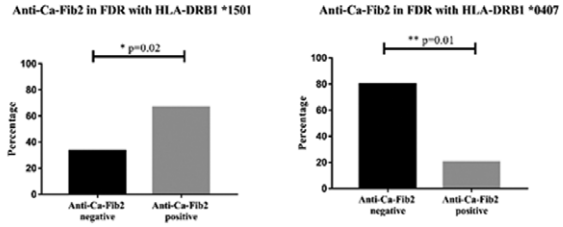
Figure 2 association of carbamylated anti-peptide antibodies with the presence of HLA DRB1 SE and non-SE in FDR



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Acknowledgments: Hospital Militar Central (Grant 2015-047), the Government Institute of Science, Technology,and Innovation,Francisco Jose de Caldas—COLCIENCIAS(Grant No. 130865740792-2014)

Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2020-eular.3861

SAT0003 ELEVATED BASELINE AND INCREASING AUTOANTIBODY LEVELS ARE ASSOCIATED WITH INCREASED RISK FOR IMMINENT ONSET OF INFLAMMATORY ARTHRITIS IN A PROSPECTIVELY STUDIED ANTI-CITRULLINATED PROTEIN ANTIBODY POSITIVE COHORT: THE TIP-RA COLLECTIVE

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Background: The Targeting Immune Responses for Prevention of RA (TIP-RA) Collaborative prospectively studies individuals at high risk for developing RA because of serum ACPA positivity in absence of baseline inflammatory arthritis (IA).

Objectives: The objective of the analyses presented herein is to evaluate the role of baseline and changing levels of ACPA and rheumatoid factor (RF) in relationship to incident IA/RA.

Methods: ACPA+ subjects and ACPA- controls were identified who did not have baseline historical or examination evidence of IA. ACPA+ was defined by serum elevation of anti-CCP3 ≥20 units (Inova). Subjects were evaluated annually or sooner if they had changes in joint symptoms. Factors including RFIgM and RFIgA (Inova) were also assessed, and relationships between autoantibody levels at baseline and over time and incident IA/RA were evaluated using t-tests, with paired testing where applicable.

Results: Baseline characteristics of ACPA+ and ACPA- subjects are in Table 1. Sixteen of the 94 (17%) ACPA+ subjects developed IA/RA a mean of 518 days from the baseline visit; 14 of these met 2010 ACR/EULAR criteria for RA at the time of detection of IA. There was a trend for ACPA+ subjects who later developed IA/RA to have higher baseline levels of anti-CCP3 compared to those who did not develop IA/RA (Table 2). In addition, those who developed IA/RA had significantly higher mean levels of RFIgM and RFIgA compared to those who did not. While not statistically significant, in longitudinal analyses in the ACPA+ subjects with incident IA/RA, anti-CCP3 levels increased from baseline to identification of IA (mean [SD] of 119 [102] to 126 [100], p=0.42). Furthermore, RFIgM levels increased from 36 [49] at baseline to 43 [51] at the time of IA (p=0.31), and RFIgA levels increased from 16 [29] to 21 [31] (p=0.10). In contrast, in ACPA+ subjects who did not develop IA/RA, anti-CCP3 levels increased only slightly over follow-up of a mean of 712 days: 75 [75] to 80 [76], p=0.70 while the levels of RFIgM and RFIgA decreased slightly during the same follow-up: for RFIgM mean [SD] levels went from 9 [22] to 8 [19], p=0.74; for RFIgA, 5 [16] to 3 [12], p=0.67.

Table 1. Baseline characteristics of ACPA+/- subjects

	ACPA- (n=162)	ACPA+ (n=94)	p-value
Age, mean	58	58	0.90
% Female	69	68	0.67
% Ever smoker	33	34	0.87
RF-IgM, mean (SD)	3.2 (10.0)	13.5 (30.2)	<0.01
RF-IgA, mean (SD)	0.3 (0.6)	6.5 (19.1)	<0.01

Table 2. Baseline characteristics of 16 ACPA+ subjects who developed incident IA/RA vs. 78 ACPA+ who did not

	Did not develop IA/RA (n=78)	Developed IA/RA (n=16)	p-value
Days from baseline to IA/RA or follow-up, mean (SD)	712 (124)	518 (295)	–
% Meeting 2010 criteria at time of IA	-	88	–
CCP3, mean (SD)	74.5 (75.3)	119.1 (102.1)	0.05
RFIgM, mean (SD)	**9 (22)**	**36 (49)**	**<0.01**
RFIgA, mean (SD)	**4 (16)**	**16 (29)**	**0.03**

Conclusion: In this prospectively followed cohort of ACPA+ subjects, higher levels of RFIgM and RFIgA at baseline were significantly associated with development of IA/RA within the follow-up period. Furthermore, there was a trend for rising levels of anti-CCP3 and RFIgM and A to be associated with development of IA/RA. These finding support the use of higher and/or rising levels of autoantibodies as additional features to predict imminent onset of IA/RA in ACPA+ individuals as well as potentially to use as outcomes of success of preventive interventions. Furthermore, the trend of increasing levels of RFIgM and RFIgA over time in individuals who developed IA/RA suggests that targeting pathways of RF development may lead to preventive interventions in a subset of RA.

References: None

Disclosure of Interests: Kevin Deane Grant/research support from: Janssen, Consultant of: Inova, ThermoFisher, Janseen, BMS and Microdrop, Gary Firestein Grant/research support from: Lilly, Janssen, Abbvie, David Boyle: None declared, Jane Buckner Grant/research support from: Bristol-Myers Squibb, Janssen, Eddie A. James Grant/research support from: Janssen, Pfizer, Sanofi, Novartis, Sylvia Posso Grant/research support from: Janssen, William Robinson Grant/research support from: Janssen, Laurie K. Moss Grant/research support from: Janssen, Jennifer Seifert Grant/research support from: Janssen, Roger Gilmore Grant/research support from: Janssen, Saman Barzideh Grant/research support from: Janssen, Navin Rao Shareholder of: Janssen Pharmaceuticals, Employee of: Janssen Pharmaceuticals, Frederic Baribaud Shareholder of: Janssen Research & Development, LLC, Employee of: Janssen Research & Development, LLC, Sunil Nagpal Shareholder of: Janssen Pharmaceuticals, Employee of: Janssen Pharmaceuticals, Alyssa Johnsen Employee of: Janssen, V. Michael Holers Grant/research support from: Janssen, Celgene, and BMS

DOI: 10.1136/annrheumdis-2020-eular.5713

SAT0004 INCREASED M1 INFLAMMATORY PHENOTYPE OF CIRCULATING MONOCYTES IS ASSOCIATED WITH HISTORY OF CARDIOVASCULAR EVENTS IN RA PATIENTS

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Background: Cardiovascular (CV) Disease is the main cause of death in Rheumatoid Arthritis (RA). Current tools like Framingham or European SCORE underestimate CV risk in RA patients. Efforts to improve the assessment including RA biomarkers (disease activity) have been only partially successful. There is a need for better biomarkers to identify AR patients at high risk for CV disease. Monocytes have an important role in plaque development. Monocytes differentiates into 2 main phenotypes M1 and M2 (1). In RA and in post-MI patients M1 monocytes are expanded (2). mTORC influences monocyte phenotype *in vitro* and has been associated with development of atheromatous plaque (3).

Objectives: To evaluate the phenotype of circulating monocyte in RA patient with or without previous CV events (RA-CV(-)RA-CV(+)), and its possible association with mTORC activity.

Methods: 9 RA-CV(+)patients aged between 18 and 65 yo with RA (EULAR/ACR 2010 criteria), were paired with RA-CV(-)patients. 6 healthy individuals (HI) were also studied. Pairing criteria were classic CV risk factors (AHA 2018), sex, age, years since RA diagnosis, comorbidities, number of DMARDs previously used and use of bDMARDS. M1 and M2 circulating Monocytes were evaluated in PBMC obtained from patients and controls by flow cytometry analysis. Intracellular inflammatory cytokines (IL1, Il6) and phosphorylated S6R (P-S6R) as a measure of mTORC activation was also evaluated. M1 was defined as CD14+HLA-DR+CCR2+ and M2 CD14+CD163+CCR2-. DAS28-RCP, DAS28-ESR and Lipid profile was also measured. The differences among groups was analysed using Mann–Whitney U nonparametric. The relationship between variables with Spearman rank correlation test.

Results: There were no differences in demographic, RA characteristic and CV risk factors between RA-CV (+) and RA-CV (-) patients. Male/Female 4/5, age 62±3 and 63±2 respectively. HI were younger than RA patients (32.5±7). CV events were 8 patients with MI and one Stroke. DAS28-RCP was 2.96±0.23 and 2.88±0.43 respectively. One patient in each group had failed to more than 2 sDMARDs

and one in each group was receiving bDMARD. M1 circulating monocytes were expanded in RA as compared to HI. This difference was at RA-CV (+) expense. RA monocytes had higher Intracellular levels of IL-1b and IL-6 as compared to HI. M1 from RA-CV (+) had higher intracellular levels of IL-1b and IL-6 than RA-CV (-). M1 monocytes have higher levels of inflammatory cytokines than M2. P-S6R protein, (mTORC activation), was higher in RA patients than HI. The highest levels of P-S6R was observed in M1 monocytes from RA-CV(+) population.

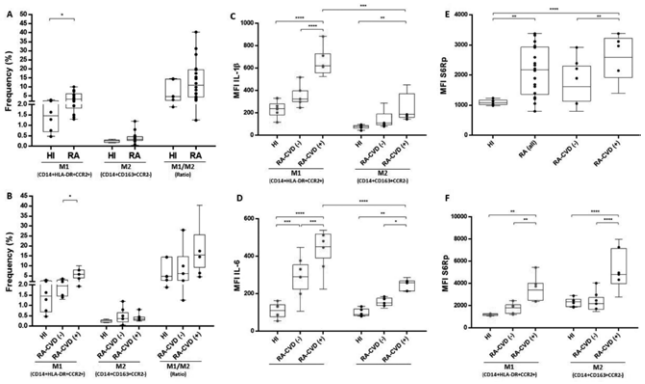

FIGURE 1. Circulating monocytes phenotype, intracellular cytokines and phosphorylated S6R in HI and RA-CV (+), RA-CV (-) and the combined RA patients.

A) *=0,02; B) *=0,016; C) ****=0,0001, **=0,002; D) ****=0,0001, ***=0,0008, **=0,001, *=0,01; E) ****0,0001, **=0,002; F) ****=0,0001, **=0,001, **=0,003.

Conclusion: RA-CV+ patients, have a significantly higher number of pro-inflammatory circulating monocytes, using a multiparametric classification method. These monocytes also express higher levels of inflammatory cytokines and higher activation of mTORC, which also participate in the development of atheromatous plaque, suggesting that these monocytes could be a key element in the non-clarified-yet, excess of CV risk of RA patients.

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Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2020-eular.6645

SAT0005 INHIBITION OF HEPATOCYTE GROWTH FACTOR/C-MET SIGNALING ABROGATES JOINT DESTRUCTION BY SUPPRESSING MIGRATION OF MONOCYTES TO SYNOVIUM IN RHEUMATOID ARTHRITIS

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Background: Hepatocyte growth factor (HGF), originally discovered as a mitogen of hepatocytes, binds to receptor-tyrosine kinase c-Met and has been shown to be a multi-functional cytokine that promotes processes such as cell proliferation, survival, differentiation, migration, and angiogenesis[1]. Since HGF/c-Met signaling also leads to tumorigenesis and cancer invasion, that has recently attracted attention as a target for anticancer agents[2]. However, in reports of rheumatoid arthritis (RA), though anti-inflammatory and antiangiogenic mechanisms related to HGF/c-Met signal inhibition have been reported, the role of HGF in RA bone destruction through monocyte migration remains unclear[3].

Objectives: To determine the expression of HGF in RA biological fluids, the role it plays in monocyte migration and the therapeutic effect of a savolitinib, a specific c-Met inhibitor, in arthritis model mice.

Methods: HGF/c-Met expression in serum, synovial fluid (SF), and synovial tissues (STs) obtained from RA patients and control subjects, as well as RA fibroblast-like synoviocytes (FLSs) was evaluated by ELISA and immunostaining. To determine the function of HGF in RA SFs, we preincubated RA SFs with a neutralizing anti-HGF antibody and measured the ability of these SFs to induce the human acute monocytic leukemia cell line (THP-1) chemotaxis. Additionally, examinations of SKG mice treated with savolitinib (2.5 mg/kg/day) for 4 weeks were conducted.

Results: HGF level in serum from RA patients was significantly higher as compared to the controls (930 ± 97 vs. 476 ± 97 pg/mL, p <0.01) and decreased by drug treatment for 24 weeks (1147 ± 284 vs. 539 ± 160 pg/mL, p <0.05). Additionally, HGF level in SF from RA patients was higher as compared to SF from osteoarthritis patients (1632 ± 366 vs. 566 ± 140 pg/mL, p <0.05). HGF and c-Met expressions were also noted in RA STs. Stimulation of RA-FLS with TNF-α increased HGF/c-Met expression in a concentration-dependent manner, and c-Met signal inhibition by SU11274 suppressed production of fractalkine/CX3CL1, CXCL16, and MIP-1α/CCL3 (mean 50%, 56%, 90%, respectively). When HGF was removed by immunoprecipitation, migration of THP-1 in RA-SF was suppressed (mean 23%). In SKG mice, savolitinib significantly suppressed ankle bone damage on μCT, with an associated reduction in number of tartrate-resistant acid phosphatase-positive osteoclasts.

Conclusion: HGF is produced by inflammation in synovium associated with RA, and then activates monocyte migration to synovium tissue and promotes bone destruction through its own chemotactic effect as well as enhanced chemokine production. These results indicate that a strategy that targets c-Met signaling may be important for resolving bone destruction in RA.

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Disclosure of Interests: None declared

DOI: 10.1136/annrheumdis-2020-eular.3410

SAT0006 SIMULTANEOUS ANALYSIS OF ANTI-CCP, RHEUMATOID FACTOR, ANTI-PAD4 AND ANTI-CARBAMYLATED PROTEIN ANTIBODIES REVEALS INTERACTION EFFECTS WITH RESPONSE TO ANTI-TNF THERAPY IN RHEUMATOID ARTHRITIS

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Background: Blocking of the Tumor Necrosis Factor (TNF) activity is a successful therapeutic approach for 2 out of 3 Rheumatoid Arthritis patients. Identifying the patients that will not respond to this therapeutic approach is a major translational goal in RA. Association of seropositivity to rheumatoid factor (RF) or anti-cyclic-citrullinated antibodies (anti-CCP) with anti-TNF response has proven inconclusive, suggesting that other yet unexplored biomarkers could be more informative for this goal.

Objectives: We tested the association of two recently introduced biomarkers in RA: anti-carbamylated protein antibodies (anti-CarP) and anti-peptidylarginine deiminase type 4 (anti-PAD4).

Methods: A prospective cohort of n=80 RA patients starting anti-TNF therapy was recruited and levels for all four autoantibodies -RF, anti-CCP, anti-CarP and anti-PAD4- were measured at baseline. The change in DAS28 score between baseline and week 12 of therapy was used as the clinical endpoint.

Results: Single marker-analysis showed no significant association with drug response. However, when testing for interactions between autoantibodies, we found highly significant associations with drug response. Anti-CCP and RF showed a positive interaction with the response to anti-TNF therapy (P=0.00068), and anti-PAD4 and antiCarP titers showed a negative interaction with the clinical response at week 12 (P=0.0062). Using an independent retrospective sample