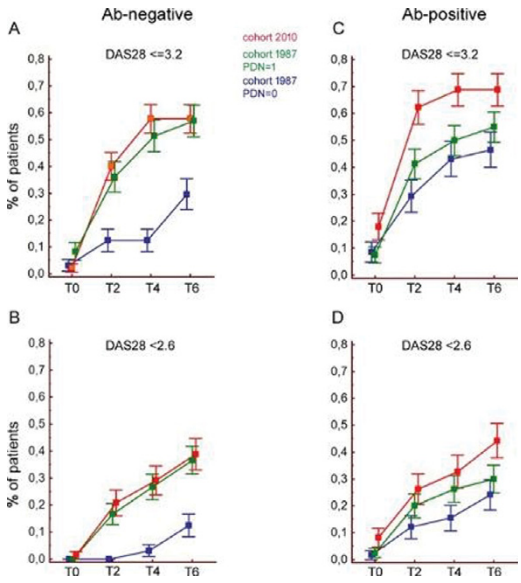

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THU0100 IN EARLY INFLAMMATORY ARTHRITIS A LYMPHOID PATHOTYPE SIGNFICANTLY ASSOCIATES WITH REQUIREMENT FOR BIOLOGIC THERAPY AT 12 MONTHS FOLLOW UP: RESULTS FROM THE PATHOBIOLOGY OF EARLY ARTHRITIS COHORT (PEAC)

G. Lliso-Ribera[1], F. Humby[1], S. Kelly[1], M. Bombardieri[1], M. Lewis[1], R. Hands[1], V. Rocher[1], F. Bene[1], A. Nerviani[1], C. Buckely[2], P. Taylor[3], I. McInnes[4], C. Pitzalis[1]. *[1]Experimental Medicine and Rheumatology, Queen Mary University London, London; [2]Centre for Translational Inflammation Research, University of Birmingham, Birmingham; [3]Kennedy Institute of Rheumatology, University of Oxford, Oxford; [4]Experimental Medicine and Rheumatology, University of Glasgow, Glasgow, United Kingdom*

Background: Early aggressive treatment in RA equates to better long term outcomes, however targeting aggressive therapies including biologics to patients with the worse prognosis is critical to deliver acceptable risk/benefit ratios and health economic improvements. Such an approach requires prognostic biomarkers, whether the well recognised heterogeneity in synovial pathobiology in early RA translates to specific disease outcomes is currently unknown.
Objectives: The aim of this study was to investigate whether in a treatment naïve early inflammatory arthritis cohort, baseline synovial pathotype significantly associates with disease outcome at 12 months.
Methods: 166 consecutive DMARD naïve patients recruited as part of PEAC at Barts Health NHS Trust with synovial tissue suitable for analysis were included. At baseline patients were classified as RA (2010 ACR/EULAR criteria) or undifferentiated (UA). All patients underwent a baseline synovial biopsy of a clinically active joint along with collection of demographic data. Patients were subsequently treated with DMARD +/- steroid therapy with aim for low disease activity (DAS <3.3). At 6 month follow up patients were escalated to biologic therapy if fulfilling UK NICE guidelines. At 12 months patients were classified as: (i) no treatment, (ii) DMARDs, and (iii) Biologic +/- DMARDs. Sequentially cut sections of baseline synovial biopsies underwent immunohistochemical staining and semi-quantitative scoring (0–4) to determine the degree of CD20+Bcells, CD3+T cells, CD68+ lining (l) and sublining (sl) macrophage and CD138+ plasma cell infiltration. Sections were categorised into 3 pathotypes, (i) Fibroid: (CD68 SL<2 and or CD3, CD20, CD138<1), (ii) Myeloid: (CD68SL>2, CD20<1 and or CD3>1) and (iii) Lymphoid: (grade 2–3 CD20+ aggregates, CD20>2).
Results: 79% were classified as RA and 21% as UA. Mean disease duration was 9.27 months. 92% (153/166) patients had follow-up at 12months. 29% (44/153) of patients were classified as fibroid, 34% (52/166) as myeloid and 37% (57/166) as lymphoid. At baseline patients with a lymphoid pathotype had a significantly higher CRP and DAS28 and were significantly more likely to be sero positive for for RF and ACPA ($p<0.05$), suggesting that a lymphoid pathotype is associated with higher levels of disease activity. At 12 months follow up a significantly higher proportion of patients classified as lymphoid vs myeloid or fibroid (58% vs 21% vs 21%) required biologic therapy.
Conclusions: Results demonstrate that in an early inflammatory arthritis cohort a lymphoid pathotype significantly associates with higher disease activity at baseline, sero positivity for RF and ACPA and a requirement for more aggressive therapy at 12 month. This supports a direct role for synovial lymphoid structures in disease pathogenesis and suggests a role as a prognostic biomarker facilitating early stratification of aggressive therapeutic intervention.

N=153	Fibroid (44)	Myeloid (52)	Lymphoid (57)	p-value
No treatment (14) n (%)	6 (42%)	6 (42%)	2 (14%)	<0.05*
DMARD (101) n (%)	30 (29%)	38 (37%)	33 (32%)	
Biologic +/– DMARD (38) n (%)	8 (21%)	8 (21%)	22 (58%)	

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THU0101 CARDIOVASCULAR MAGNETIC RESONANCE IMAGING CHARACTERISATION OF CARDIOVASCULAR ABNORMALITIES IN INDIVIDUALS AT RISK OF DEVELOPING RHEUMATOID ARTHRITIS

G.J. Fent[1], L. Hunt[2,3], K.S. Mankia[4,5], B. Erhayiem[1], J.R. Foley[1], P. Garg[1], P.P. Swoboda[1], J. Andrews[4,5], J.P. Greenwood[1], P. Emery[4,5], S. Plein[1], M.H. Buch[1,5]. *[1]Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds, UK; [2]NIHR Leeds Musculoskeletal Medicine, University of Leeds, United Kingdom; [3]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, United Kingdom; [4]Leeds Institute of Rheumatic and Musculoskeletal Medicine; [5]NIHR Leeds Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom*

Background: Inflammation is the primary contributor to excess cardiovascular (CV) disease in rheumatoid arthritis (RA), with evidence of subclinical abnormalities observed even in treatment-naïve, early RA [1]. Preliminary reports suggest citrullinated proteins are present in atherosclerotic plaque [2]. It is unclear whether immunological changes of anti-citrullinated protein antibody (anti-CCP+) positive individuals "at risk" of developing RA are associated with CV abnormality.
Objectives: To perform a pilot study to explore whether subclinical CV abnormalities are present in anti-CCP+ individuals at risk of developing RA.
Methods: Sixteen consecutive patients with non specific MSK symptoms but no synovitis, detectable anti-CCP antibody and 30 age-matched healthy controls (HC) underwent a multi-parametric 3.0T (Philips Achieva) cardiovascular magnetic resonance (CMR) study. Neither group had any history of CV disease. At-risk individuals were categorised as low and high absolute risk for RA development (<50% and ≥50% respectively) according to a published risk model [3]. CMR post-processing was performed using CVI [42] (Circle Cardiovascular Imaging, Canada).
Results: HC and at risk individuals were well matched for baseline characteristics (table 1). Aortic strain values (distensibility, strain and stiffness index β) were lower, indicating increased aortic stiffness, in at-risk individuals than HC, numerically most pronounced those classified high risk (table 2). There were no differences in LV mass and function, late gadolinium enhancement, myocardial T1 (measure of myocardial composition) or LV S prime (longitudinal LV systolic function) (table 2).

Table 1. Baseline characteristics

	All 'at risk' RA patients (n= 16)	Healthy controls (n=30)	p value
Age (years)	53±11	50 ± 15	0.59
Males	4/16 (25%)	10/30 (33%)	0.57
Systolic BP (mmHg)	121±17	120±13	0.82
Diastolic BP (mmHg)	64±11	64±11	0.81
BMI (kg/m^2)	28±5	27±6	0.47
Diabetes	2/16	0/30	0.05
Active smoker	1/16 (6%)	3/30 (10%)	0.68
Ex-smoker	11/16 (69%)	5/30 (17%)	0.001
Mean absolute pre-	45%	-	-

Table 2. Results table

	All 'at risk' RA individuals (n= 16)	Low 'at risk' RA individuals (n=10)	High 'at risk' RA individuals (n=6)	Healthy controls (n=30)	p value
Aortic Distensibility (10^{-3}mmHg)	3.6±1.4	4.1±1.5	2.8±0.5	4.7 ± 2.0	0.05
Aortic strain	0.20±0.06	0.21±0.07	0.18±0.03	0.25 ± 0.09	0.03
Aortic stiffness index, β	3.5±1.0	3.2±1.0	4.0±0.8	2.7 ± 0.8	0.007
Myocardial native T1	1215±35	1213±36	1218±37	1202 ± 36	0.25
Late Gadolinium enhancement	1/16	0/6	1/10	1/30	-
LV ejection fraction (%)	62±4	62±5	63±3	62±5	0.94
RV ejection fraction (%)	55±6	54±4	58±7	54±6	0.47
Indexed LV mass (g/m^2)	46±10	45±8	49±14	49±8	0.29
Indexed LV volume (ml/m^2)	83±12	81±13	87±12	80±11	0.34
LV S prime (s-1)	1.1±0.1	1.2±0.1	1.0±0.1	1.1±0.1	0.37

Conclusions: Anti-CCP+ individuals with non-specific MSK symptoms (in particular, a high risk group), exhibit increased aortic stiffness. This suggests presence of CV abnormalities prior to development of RA and implies a role of autoantibody-mediated development of atherosclerosis. These findings warrant further investigation in larger scale studies.

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THU0102 CLINICAL DISEASE ACTIVITY MEASURES ARE IMPORTANT DRIVERS OF MAJOR CHANGE IN MEDICAL TREATMENT IN US VETERANS ENROLLED IN THE VETERANS AFFAIRS RHEUMATOID ARTHRITIS (VARA) REGISTRY

G.W. Cannon[1,1], C.-C. Teng[2], N.A. Accortt[3], D. Collier[3], S. Mehrotra[2], B.C. Sauer[2]. *[1]Rheumatology; [2]Salt Lake City Va Medical Center, Salt Lake City; [3]Amgen, Thousand Oaks, United States*

Background: Current guidelines encourage the measurement of rheumatoid arthritis (RA) disease activity and directing therapy to achieve a low disease state or remission (treat-to-target). Many RA patients with documented moderate to severe disease activity remain on their current therapy without change.

Objectives: This study investigated Veterans Affairs (VA) clinical data to identify patient factors associated with a major change in RA therapy and to determine the relative importance of these different factors.

Methods: US Veterans enrolled in the VARA registry were included if they had: 1) high/moderate disease activity (DAS28≥3.2) at index date, 2) 18 months of VA data prior to the index date and 3) two or more other DAS28 measured during the preceding 18 months separated by at least three months. A major change was report if within 7 days before to 90 days after the index date there was either: 1) initiation or escalation of DMARDs, 2) initiation or increase dose of prednisone and/or 3) ≥2 joint injections.

Baseline DAS28 was estimated during the observation period prior to the index date using an area under the curve calculation and compared to the DAS28 at the index date. Patients were categorized as have a worsening or improvement of disease if the DAS28 at index date was 0.6 higher or lower than the average DAS28 during the observation period respectively. Other patients were categorized as no change in DAS28.

Analyses of clinical variables including components of the DAS28 and patient and physician reported measures were compared in patients with and patients without a major change in therapy.

Results: Of 941 patients who met study criteria, only 388/941 (41.2%) had a major change of therapy. Patients with worsening DAS28 were more likely to have a major change 183/369 (49.5%) than no DAS28 change 170/454 (37.4%) and improved DAS28 35/118 (29.6%) (P<0.001). Clinical variables were strongly associated with changes in therapy among patients with worsening disease activity and not as strongly associated with change in therapy in those with no change disease activity. Clinical variables were not significantly associated with major change in patients with disease improvement, though that group had the smallest sample size. Ten representative clinical variables with the highest association with major change are included below.

	Comparison of Patients with Major Change to Patients without Major Change					
Demographic elements	DAS28 worsening (n=369)		DAS 28 no change (n=454)		DAS 28 improved (n=118)	
Major Change at Index Date - Number (%)	183/369 (49.5%)		170/454 (37.4%)		35/118 (29.6%)	
Age at RA Disease Onset - Mean (SD)	52.4±13.7		51.4±13.7		50.9±12.9	
Age at Index Date - Mean (SD)	65.3±10.6		65.6±11.0		64.0±10.8	
Male - Number (%)	328 (88.9%)		410 (90.3%)		99 (84.0%)	
Clinical Variables from VARA registry	RR (CI 95)	p-value	RR (CI 95)	p-value	RR (CI 95)	p-value
DAS28 Score At Index Date	1.25 (1.11 - 1.42)	<0.001	1.30 (1.12 - 1.51)	0.001	1.23(0.82 - 1.82)	0.318
Baseline DAS28 Score during 18 months observation period	1.20 (1.05 - 1.37)	0.009	1.27 (1.09 - 1.47)	0.002	1.27 (0.86 - 1.87)	0.219
Swollen Joint Count	1.03 (1.00 - 1.04)	0.031	1.05 (1.01 - 1.08)	0.006	1.06 (0.99 - 1.12)	0.070
Tender Joint Count	1.02 (1.00 - 1.04)	0.027	1.01 (0.98 - 1.03)	0.530	0.98 (0.91 - 1.07)	0.671
Modified Health Assessment Questionnaire (MD HAQ)	1.08 (0.87 - 1.37)	0.051	1.03 (0.81 - 1.31)	0.743	0.90 (0.50 - 1.61)	0.722
Pain Score	1.07 (1.01 - 1.13)	0.028	1.04 (0.99 - 1.10)	0.145	0.93 (0.83 - 1.05)	0.257
Patient Global Assessment	1.01 (1.00 - 1.01)	0.093	1.01 (1.00 - 1.02)	0.014	1.00 (0.98 - 1.01)	0.560
Physician Global Assessment	1.00 (0.99 - 1.01)	0.474	1.01 (1.00 - 1.02)	0.002	1.01 (0.99 - 1.02)	0.402
Erythrocyte Sedimentation Rate	1.01 (1.00 - 1.01)	0.073	1.00 (1.00 - 1.01)	0.582	1.00 (0.99 - 1.02)	0.630
C-reactive Protein	1.04 (1.00 - 1.08)	0.056	1.08 (1.00 - 1.17)	0.990	1.08 (0.92 - 1.28)	0.344

Conclusions: More than half of the patients with moderate disease activity did not have a major change in therapy. The likelihood of a major change in therapy increased with worsening disease activity. The clinical variables assessed were more strongly associated with change in therapy in patients with worsening of disease. Clinical disease activity measures are highly associated with the decision to initiate major changes. Future work will investigate the potential added value of administrative variables. This work emphasizes the need for methods to systematically collect and utilize clinical disease activity measurements, particularly longitudinally, to improve the treat-to-target strategy.

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THU0103 ANTI-RA33 AUTOANTIBODIES ARE ASSOCIATED WITH THERAPEUTIC RESPONSES TO METHOTREXATE AND ANTI-TNF TREATMENT IN PATIENTS WITH RHEUMATOID ARTHRITIS

G. Steiner[1], D. Sieghart[1], P. Studenic[1], T. Horn[2], D. Aletaha[1], J. Smolen[1]. *[1]Internal Medicine III-Rheumatology, Medical University Vienna; [2]Phadia Austria GmbH, Thermo Fisher Scientific, Vienna, Austria*

Background: Besides the determination of rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA), anti-RA33 antibodies (which are directed to the nuclear antigen hnRNP-A2) could be of additional diagnostic and/or prognostic value in patients with rheumatoid arthritis (RA) because they are also found in RF/ACPA negative patients (1, 2).

Objectives: So far, published data on anti-RA33 antibodies refer only to the IgG isotype. It was therefore the aim of this study to measure the prevalence of anti-RA33 IgG, IgM and IgA antibodies in patients with RA and to determine their potential prognostic value regarding prediction of response to treatment.

Methods: A total of 255 patients were tested for the presence of IgG, IgM and IgA anti-RA33 antibodies by a newly developed EliA® (Thermo Fisher Scientific). All patients had initially been treated with conventional synthetic drugs (mostly methotrexate) and were subsequently treated with at least one TNF inhibitor. Therapeutic responses to MTX and TNF blocking biologicals were calculated in an inception cohort (n=104) who had started their DMARD therapy at our clinic. To define therapeutic responses the simplified disease activity index (SDAI)50 and American College of Rheumatology (ACR)20 responses were calculated.

Results: Among the 255 patients, 11% tested positive for anti-RA33 IgG antibodies, 15% for IgM antibodies and 6% for IgA antibodies. Altogether, 62 patients (24%) had at least one type of anti-RA33 antibody: 24 patients were RF-negative, 26 were ACPA-negative and 18 were RF/ACPA double negative. Thus, in 32 patients (13%), anti-RA33 was the only antibody specificity. Regarding response to anti-TNF therapy (Figure 1A), in the group of patients testing positive for anti-RA33 antibodies of any isotype (with or without concomitant RF and/or ACPA) the percentage of SDAI50 responders (24%) was significantly lower (p=0.0117) than in anti-RA33 negative (but RF/ACPA positive) patients (42% responders) and similar to the group of completely seronegative patients (21% responders). In contrast, regarding responses to MTX (Figure 1B) the percentage of SDAI50 responders was significantly higher (p<0.0001) among anti-RA33 positive patients (with or without RF and/or ACPA) (59% responders) compared to anti-RA33 negative (but RF/ACPA positive) patients (37% responders) and seronegative patients (24% responders).

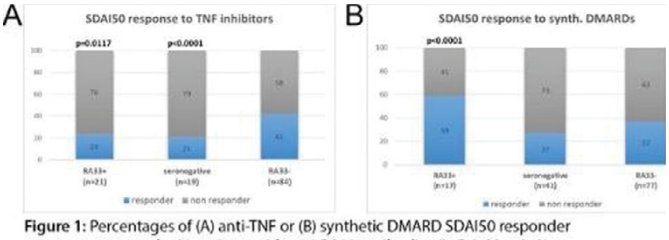

Figure 1: Percentages of (A) anti-TNF or (B) synthetic DMARD SDAI50 responder versus non responder in patients with anti-RA33 antibodies (IgG, IgM or IgA), seronegative patients (RA33-RF-ACPA-) compared to RA33 negative patients.

Conclusions: In agreement with previous findings (1,2) anti-RA33 antibodies reduced the diagnostic gap left by ACPA and RF and thus the percentage of seronegative patients by 13%. Importantly, the presence of anti-RA33 antibodies was associated with a favourable response to MTX on the one hand and with a diminished response to TNF inhibitors on the other hand. Therefore, these antibodies appear to have some prognostic value for prediction of therapeutic responses and could become helpful tools in therapeutic decision making.

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