The combination of rheumatoid factors with antibody systems targeting citrullinated, carbamylated and peptidyl arginine deiminase autoantigens distinguishes rheumatoid arthritis

Thierry Dervieux, John Conklin, Tyson O’Malley, Kelley Brady, Roberta Alexander, Jing Shi, Claudia Ibarra, Michael Mahler, Joel Kremers, Michael E. Weinblatt, Arthur Weinstein.

Background: Novel antibody systems including anti-Carbamylated Protein Antibody (anti-CarP IgG) and anti-Peptidyl Arginine Deiminease Antibody (anti-PAD4 IgG) are emerging as independent diagnostic and prognostic biomarkers for Rheumatoid Arthritis (RA) [ref, 1-3]. As such, these antibody systems may add value to rheumatoid factor (RF) and anti-citrullinated peptide antibody (ACPA IgG), the hallmark antibodies in RA.

Objectives: We evaluated the diagnostic performance of Rheumatoid Factor (RF) with antibody systems targeting citrullinated, carbamylated and PAD4 autoantigens in RA.

Methods: The cohort consisted of 638 consenting subjects with RA (fulfilling the 1987 or 2010 ACR classification criteria, mean age: 59.8±0.5 years [SEM], 80% female) and a control group of 775 subjects (mean age: 44.7±0.5 years, 85% females, including Systemic Lupus Erythematosus [n=369], primary Sjögren Syndrome [n=64], Primary Fibromyalgia [n=85], other connective tissue diseases [n=63], and a group of normal healthy donors [n=194]). Autoantibodies titers from serum were measured using fluoroenzyme immunoassays (anti-RF [IgM] and anti-CCP [IgG]; Phadia Upsala, Sweden), ELISA (anti-CarP [IgG], research use only [RUO], Inova Diagnostics, San Diego) and bead-based Aptiva™ technology (anti-PAD4 [IgG], RUO, Inova Diagnostics) in a clinical laboratory accredited by the College of American Pathologists. For each positive antibody (above the cutoff) a score of 1 was assigned and the cumulative presence of the 4 antibodies was determined [range 0-4]. The ability of the biomarkers to distinguish RA from controls was calculated using sensitivity, specificity and interval likelihood ratio (LR). Positive Predictive Value (PPV) was estimated at 10% pre-test probability. Statistics consisted of Mann-Whitney-U test, Chi-square test.

Results: In this cohort anti-CarP IgG (>20 Units) yielded 33.5% sensitivity and 77.9% specificity. Anti-PAD4 (>1000 Units) yielded 35.0% sensitivity and 95.0% specificity. RF IgM (>5 Units/ml) and anti-CCP (>10 Units/ml) were 67.4% and 66.5% sensitive, respectively (87.5% and 97.0% specific, respectively). RA presented 5-fold higher 4-antibody system scores (2.02±0.05) than controls (0.42±0.02; p<0.001). Scores greater than 2 yielded 42% sensitivity and 98.8% specificity. A total of 82 subjects presented with the full-house 4 antibodies (score = 4) while 81 of them had RA (99.9% specificity). Interval LR and PV for each of the 4-antibody system are presented in the Table. There was no difference in the 4-antibody score between RA who fulfilled the 1987 ACR or 2010 ACR criteria (1.99±0.07 vs 2.08±0.09; p=0.40). In the subset of subjects newly diagnosed (less than one year) the average 4-antibody system score for RA (n=33) was 1.72±0.22 (36.3% with score greater than 2) and 0.58±0.12 for other diseases (0% with score greater than 2, 100% specific; p<0.01).

Conclusion: This cumulative combination of antibody systems targeting citrullinated, carbamylated, PAD4 and Fc autoantigens (RF IgM) is highly specific for RA. It may be useful in diagnosing and classifying RA even in symptomatic patients who present early in the course of disease.

References:

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Table I: Combination of RF IgM, anti-CCP (IgG), anti-CarP (IgG) and anti-PAD4 (IgG)

<table>
<thead>
<tr>
<th>Score</th>
<th>RA (%)</th>
<th>CTL (%)</th>
<th>Likelihood Ratio [CI 95%]</th>
<th>Pre-test Probability</th>
<th>Post-test Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>20.5%</td>
<td>65.8%</td>
<td>0.31 [0.27 to 0.35]</td>
<td>10%</td>
<td>3.4%</td>
</tr>
<tr>
<td>1</td>
<td>11.6%</td>
<td>27.2%</td>
<td>0.43 [0.33 to 0.54]</td>
<td>10%</td>
<td>4.5%</td>
</tr>
<tr>
<td>2</td>
<td>25.5%</td>
<td>5.8%[45]</td>
<td>4.40 [3.22 to 6.00]</td>
<td>10%</td>
<td>3.2%</td>
</tr>
<tr>
<td>3</td>
<td>29.6%</td>
<td>1.0%[8]</td>
<td>28.70 [14.26 to 57.77]</td>
<td>10%</td>
<td>76.1%</td>
</tr>
<tr>
<td>4</td>
<td>12.7%</td>
<td>1.0%[1]</td>
<td>98.39 [13.73 to 705.04]</td>
<td>10%</td>
<td>91.6%</td>
</tr>
</tbody>
</table>

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Ultrasound predicts imminent progression to arthritis in anti-CCP positive at-risk individuals

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Background: Ultrasound (US) Power Doppler (PD) signal is predictive for development of inflammatory arthritis (IA) in anti-cyclic citrullinated protein antibodies positive (CCP+) individuals with musculoskeletal (MSK) symptoms but no clinical synovitis (CS) [1]. Our previous data showed a late increase in the overall US inflammation before arthritis development, suggesting that a sub-clinical phase of synovitis could be detected [2]. This abstract describes the prediction of PD abnormalities in the months following US scan.

Objectives: 1. Presence of PD in one joint is predictive of imminent progression to IA in the next 3months.

2. A rise in the number of joints with presence of PD increases the odds of progression to IA.

Methods: In a single-centre prospective observational cohort between June 2008 and December 2018, 307 CCP+ patients with a new MSK complaint were included in the analysis (TPDs, hands, wrists, elbows, ankles and knees). Patients with palindromic rheumatism were excluded.

Results: Data from 66 CCP+ at-risk patients with developed CS (progressors) are compared to 211 CCP+ patients who did not (non-progressors). Age and gender are similar, the mean follow-up of the non-progressors is higher, with significantly more smokers and high titer CCP in the progressors group (Table 1).

Overall, progressors have more joints with PD than non-progressors (Figure 1). Patients with PD in one joint are more likely to develop CS in the following 3 months compared to those without PD (OR 7.52) and this remain significant when only the hands and wrists are included.
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HAVE THE CLINICAL CHARACTERISTICS OF RHEUMATOID ARTHRITIS AT PRESENTATION BECOME MILDER OVER TIME? RESULTS FROM A NATIONWIDE STUDY OVER THREE DECADES IN SWEDEN

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Background: The course of rheumatoid arthritis (RA) has become milder during the last decades, which could at least partly be attributed to major advances in the pharmacological treatment of the disease and the implementation of “treat to target”-strategies (1,2). It has also been suggested that RA is already milder at presentation (3).

Objectives: To investigate whether the clinical status, markers of inflammation, functional status, and patient and evaluator reported disease activity measures in patients with newly diagnosed RA, have improved over the recent decades.

Methods: Baseline data on all DMARD-naive patients with early RA (<6 months duration) included in the nationwide Swedish Rheumatology Quality registry (SRQ) between 1991 and 2014 were retrieved. The RA diagnosis relied on the clinical judgement of the treating physician and the information comprised swollen and tender joints count (SJC; TJC), markers of inflammation (CRP; ESR), functional status (HAQ; DASI), patient’s and evaluator’s assessment of global disease activity (PtGA; EGA) and patient’s assessment of pain (on a visual analog scale, VAS; 0-100 mm). Baseline demographic and disease characteristics were compared between patients with disease onset 1991-2000 vs. those with onset 2011-2014, using Mann-Whitney U test and Pearson’s chi-squared test.

Results: A total of 6559 early RA patients were included. Over the study period of 23 years the majority of the patients were women (68%), and the mean age at inclusion increased from 57.4 to 59.1 years. Results are summarised in Table 1. Mean CRP, ESR, TJC and SJC all decreased significantly between the two time periods compared, which was also the case for HAQ. In contrast, mean pain, PtGA and EGA increased significantly between the time periods. Furthermore, time from symptom onset to inclusion was shorter 2011-2014.

Table 1. Mean (SD) 1990s 2000s 2011-2014 p-value

Number of patients 1227 4344 988 -
Age at inclusion (years) 67.3% 67.6% 70.4% 0.12
Female gender 57.4 (15.4) 58.4 (15.0) 59.1 (14.7) 0.006
Pain (VAS 0-100) 49.5 (26.1) 52.5 (25.5) 53.4 (26.4) <0.001
PtGA (VAS 0-100) 50.3 (19.5) 54.4 (19.4) 54.8 (20.1) <0.001
EGA (VAS 0-100) 54.6 (26.7) 52.4 (25.5) 51.8 (26.7) 0.006

*1990s vs 2011-2014

Conclusion: In Swedish patients with early RA, baseline joint counts and inflammatory markers improved over the last three decades. This could partly be explained by shorter symptom duration at diagnosis but also suggests that, at onset, RA might be an inherently milder disease today. However, pain and patient’s global assessment and evaluator’s global assessment of disease activity increased over the same period of time, possibly indicating changes in both patients’ and evaluators’ expectations for management of early RA today

REFERENCES: