12 THE TRANSCRIPTOMIC ANALYSIS FROM PBMC IS A POWERFUL APPROACH TO IDENTIFY SPECIFIC SIGNATURES ABLE TO PREDICT RESPONSES FOR EACH TNF α BLOCKING AGENT

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Background The number of RA biological treatments is increasing but 30 to 40% of patients do not respond to tumour necrosis factor α (TNF α) blocking agents. One way to optimise the drug prescription is to identify predictive markers of drug responsiveness for each biologic agent. The authors already identified a gene combination able to predict infliximab responsiveness by transcriptomic analyses. The question is to know if this approach is enough sensitive to identify specific gene expression profile for the different TNF α blocking agents.

Objectives To identify specific gene expression profiles able to predict the response of RA patients treated with methotrexate (MTX)/adalimumab (ADA) or MTX/etanercept (ETA).

Methods Thirty-one RA patients were randomised to receive subcutaneously either ADA (40 mg each other week) or ETA (50 mg per week). Twenty RA patients (average age: 50 $\pm$ 16 years old (yo), MTX: 14 $\pm$ 6 mg/week (w), initial DAS28: 5 $\pm$ 1) received ADA while eleven RA patients (age: 55 $\pm$ 15 yo, MTX: 18 $\pm$ 2 mg/w, initial DAS28: 5 $\pm$ 1) received ETA. The drug efficacy was evaluated with the DAS28 score after 3, 6 months and after one year of treatment according to the EULAR

response criteria. A blood sample was carried out in patients just before the first injection of treatment in order to isolate peripheral blood mononuclear cells (PBMC) and extract total RNA. cRNAs were synthesised, amplified, labelled and purified using the Quick AMP labelling Agilent kits. Labeled cRNAs were hybridised to Agilent 4×44 K array and scanned with an Agilent Scanner. Microarray data were extracted and normalised with the Feature Extraction software. Next, a supervised analysis was performed using t-test (GeneSpring GX software) in order to identify gene expression profiles able to separate perfectly responders (R) and moderate responders (MR) to each drug. The gene expression profiles obtained for ADA and ETA were further compared to know if the authors have a specific signature for each drug.

Results Demographic, clinical and biological characteristics of all the patients were comparable whatever the treatment administered. From the 20 patients treated with ADA, a combination of 25 transcripts ($p < 0.01$) was able to separate perfectly R (11/20) and MR (9/20). Among the 11 patients who have been treated with ETA, 3/11 were classified as R and 8/11 as MR. A combination of 2074 transcripts ($p < 0.01$) was able to separate perfectly R and MR to ETA. When the authors compared these two combinations of transcripts, just an overlap of 2 transcripts was found between them, leading us to consider that the signatures obtained for ADA and ETA are drug specific.

Conclusion The authors identified a specific drug signature able to separate perfectly R and MR to either MTX/ADA or MTX/ETA. This study has shown for the first time that the transcriptomic approach is a sensitive, relevant and powerful tool to identify specific predictive markers for each molecule, not only through the different classes of immunotherapies but also in a same class of drug such as TNF α blocking agents.