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

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Background

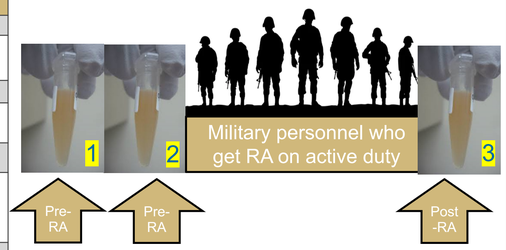
- Rheumatoid arthritis (RA) has a 'pre-RA' period during which there are autoantibody elevations prior to the onset of clinically-apparent inflammatory arthritis (i.e. clinical RA).[1,2]
- Objective: to evaluate the role of multiple autoantibody systems in potentially identifying a signature in the pre-RA period that indicates imminent onset of clinical RA.

Methods

- Case-control study: 148 individuals with two pre- and one post-RA diagnosis serum samples from the Department of Defense Serum Repository, and matched controls.
- Tested for anti-CCP3, five ACPA fine-specificities, anti-PAD, anti-CarP, RF IgA and IgM.
- Analyses included comparison of positivity of autoantibodies over time from pre-RA to post-RA, and comparison between RA and controls.
- Positivity determined as levels present <= 1% in a separate set of controls.
- Total autoantibody positivity count was determined using those autoantibodies that were significantly different between RA and controls.

Results

	>3 years pre-RA	<=3 years, >60 days pre-RA	Post-RA	Controls	p-value Pre-RA to controls
n	148	148	148	308	-
Days to Diagnosis of RA, mean (SD) [mean years]	-3711 (1915) [~10.1 yrs]	-437 (252) [~1.2 yrs]	+409 (288) [~1.1 yrs]	-	-
Age at sample, mean (SD)	26.7 (7.2)	35.5 (8.1)	37.9 (7.9)	24.8 (6.5)	0.314
Age at diagnosis of RA, mean (SD)	36.7 (8.0)	-	-	-	-
n, (%) Female	82 (55.4%)	-	-	156 (50.6%)	0.423
Race n, (%) White n, (%) Black n, (%) Hispanic	 80 (54.1%) 40 (27.0%) 14 (9.5%)	-	-	 163 (52.9%) 79 (25.6%) 37 (12.0%)	0.752
n, (%) meeting 1987 ACR RA criteria	146/148 (98.6%)	-	-	-	-



	>3 years pre-RA (n=148)	<=3 years, >60 days pre-RA (n=148)	post-RA diagnosis (n=148)	p-value pre-RA time points	p-value pre-RA and post-RA	Controls (n=307)	p-value Post-RA vs Controls
Anti-CCP3 IgG, n (%)	23 (15.5%)	90 (60.8%)	90 (60.8%)	<0.001	1.000	3 (1.0%)	<0.001
Anti-PAD1 IgG, n (%)	3 (2.1%)	9 (6.1%)	15 (10.1%)	0.031	0.146	0 (0%)	<0.001
Anti-PAD2 IgG, n (%)	0 (0%)	2 (1.4%)	0 (0%)	0.500	0.500	0 (0%)	-
Anti-PAD3 IgG, n (%)	0 (0%)	1 (0.7%)	0 (0%)	1.000	1.000	0 (0%)	-
Anti-PAD4 IgG, n (%)	4 (2.7%)	9 (6.1%)	13 (8.8%)	0.063	0.219	2 (0.7%)	<0.001
Anti-PAD6 IgG, n (%)	1 (0.7%)	1 (0.7%)	1 (0.7%)	1.000	1.000	2 (0.7%)	1.000
Anti-Vimentin 2 IgG, n (%)	12 (8.1%)	63 (42.6%)	65 (43.9%)	<0.001	0.678	2 (0.7%)	<0.001
Anti-Histone 2 IgG, n (%)	0 (0%)	2 (1.4%)	2 (1.4%)	0.500	1.000	1 (0.3%)	0.244
Anti-Fibrinogen IgG, n (%)	12 (8.1%)	63 (42.6%)	65 (43.9%)	<0.001	0.832	1 (0.3%)	<0.001
Anti-Histone 1 IgG, n (%)	9 (6.1%)	25 (16.9%)	30 (20.3%)	<0.001	0.383	3 (1.0%)	<0.001
Anti-Vimentin 1 IgG, n (%)	0 (0%)	1 (0.7%)	1 (0.7%)	1.000	1.000	1 (0.3%)	0.541
RFIgA, n (%)	16 (10.8%)	67 (45.3%)	68 (45.9%)	<0.001	1.000	6 (2.0%)	<0.001
RFIgM, n (%)	19 (12.8%)	68 (45.9%)	73 (49.3%)	<0.001	0.472	5 (1.6%)	<0.001
CCP3, RFIgA and RFIgM positive, n (%)	8 (5.4%)	46 (31.1%)	47 (31.8%)	<0.001	1.000	0 (0.0%)	<0.001
Total Autoantibody Positivity Count, mean (SD)	0.5 (1.2)	1.9 (1.8)	2.2 (1.8)	<0.001	0.020	0.6 (0.4)	<0.001
Total Autoantibody Positivity Count, median [25, 75]*	0 [0, 0]	2.0 [0, 3.0]	2.0 [0, 3.8]	<0.001	0.020	0 [0,0]	<0.001

*An autoantibody positive count of >=2 was significantly associated with a time point <3 years prior RA diagnosis: AUC 0.85, 95% CI 0.78-0.90, p<0.001; sensitivity 77.8%, specificity 86.7%, positive predictive value [PPV] 77.8%, negative predictive value [NPV] 86.7%

Conclusions

Multiple autoantibody systems differ in RA from controls, and increase in positivity over time in pre-RA

- Anti-CCP3, anti-PAD1 and 4, anti-histone 1, anti-vimentin 2, anti-fibrinogen, RF IgA and IgM

Autoantibody counts using the 7 that were significantly different between RA and controls:

- Differ in RA from controls
- Increase pre-RA and post-RA
- In pre-RA, antibody count >=2 significantly associated with <3 years to diagnosis (AUC 0.85, positive predictive value ~78%)

Implications

- A simple model using antibody counts could be used in individuals who are at-risk for future RA to estimate imminent onset (i.e. <3 years) of clinical RA.
- Models will be tested in future prospective studies and in clinical prevention trials

Disclosures: KD Deane has received consultant fees and in-kind materials from Werfen. M Mahler is an employee of Werfen.

References:

1. Deane KD, Holers VM. Rheumatoid arthritis pathogenesis, prediction, and prevention: an emerging paradigm shift. Arth Rheum 2021;73:181-93.
2. Sokolove J, Bromberg R, Deane KD, et al. Autoantibody epitope spreading in the pre-clinical phase predicts progression to rheumatoid arthritis. PLoS One 2012;7:e35296.