THE INTERFERON TYPE I SIGNATURE TOWARDS PREDICTION OF NON-RESPONSE TO RITUXIMAB IN RHEUMATOID ARTHRITIS PATIENTS

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Background and objectives B cell depletion therapy is efficacious in rheumatoid arthritis (RA) patients failing on tumour necrosis factor (TNF) blocking agents. However, approximately 40–50% of rituximab (RTX) treated RA patients have a poor response. The authors investigated whether baseline gene expression levels can discriminate between clinical non-responders and responders to RTX.

Materials and methods In 14 consecutive RA patients starting with RTX (test cohort), gene expression profiling on whole peripheral blood RNA was performed by Illumina HumanHT beadchip microarrays. Supervised cluster analysis (patients ranked on difference in 28 joints disease activity score (DAS28) after 6 months RTX) identified genes expressed differently at baseline in case of non-response (both ΔDAS28<1.2 and EULAR non-response). Genes of interest were measured by quantitative real-time PCR and tested for their predictive value using receiver operating characteristics (ROC) curves in an independent validation cohort (n=26).

Results Genome-wide microarray analysis revealed a marked variation in the peripheral blood cells between RA patients before the start of RTX treatment. Here, the authors demonstrated that only a cluster consisting of interferon (IFN) type I network genes, represented by a set of IFN type I response genes (IRGs), that is, LY6E, HERC5, IFI44L, ISG15, MxA, MxB, EPSTI1 and RSAD2, was associated with ΔDAS28 and EULAR response outcome (p=0.0074 and p=0.0599, respectively). Based on the 8 IRGs an IFN-score was calculated that reached an AUC of 0.82 to separate non-responders from responders in an independent validation cohort of 26 patients using ROC curves analysis according to ΔDAS28<1.2 criteria. Advanced classifier analysis yielded a 3 IRG-set that reached an AUC of 87%. Comparable findings applied to EULAR non-response criteria.

Conclusions This study demonstrates clinical utility for the use of baseline IRG expression levels as predictive biomarker for non-response to RTX in RA.