BASELINE METABOLIC PROFILES OF EARLY RHEUMATOID ARTHRITIS PATIENTS ACHIEVING SUSTAINED DRUG-FREE REMISSION AFTER INITIATING TREAT-TO-TARGET TOCILIZUMAB, METHOTREXATE OR THE COMBINATION

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1. Introduction

For patients with newly diagnosed Rheumatoid arthritis (RA), treatment aim is early, rapid, and sustained remission. However, still a significant number of patients respond insufficiently to first-line drug methotrexate (MTX) or new biological drug tocilizumab (TCZ). Metabolic analysis prior to therapy could provide potential biomarkers of disease activity and response to treatment. The aim of this study was to identify relevant metabolites and important metabolomic pathways associated with achieving sustained drug-free remission (sDFR) after a treat-to-target tocilizumab- or methotrexate-based strategy initiated in early RA patients.

2. Approach

Serum samples were analysed of 60 patients from U-Act-Early trial and initiated treatment with MTX, TCZ, or the combination and who were thereafter able to achieve sDFR (n=37); as controls, patients were selected who never achieved a drug-free status (n=23). Metabolomic measurements were performed on an oxidative stress, amine and oxylipin platform covering various compounds. Partial least square discriminant (PLSDA) analyses were performed to identify, per strategy arm, relevant metabolites as potential treatment predictors of which the biological pathways were studied.

3. Results

In the combination, TCZ, and MTX strategy, respectively, 19, 13 and 12 relevant metabolites were found, which were subsequently used for pathway analyses. The most significant pathway in the combination, TCZ and MTX strategy was “histidine metabolism” ($p<0.001$), “arachidonic acid metabolism” ($p=0.018$) and “arginine and proline metabolism” ($p=0.022$) respectively. These pathways have treatment-specific drug interactions with metabolites affecting either the signalling of interleukin-6, which is inhibited by TCZ, or affecting protein synthesis from amino acids, which is inhibited by MTX.

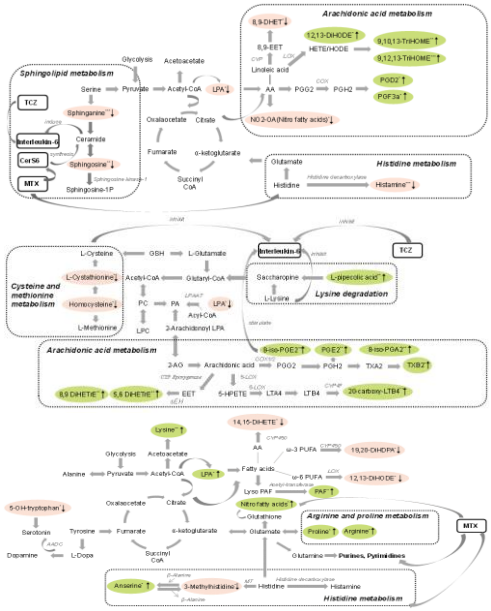

Figure 1. Pathway analysis within the identified metabolites in the (a) tocilizumab plus methotrexate, (b) tocilizumab, and (c) methotrexate arms. Metabolites depicted in red nodes have on average lower concentration in the sDFR group compared to controls; those depicted in green nodes have a higher concentration.

4. Discussion

In line with our previous observations, by analysing relevant transcripts and proteins within the same patients, the metabolic profiles found to be different between the strategy arms further support the hypothesis that achieving sDFR is not only dependent of predisposing biomarkers, but also on the specific treatment that has been initiated. Signature metabolite biomarkers have been identified which potentially could act as key prognostic factors for applying personalized care but need to be validated in large replication studies before they can be used in clinical practice.