Autoantibody Profiles Predict Responsiveness To Methotrexate and Anti-TNF Therapy In Early Rheumatoid Arthritis

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Introduction

Novel therapeutic concepts in early rheumatoid arthritis (ERA) are aiming for an early intervention and effective control of disease activity reaching remission. Most current guidelines recommend methotrexate (MTX) as the first DMARD even though at least for half of these patients MTX alone is not sufficient to achieve this goal. Currently, the clinical response to the first and probably second DMARD is used to guide further therapeutic approaches. We applied Serotag® autoantibody profiling technology to identify sets of antigens predicting clinical response in ERA patients treated with MTX alone or combined with Adalimumab (ADA) in an induction trial (HIT HARD study; Detert et al. (2013) Ann Rheum Dis 72:844-850).

Conclusions

• This study demonstrates the utility for the use of baseline autoantibody levels for predicting the clinical response of ERA patients to an induction therapy.
• Distinct autoantibody signatures were identified and combined to marker panels enabling classification into likely responders or non-responders to MTX alone and ADA/MTX combination therapy.
• Further validation studies are needed to translated these panels into assays for guiding treatment selection.

Methods

Autoantibody reactivities of ERA patient and healthy control sera were screened against 6,000 E.coli expressed antigens using Luminex-based Serotag® technology (Fig. 1).

Study Design

The HIT HARD study is a multi-center, double-blind, randomized placebo-controlled trial. Patients with DMARD-naïve, active early RA were treated with ADA (40 mg) plus MTX (15 mg/week) in combination with placebo (PBO) plus MTX (15 mg/week) for 24 weeks followed by MTX monotherapy until week 48.

Data analysis

Antigens were assessed and prioritized based on univariate and multivariate association with DAAS28 remission (DAAS28≤2.6) in both treatment arms. Univariate associations between autoantibody levels and clinical measures were assessed using Mann-Whitney U test and Spearman’s rank correlations. Multivariate modeling within a nested cross-validation was performed using powered partial least squares discriminant analysis (PPLS-DA) approaches with forward stepwise selection of biomarkers. Biomarkers were then ranked based on the number of times the marker passed statistical significance criteria in univariate analyses, ranks for multivariate analysis and fold-change (>1.5).

Results

Baseline Serological Status and Treatment Effects

We first determined the baseline serological status for anti-citrullinated peptide antibodies (anti-citpPep) compared to healthy volunteers (HV, n=116). Anti-citPep positivity was not associated with DAAS 28 remission in ERA patients (Fig. 4a). Although many studies have investigated the increase of anti-nuclear autoantibodies (ANA) during long-term TNF inhibitor treatment, only few data are available regarding the decrease in autoantibody levels over time. We found a reduction in autoantibody reactivity in both treatment arms which was more pronounced in patients in remission compared to those not achieving remission (Fig 4b).

Autoantibody Clusters in Pre-Treatment Samples

Specific autoantibody clusters were associated with DAAS28 remission in ERA after 24 weeks in both treatment arms (Fig. 5).

Acknowledgements

We thank Tanja Braun for study management and the German Federal Ministry of Education and Research (BMBF, grant number: 01KQ0602).

Fig. 1: Serotag® process

Fig. 3: Antigens prioritized by univariate analysis

Fig. 4: Baseline serological status and treatment effects

Fig. 5: Autoantibody clusters in pre-treatment samples

Fig. 6: PPLS-DA score plot

RA is a heterogeneous disease and some degree of heterogeneity was seen in the clustered heat maps of pre-treatment samples (Fig. 5). Therefore, a wider set of antigens was used to calculate marker panels. Receiver operating characteristics (ROC) analysis was used to define the antigen panels with the best classification accuracy. For each treatment arm specific marker panels were found that could help to identify ERA patients who will or will not achieve remission.

Fig. 7: Autoantibody clusters in pre-treatment samples