years of follow-up. Pairwise post-hoc comparisons were performed by Bonferroni correction. Area Under the Receiver Operating Characteristics (AUROC) of cellular changes in FBC components to predict LOR at different time points were calculated. Latent class mixed models were used to investigate trajectories of change in cellular components of the FBC from baseline to one year. Further survival analysis to predict LOR of TNFi was done by using the latent class model and adjusted by clinical parameters, demographics and concomitant treatment.

Results: 92 and 43 biologic-naïve RA patients who attained remission were included from cohorts 1 and 2 respectively. 73 (54%) were treated with adalimumab and 62 (46%) with etanercept. 87 (64%) of patients lost remission over a 10-year period with median time to LOR of 3.3 years (95% CI 2.6-3.7).

Among the cellular components of FBC, monocyte count changes in the first year after initiation of TNFi fell significantly in those who maintained remission over the five years of follow-up, compared to those who lost remission [$p < 0.001$ for all years evaluated] (Figure 1). AUROC of monocyte count change at 6 months and 12 months, to predict LOR from year 1 to year 5 (after TNFi initiation) and after 5 years, ranged between 0.70-0.90. Three latent classes were identified based on monocyte count changes over time: 1-decrease ($N=41$), 2-increase ($N=7$) and 3- no change ($N=87$). Among these latent classes, patients in class 1, sustained remission for longer (unadjusted log-rank $p=0.001$) compared to the other 2 classes. Monocyte latent classes as a predictor of LOR was further tested by cox-regression, where variables (anti-citrullinated protein antibody/ACPA, concomitant methotrexate, baseline DAS28-ESR) were selected by elastic net regularisation and further adjusted by use of steroid, age and gender. Class 2 and Class 3 monocyte latent classes showed a hazard ratio (HR) of 3.15 (95% CI 1.02-9.74, $p = 0.046$, n. of event = 6/7) and 5.48 (95% CI 2.6-11.57, $p < 0.001$, n. of event = 73/87) respectively compared to Class 1. ACPA positivity also increased the risk of LOR with HR of 2.13 and 95% CI 1.04-4.37, $p = 0.04$ (n. of event = 78/117) compared to seronegative patients (n. of event = 9/18).

Conclusion: In seropositive RA patients treated with TNFi, a reduction of total monocyte count in the first year was associated with maintenance of remission in subsequent years. Further studies are required to determine whether these effects are specific to TNFi or reflect sustained remission in RA irrespective of therapy.

Figure 1 (A-F). Mean change (with 95% confidence interval) in absolute count of monocyte after initiation of tumour necrosis factor inhibitor grouped by years of follow-up and stratified by loss of remission. N = number indicate cumulative number of patients who lost remission by the end of each year.

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POS0441

DEVELOPMENT OF RHEUMATOID ARTHRITIS AMONG ANTI-CITRULLINATED PROTEIN ANTIBODIES POSITIVE ASYMPTOMATIC INDIVIDUALS: A PROSPECTIVE OBSERVATIONAL STUDY

S. Mizuki¹, K. Horie¹, K. Imabayashi¹, K. Mishima², K. Oryoji¹. ¹Matsuyama Red Cross Hospital, The Center for Rheumatic Diseases, Matsuyama, Japan; ²Matsuyama Red Cross Hospital, The Center for Rheumatic Diseases, Matsuyama, Japan

Background: In the individuals with genetic and environmental risk factors, immune events at mucosal surfaces occur and may precede systemic autoimmunity. Anti-citrullinated protein antibodies (ACPA) are present in the serum for an average of 3-5 years prior to the onset of rheumatoid arthritis (RA) during an asymptomatic period. In ACPA-positive individuals, the additional presence of RA-related risk factors appears to add significant power for the development of RA. To date, there have been few reports in which clinical courses of ACPA-positive asymptomatic individuals were investigated prospectively.

Objectives: To observe the clinical time course of ACPA-positive healthy population for the development of RA.

Methods: Healthy volunteers without joint pain or stiffness, who attended the comprehensive health screening of our hospital, were enrolled in this prospective observational study. The serum ACPA levels were quantified by Ig-G anti-cyclic citrullinated peptide enzyme-linked immunosorbent assay with levels > 4.4 U/mL considered positive. ACPA-positive subjects were followed by rheumatologists of our department clinically or a questionnaire sent by mail for screening to detect arthritis.

Results: 5,971 healthy individuals without joint symptoms were included. Ninety-two (1.5%) were positive for ACPA. Of these, 19 (20.7%) developed RA and two were suspected as RA by mail questionnaire. Their average age were 58-years, and women were 68%. The average duration between the date of serum sampling and diagnosis was 10.7 months. ACPA-positive individuals who developed to RA had higher serum ACPA and Ig-M rheumatoid factor levels than ACPA-positive individuals who did not (P value by Mann-Whitney U test: 0.002, 0.005, respectively).

Conclusion: Among ACPA-positive asymptomatic individuals, 20% developed RA. The higher titer of ACPA and Ig-M rheumatoid factor levels are risk factors for developing RA.

Disclosure of Interests: None declared

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POS0442

RELATIONSHIP BETWEEN PARAOXONASE-1 GENOTYPE, ACTIVITY AND MAJOR ADVERSE CARDIOVASCULAR EVENTS IN PATIENTS WITH RHEUMATOID ARTHRITIS RECEIVING TOFACITINIB

C. Charles-Schoeman¹, C. Hyde², S. Guan³, N. Parikh¹, J. Wang¹, A. Shahbazian¹, L. Stockert⁴, J. Andrews⁴. ¹University of California, Department of Medicine, Los Angeles, CA, United States of America; ²Pfizer Inc, Inflammation and Immunology, Groton, CT, United States of America; ³Pfizer Inc, Inflammation and Immunology, Cambridge, MA, United States of America; ⁴Pfizer Inc, Inflammation and Immunology, Collegeville, PA, United States of America

Background: Paraoxonase-1 (PON1) is a high-density lipoprotein (HDL)-associated enzyme with paraoxonase, lactonase and arylesterase activities.¹ PON1 contributes to the antioxidant properties of HDL, and is being investigated for its atheroprotective properties.¹ Patients (pts) with rheumatoid arthritis (RA) who are homozygous for the RR genotype of the Q192R gene polymorphism on PON1 (rs662) have increased paraoxonase activity, and lower risk of carotid plaques, vs those with QQ or QR genotypes.² Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA.

Objectives: To investigate the relationship between PON1 genotype/activity and risk of major adverse cardiovascular events (MACE) in the tofacitinib RA clinical programme.

Methods: In this post hoc analysis, data were pooled from pts enrolled in nine Phase 2/3 studies of tofacitinib in RA. Enzyme activities in pt plasma samples were measured at individual study baseline (BL) and at follow-up visits using three substrates: paraoxon (paraoxonase activity), dihydrocoumarin (lactonase activity) and phenylacetate (arylesterase activity). The effect of the PON1 Q192R genotype (QQ, QR or RR) on BL paraoxonase/lactonase/arylesterase activity was assessed using linear regression for each study, with age and sex as covariates, and then fixed-effect meta-analysis assessed effects across studies. The risk of MACE by enzyme activity was determined using Cox proportional hazards regression stratified by clinical studies. Univariate regression against BL enzyme activity and other risk factors, as well as both minimally and fully adjusted multivariable regressions against time-varying enzyme activity, are presented.

Results: The analysis included 1969 pts with RA who received ≥ 1 dose of tofacitinib and had PON1 activity measures available at BL; 39 pts had ≥ 1

MACE event. Compared with the QQ genotype, the RR genotype had a highly significant positive association with BL paraoxonase activity, and a highly significant negative association with BL lactonase and arylesterase activity (Table 1). A univariate analysis identified several BL covariates significantly associated with risk of MACE (Figure 1a). Time-varying models found a highly significant association of increased paraoxonase activity over time with lower risk of future MACE, even after controlling for low-density lipoprotein or HDL cholesterol levels, and other traditional cardiovascular (CV) risk factors identified in univariate analysis (Figure 1b), with similar findings for lactonase and arylesterase (data not shown).

Table 1. Effect of PON1 genotype (RR vs QQ) on BL enzyme activity

	n	Estimate	95% CI	p value	Cochran's Q test
Paraoxonase	1229	1.035	0.93, 1.141	<0.0001	0.209
Lactonase	1188	-0.375	-0.505, -0.246	<0.0001	0.025
Arylesterase	1231	-1.016	-1.382, -0.649	<0.0001	0.251

Fixed-effects model; estimate >0 favours RR genotype and <0 favours QQ genotype. BL, baseline; CI, confidence interval

Figure. Associations between a) BL covariates and occurrence of MACE (univariate analysis) and b) BL and time-varying covariates and occurrence of MACE (univariate and multivariate adjusted analyses)

HR, hazard ratio; 95% CI, 95% confidence interval; EUR, European; FDR, false discovery rate; nRII2, hazard ratio; LDL, low-density lipoprotein; nRII2, standard deviation; QR, quartile; Y, yes; N, no.

Conclusion: Higher activity of the HDL-associated protein PON1 over time was associated with a significantly reduced risk of future MACE in pts with RA receiving tofacitinib, after controlling for traditional CV risk factors and cholesterol levels. Further investigation of PON1 as a novel functional lipid biomarker to assess CV risk in pts with RA is warranted.

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POS0443

EXPLORING NOVEL TENOSYNOVITIS AND COMBINED INFLAMMATION IMAGING OUTCOMES: RESULTS FROM A RANDOMISED CONTROLLED TRIAL IN EARLY RHEUMATOID ARTHRITIS

P.G. Conaghan^{1,2}, M. Østergaard^{3,4}, O. Troum⁵, Z. Xie⁶, A. Brett⁷, M. Snyder⁸, A. Ebrahim⁹, D. Chapman⁹, G. Sawyerr⁹, J. Andrews⁹. ¹University of Leeds, Leeds Institute of Rheumatic and Musculoskeletal Medicine, Leeds, United Kingdom; ²National Institute for Health Research Leeds Biomedical Research Centre, Leeds, United Kingdom; ³Rigshospitalet, Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Glostrup, Denmark; ⁴University of Copenhagen, Department of Clinical Medicine, Copenhagen, Denmark; ⁵University of Southern California Keck School of Medicine, Division of Rheumatology, Santa Monica, CA, United States of America; ⁶Pfizer Inc, Inflammation and Immunology, Groton, CT, United States of America; ⁷Imorphics Ltd, Clinical Trials Group, Manchester, United Kingdom; ⁸Pfizer Inc, Inflammation and Immunology, Collegeville, PA, United States of America; ⁹Pfizer Inc, Inflammation and Immunology, New York, NY, United States of America

Background: Magnetic resonance imaging (MRI) trial outcomes have largely focused on synovitis, bone marrow oedema (BME) and erosions. Tenosynovitis is a common manifestation of rheumatoid arthritis (RA), but is relatively understudied; a combined inflammation score (CIS) summing synovitis, BME and tenosynovitis may be a highly responsive measure. We previously showed the responsiveness of the Outcome Measures in Rheumatology (OMERACT) RA MRI scoring system (RAMRIS) and a machine-learning derived automated tool (RAMRIQ) in a randomised controlled trial (RCT) of tofacitinib and methotrexate (MTX) in MTX-naïve patients (pts) with early RA.¹

Objectives: This post hoc analysis assessed the impact of tofacitinib ± MTX on MRI tenosynovitis and CIS in pts with early RA using semiquantitative and quantitative MRI outcomes.

Methods: Study A3921068 (NCT01164579), a 1-year, exploratory, Phase 2, RCT, compared tofacitinib 10mg twice daily (BID) ± MTX, and MTX monotherapy, in MTX-naïve pts with early RA.¹ MRI of unilateral wrist and metacarpophalangeal joints was performed at screening/baseline (BL) and Months (M)1/3/6/12. MRI tenosynovitis and CIS were assessed using RAMRIS and RAMRIQ. Changes from BL (Δ) in RAMRIS and RAMRIQ tenosynovitis and CIS were evaluated at M1/3/6/12. Data were assessed using a mixed-effect model for repeated measures, with treatment arms as factors and BL values as covariates. Using data pooled across treatment arms, Spearman's rank correlation coefficients were calculated for associations between BL RAMRIS and BL RAMRIQ tenosynovitis and CIS vs BL Disease Activity Score in 28 joints, C-reactive protein (DAS28-4[CRP]), and ΔRAMRIS and ΔRAMRIQ tenosynovitis and CIS at M12 vs ΔDAS28-4[CRP] at M12.

Results: In total, 109 pts were randomised and treated. ΔRAMRIS and ΔRAMRIQ tenosynovitis and CIS were generally significantly greater at M3/6/12 in pts receiving tofacitinib ± MTX vs MTX, while ΔRAMRIQ CIS was also significantly greater at M1 (Figure 1). Compared with RAMRIS, RAMRIQ outcomes were generally more responsive to treatment with tofacitinib ± MTX. Significant correlations were seen between BL RAMRIS and BL RAMRIQ tenosynovitis and BL DAS28-4[CRP], and between ΔRAMRIS and ΔRAMRIQ tenosynovitis and CIS at M12 vs ΔDAS28-4[CRP] at M12 (Table 1). In general, stronger correlations were seen between BL DAS28-4[CRP] and BL RAMRIS vs BL RAMRIQ parameters, while correlations were similar between ΔDAS28-4[CRP] at M12 and ΔRAMRIS and ΔRAMRIQ parameters at M12.

Figure. a) RAMRIS tenosynovitis, b) RAMRIQ tenosynovitis, c) RAMRIS CIS and d) RAMRIQ CIS at Months 1, 3, 6 and 12 (A3)

BL, baseline; CIS, combined inflammation score; MTX, methotrexate; nRII2, hazard ratio; nRII2, standard deviation; QR, quartile; Y, yes; N, no.