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THU0071

THE COMBINATION OF RHEUMATOID FACTORS WITH ANTIBODY SYSTEMS TARGETING CITRULLINATED, CARBAMYLATED AND PEPTIDYL ARGININE DEIMINASE AUTOANTIGENS DISTINGUISHES RHEUMATOID ARTHRITIS

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Background: Novel antibody systems including anti-Carbamylated Protein Antibody (anti-CarP IgG) and anti-Peptidyl Arginine Deiminase 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 (IgM) 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 Sjogren's 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 AptivaTM technology (anti-PAD4 [IgG], RUO, Inova Diagnostics) in a clinical laboratory accredited by the College of American Pathologists. For each positive antibody (above each 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 and Chi-square tests.

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<0.01). 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% specific). Interval LR and PV for each of the 4-antibody score 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.

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Table 1: Combination of Rf IgM, anti-CCP (IgG), anti-CarP (IgG) and anti-PAD4 (IgG)

Score	RA (% N)	CTL (% N)	Likelihood Ratio [CI 95%]	Pre-test Probability	Post-test Probability	Change
0	20.5% (131/638)	65.8% (510/775)	0.31 [0.27 to 0.37]	10%	3.4%	-6.6%
1	11.6% (74/638)	27.2% (211/775)	0.43 [0.33 to 0.54]	10%	4.5%	-5.5%
2	25.5% (163/638)	5.8% (45/775)	4.40 [3.22 to 6.02]	10%	32.8%	22.8%
3	29.6% (189/638)	1.0% (8/775)	28.70 [14.26 to 57.77]	10%	76.1%	66.1%
4	12.7% (81/638)	0.1% (1/775)	98.39 [13.73 to 705.04]	10%	91.6%	81.6%

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THU0072

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 the 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 3 months.

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 symptom but no synovitis were followed until CS occurred. Clinical and US findings were analysed. Following our previous study, we compared progression in the 3, 12 or >12 months after a US scan. 38 joints were included in the analysis (MTPs, hands, wrists, elbows, ankles and knees). Patients with palindromic rheumatism were excluded.

Results: Data from 96 CCP+ at-risk patients who 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 titre CCP in the progressors group (Table1).

Overall, progressors have more joints with PD than non-progressors (Figure1). 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

(Table2). The highest OR is shown when PD $\geq$ 2 is found in at least one wrist. Similarly, there is a significant but smaller prediction of progression between 3 to 12 months after US (Table2).

When a new joint develops PD, the likelihood of progression to IA within the next 3 months increases (Table2). This is especially predictive with wrists involvement (OR 3.10). Prediction of progression between 3 to 12 months before CS is significantly different between groups, with a higher OR for the wrists.

Conclusion: The presence of PD in one joint and every new joint with PD are both predictive of progression to IA within the next 3months. These results should lead to a logical programme for therapy and follow-up.

Abstract THU0072– Figure 1

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Table 1. demographics

	Progressors	Non-progressors	p-value
N	96	211	
Age*	53.4 (13)	49.8 (13.2)	0.494
CCP titre: High/Low(%)	92.7/7.3	50.2/48.8	0.000
Gender F/M(%)	74/26	74.9/25.1	0.863
Weeks follow-up*	76.44 (93.5)	189.9 (126.5)	0.000
Smoker: Ever/Never (%)	72.9/27.1	48.3/51.7	0.000

*Mean(SD)

Table 2. Probability of progression

if PD $\geq$ 1 in $\geq$ 1 joint									
	<3M			3-12M			>12M		
	OR (CI)	P-value	n	OR	P-value	n	OR	P-value	n
All joints	7.52 (2.9,18.9)	0.000	161	3.17	0.006	174	0.177		125
Hands	5.01 (2.1,11.9)	0.000	187	3.39	0.004	219	0.174		148
Wrists	4.47 (1.9,10.5)	0.001	188	5.21	0.000	219	0.999		148
for every new joint with PD $\geq$ 1									
	<3M			3-12M			>12M		
	OR (CI)	P-value	n	OR	P-value	n	OR	P-value	n
All joints	1.71 (1.3,2.3)	0.000	161	1.38	0.020	174	0.678		125
Hands	1.83 (1.2,2.7)	0.003	187	1.72	0.013	219	0.301		148
Wrists	3.10 (1.6,5.8)	0.000	188	3.05	0.000	219	0.998		148
if PD $\geq$ 2 in $\geq$ 1 joint									
	<3M			3-12M			>12M		
	OR (CI)	P-value	n	OR	P-value	n	OR	P-value	n
All joints	2.63 (1.5,4.5)	0.001	161	2.29	0.012	174	0.128		125
Hands	2.89 (1.4,5.9)	0.004	187		0.137	219	0.078		148
Wrists	12.11 (3.2,46.5)	0.000	188	5.78	0.015	219	0.999		148

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THU0073

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-naïve 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; 0-3), 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)	57.4 (15.4)	58.4 (15.0)	59.1 (14.7)	0.006
Female gender	67.3%	67.6%	70.4%	0.12
Time from symptom onset (months)	3.8 (1.5)	3.6 (1.5)	3.3 (1.5)	<0.001
CRP (mg/L)	33.1 (36.3)	29.3 (36.7)	22.6 (29.9)	<0.001
ESR (mm)	36.4 (25.8)	35.4 (24.8)	32.4 (23.7)	<0.001
TJC (0-28)	8.0 (6.6)	8.0 (6.1)	7.1 (6.0)	0.005
SJC (0-28)	9.5 (5.9)	9.0 (5.8)	7.6 (5.5)	<0.001
HAQ (0-3)	1.1 (0.6)	1.1 (0.6)	1.0 (0.6)	0.028
EGA (VAS 0-100)	50.3 (19.5)	54.4 (19.4)	54.8 (20.1)	<0.001
Pain (VAS 0-100)	49.5 (26.1)	52.3 (25.5)	53.4 (26.4)	<0.001
PtGA (VAS 0-100)	48.6 (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

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