Testing of Multiple Autoantibodies Identifies Expansion of Targeted Antigens and a Method to Identify Imminent Onset of Clinical Rheumatoid Arthritis

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ABSTRACT BODY:

Purpose of Study: Rheumatoid arthritis (RA) has a period termed 'pre-RA' during which there are autoantibody elevations prior to the onset of clinically-apparent inflammatory arthritis (i.e. clinical RA). Multiple autoantibody systems including antibodies to citrullinated proteins (ACPA), rheumatoid factor (RF), anti- peptidyl arginine deiminase (anti-PAD) and anti-carbamylated proteins (anti-CarP) have been described in pre- RA; however, few studies have tested all antibodies in a single pre-RA cohort. The objective of this study was to test multiple autoantibody systems in pre-RA, and evaluate the role of these autoantibodies in potentially identifying a signature in the pre-RA period that indicates imminent onset of clinical RA.

Methods Used: We evaluated 148 individuals with two pre- and one post-RA diagnosis serum samples available from the Department of Defense Serum Repository (DoDSR), and matched controls. Samples were tested for anti-CCP3, five ACPA fine specificities, anti-PAD, anti-CarP and RFIgA and IgM (Werfen). Positive levels for autoantibodies were determined using levels present in <=1% in a separate set of DoDSR controls. Analyses included comparison of positivity of autoantibodies over time in pre-RA and post-RA, and comparisons between RA and controls.

Summary of Results: The individuals with RA had a mean age at diagnosis of RA of ~37 years, were ~55% female and had post-RA positivity of anti-CCP3 of 60.8%, RFIgA of 45.9% and RFIgM of 45.9%. Positivity of anti-CCP3, RFIgA and IgM, anti-PAD1 and PAD4, anti-vimentin 2, anti-fibrinogen and anti-histone 1 increased over time in pre-RA and were significantly different than controls; however, positivity rates were overall similar in immediate pre-RA samples compared to post-RA samples. Counts of autoantibodies also increased over time in pre-RA, and within anti-CCP3 positive samples, a higher total autoantibody count was significantly associated with a time period <=3 years prior to RA diagnosis.

Conclusions: Multiple autoantibodies including anti-CCP3, RFIgA and M, ACPA fine specificities and anti-PAD antibodies are present in pre-RA, although anti-CCP3 and

RFs have the highest positivity rates. This confirms prior findings, however also expands upon them by demonstrating the rates of these antibodies in a single cohort. In addition, in anti-CCP3 positive samples, an increasing total antibody count indicates a sample is <=3 years prior to RA diagnosis; when further validated, that could serve as a model to predict imminent RA.