study, baseline serum was analysed of 24 patients (n=13 achieved sDFR, n=11 controls) treated-to-target with tocilizumab (TCZ) therapy in the U-Act-Early trial. TCZ (intravenously, 8 mg/kg) was given every 4 weeks; if no remission, hydroxychloroquine (HCQ) was added and if subsequently remission was still not achieved, HCQ was replaced by (oral) methotrexate. Thereafter, if the target, remission, still was not achieved, patients switched to standard of care (e.g. tumour necrosis factor inhibitor). Provided remission persisted, therapy was tapered and subsequently discontinued. sDFR was reached when patients remained ≥ 3 months in remission while being drug-free until the end of the study period; those not able to discontinue therapy were selected as controls. Luminex[®] multi-analyte profiling (xMAP[®]) was used to measure 85 inflammatory proteins; partial least square discriminant analyses (PLS-DA) was applied to identify relevant proteins associated with achieving sDFR.

Results: No significant differences in clinical baseline characteristics were found between those achieving sDFR vs controls ($p > 0.05$). PLS-DA identified 14 proteins of which 6/14 (n/N) were associated with a decreased chance of achieving sDFR. The protein considered most important (i.e. highest variable on importance (VIP) score) was chemokine (C-C motif) ligand 20 (CCL20, VIP 1.49). In total, 88 significantly enriched Gene Ontology (GO) terms were identified analysing the proteins; 5 terms, of which "positive regulation of leukocyte migration" ($p < 3.41 \times 10^{-2}$) and "leukocyte chemotaxis" ($p < 3.49 \times 10^{-3}$) were found in both proteomic and transcriptomic analyses. Significant transcript-protein correlations are shown in figure 1; the TIMP metalloproteinase inhibitor 1 (TIMP-1) protein showed the highest number (n=12) of correlations.