8 IDENTIFICATION OF A SET OF EIGHT PROTEINS ABLE TO PREDICT THE RESPONSE TO METHOTREXATE/ ETANERCEPT IN RHEUMATOID ARTHRITIS PATIENTS

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Background The number of biologic agents in rheumatoid arthritis (RA) is continuously increasing. However, clinicians observe that around 30–40% of treated patients fail to respond to tumour necrosis factor α blocking agents. One way to optimise the drug prescription is to identify predictive markers of drug responsiveness.

Objectives To identify a combination of proteins whose expression profile would predict the RA patients responses to the association of methotrexate (MTX) and etanercept (ETA).

Methods A set of 10 patients with active RA (average age: 54±16 years old, RA duration: 9±9 years, MTX: 18±3 mg/week, DAS28: 5.5±1.0) was treated by a subcutaneous injection of ETA (50 mg/week). The clinical efficacy of these drugs was evaluated with the DAS28 score after 3, 6 and 12 months of treatment according to the EULAR response criteria. For proteomic analysis, a blood sample was carried out in patients prior to the first injection in order to extract peripheral blood mononuclear cells (PBMC). A relative quantification of protein expression from seven samples of PBMC was performed by mass spectrometry, after labelling with stable isotopes (Isobaric Tags for Relative and Absolute Quantification: iTRAQ). Protein identification and differential analysis between the samples from responders (R) and non-responders (NR) were made with the Spectrum Mill software (Agilent). The statistical treatment using iQuantitator has enabled the relative protein quantification for each patient. From five others samples of PBMC, a complementary approach based exclusively on mass spectrometry was implemented (the 'label free approach'). 'Label-free' quantification is based on extracted ion chromatograms to determine the differential expression. The differential analysis was achieved with SIEVE (Thermofisher), a label-free dedicated software to compare LC/MS data from LTQ Orbitrap (Thermofisher) analysis.

Results Among the 10 patients, 6 out of 10 were classified as R. When merging the two independent experimental approaches, the authors got consistent results for eight overexpressed proteins and two underexpressed proteins among all patients responding to treatment.

Conclusions For the first time, the authors identified a proteomic signature from PBMC able to predict MTX/ETA

response. These proteins would thus represent valuable candidates for biomarkers of response to this treatment option that should be validated on a larger population. In addition, among the identified proteins, several proteins are also present in plasma, offering the possibility to explore their predictive value by ELISA tests.