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Blood RNA sequencing reveals immunological processes associated with the response to abatacept in rheumatoid arthritis.

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Background. Abatacept (CTLA4-Ig) is an approved biological therapy for the treatment of rheumatoid arthritis (RA). Similar to other biological agents, most patients (60%) respond significantly to this therapy. To date, however, the biological mechanisms underlying the lack of efficacy for this drug are unknown.

Objetives. The objectives of the present study were to characterize the biological processes underlying the lack of efficacy of abatacept and to evaluate the blood transcriptome as a valid source for drug response prediction.

Methods:. A total of n=57 patients diagnosed with RA were recruited for this study from 16 rheumatology departments in Spain. All patients were >18 years old and, had >6 months of disease evolution. The primary clinical response to abatacept was defined at week 12 using the EULAR criteria. Good and moderate responders were aggregated into a single response group, and compared to the no response group of patients. Blood RNA was collected from all patients at baseline. From a subgroup of patients (n=31), blood RNA was also obtained at weeks 12, 24 and 48 of treatment with abatacept. Gene expression levels were determined using paired-end RNA-seq (Illumina). Differential gene expression, association to biological processes, longitudinal association analysis and building of the multigenic predictor were performed using the R software and the specialized Bioconductor libraries. The the prediction accuracy was evaluated using the ROC AUC.

Results. From the 57 patients treated with abatacept, n=10 (17.5%) were good EULAR responders, n=24 (42%) moderate EULAR responders and n=23 (40.5%) non-responders at week 12 of therapy. Biological process analysis identified two significantly distinct biological profiles between responders and non-responders. In responders, we found an association to pathways associated with the effector phase of T cells (e.g. interleukin-15 and 2 signalling, $P < 0.05$). Non-responder patients showed instead a strong association to biological processes associated with antigen presentation and activation of T cells ($P < 0.005$). Using the baseline gene expression profiles, we built a multigenic predictor of response to abatacept with an AUC = 75%. In the longitudinal cohort, patients were stratified based on reaching an inactive state (i.e. DAS28 < 3.2). Using this endpoint measure, the longitudinal analysis of the 4 time points corroborated the association of response with antigen presentation ($P < 0.01$).

Conclusion. The analysis of blood RNA profiles of RA patients has enabled the identification of specific biological processes associated with the lack of response to abatacept. Also, we demonstrate that blood expression profiles can be predictive of the response to the drug at week 12 of therapy.