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Rheumatoid arthritis - aetiology, pathogenesis and animal models

THU0063

DIFFERENTIAL PHARMACODYNAMIC EFFECTS OF ABATACEPT AND ADALIMUMAB ON THE SERUM PROTEOME OF PATIENTS WITH RA USING THE SOMASCAN® PLATFORM

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Background: Abatacept (ABA) versus adalimumab (ADA) comparison in biologic-naïve RA subjects with background MTX (AMPLE) was a Phase IIIb clinical trial to compare the safety, efficacy and radiographic outcomes of ABA vs ADA in patients with RA who exhibited an inadequate response to MTX and who were naïve to biologic DMARDs.¹ While both therapies demonstrated similar efficacy across multiple outcomes, their mechanisms of action (MoAs) are quite different; ABA is a T-cell co-stimulation modulator and ADA is a TNF α inhibitor. Previous transcriptomic analysis of the whole blood samples showed differential pharmacodynamic (PD) effects between the treatments.¹⁻³

Objectives: To expand our understanding of differential PD changes in the serum proteome over time in patients treated with ABA or ADA in AMPLE using a novel proteomic platform.

Methods: Serum was available from 440 patients in AMPLE at four time points (Days 1, 85, 365 and 729). Serum samples from the patients in AMPLE and 123 healthy individuals with matching demographics were subjected to proteomic quantification by a highly multiplexed DNA aptamer technology with wide dynamic ranges (SomaLogic SomaScan® platform).⁴ A linear model analysis was used to identify protein abundance changes over time and changes specific to treatment. Other covariates included in the model were country of origin, ethnicity and sex. Additionally, patient effect was adjusted for as a random factor.

Results: Both treatments exhibited a significant PD effect on serum proteome over the course of the 2-year trial, with 73 proteins modulated by ABA and 125 by ADA. There were large overlaps between the two treatments, including proteins associated with RA, such as C-X-C motif chemokine ligand 13 (CXCL13), matrix metalloproteinase-3 (MMP3) and serum amyloid A1/A2 (SAA1/2). Changes in the levels of these proteins may be indicative of general improvement of the disease. The proteins modulated by the treatments were enriched in the G-protein coupled receptor (GPCR) signalling and innate immunity pathways. Among the proteins that exhibited significantly different PD effects between the treatments were CRP, CC chemokine ligand 17 (CCL17) and β -defensin 112 (Figure). While patients showed marked improvement in their symptoms after 2 years of treatment, the overall serum proteomic profiles of the patients were still different from those of a normal healthy population.

Conclusion: The SomaScan® platform provides a robust method for quantifying the PD change in a broad portion of the serum proteome in clinical trials. In AMPLE, abatacept was more selective than adalimumab in modulating protein biomarkers in patients with RA, though there was large overlap in proteins modulated by both treatments. The treatment-specific changes may reflect the different MoAs leading to similar clinical outcomes. While patients in both groups benefited from treatments, their serum proteome remained notably different from that of a healthy population. Further analysis by responder status may provide additional links between the treatment responses and proteomic changes. Proteomic approaches as described in our study could contribute to clinical trials and help shape treatment strategies for patients with RA.

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Figure. Serum Proteins With Differential PD Effects to Abatacept and Adalimumab

CCL17=CC chemokine ligand 17; CDH11=cadherin 11; CFHR4=complement factor H-related protein 4; CXCL2=cytochrome c oxidase subunit 7A-related protein, mitochondrial; CXCL11=C-X-C motif chemokine ligand 11; DEF112= β -defensin 112; HIST2H2BE=histone H2B type 2-E; HIST3H2A=histone H2A type 3; HIST3H2BB=histone H2B type 3-B; PD=pharmacodynamic; SLC5A5=sodium/iodide cotransporter; SORD=sorbitol dehydrogenase

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ANTIBODY-RESPONSE MATURATION IN THE PHASE OF CLINICALLY SUSPECT ARTHRALGIA AND ITS RELATION WITH PROGRESSION TO RHEUMATOID ARTHRITIS

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Background: Auto-antibodies in rheumatoid arthritis (RA) are often present years before disease onset but their mere presence does not seem enough to induce RA. Because several nested-case control studies have shown that autoantibody-response maturation precedes disease onset, it is suggested that it plays a role in disease triggering. At present, it is undetermined whether autoantibody-response maturation occurs in the symptomatic phase preceding clinical arthritis (i.e. Clinically Suspect Arthralgia, CSA), or whether it occurs even earlier in the asymptomatic phase. Secondly, if autoantibody-response maturation is a final step towards clinical disease development, maturation is expected to be present in the patients that progress from CSA to RA, but not in CSA-patients that do not progress.

Objectives: To better understand the timeframe of autoantibody-response maturation and its relation to development of RA, we investigated autoantibody-response maturation in patients with CSA that did and did not progress to clinically apparent inflammatory arthritis (IA).

Methods: In serum from 148 CSA-patients, we determined the presence and levels of three autoantibodies (ACPA, anti-CarP and AAPA), with three isotypes each (IgM, IgG, IgA), resulting in 9 autoantibody measurements per patient per time-point. Measurements were performed on sera obtained at first presentation at the outpatient clinic and when patients developed IA or else after two years. In-house ELISA was used for all measurements. Three analyses were performed, in patients that progressed to IA (n=56) and in patients that did not progress (n=92) separately. First, in patients negative for all measurements at baseline, we determined the frequency of conversion to seropositivity. Second, in patients with at least one positive test at baseline, we studied the frequency of autoantibody positivity over time. Finally, we determined the change in autoantibody levels in patients positive for the respective autoantibodies at baseline. Frequencies and medians were reported. Statistical significance was tested with Fisher's Exact test and GEE, taking into account that measurements within one autoantibody type (ACPA, anti-CarP or AAPA) can be correlated.

Results: First we studied patients negative for all antibodies at baseline (54% of patients that progressed to IA and 76% of patients that did not progress). 17% of patients that progressed to IA became positive over time, compared to 6% of the patients that did not develop IA (p=0.12). Then we studied patients in whom at least one autoantibody was present at baseline and evaluated autoantibody-positivity over time. In patients that progressed to IA, the number