of antibodies against individual citrullinated peptides (ACPA; Hansson M et al. Arthritis Res Ther 2012;14:R201). We have also developed a method for the quantification of autoantibodies in immune complexes (IC; Sohrabian et al. Ann Rheum Dis 2015;74(Suppl 1):A74). Here we have combined these techniques to determine ACPA profiles in RA IC.

Objectives: To investigate if measurement of specific ACPA in synovial fluids (SF) and in IC from sera and SF can provide more prognostic information than conventional measurement of total ACPA and rheumatoid factor (RF) in serum.

Methods: Seventy-seven RA patients with knee synovitis were treated with intra-articular triamcinolone hexacetonide, and followed until relapse. DAS28 and radiographic joint damage according to Larson-Dale were recorded. Anti-CCP2, IgM and IgA RF and circulating C1q-binding immune complexes (CIC) were determined in paired sera and SF. IC were purified from sera and SF by binding to C1q-coated beads, and thereafter eluted with a procedure developed in our laboratory. Antibodies against 19 citrullinated peptides were investigated with a custom-made microarray assay based on the ImmunoCAP ISAC system (Phadia AB, Sweden) in sera and SF as well as in IC from sera and SF. The target peptides were filaggrin 307–324 (CCP1), vimentin peptides 60–75 and 2–17, fibrinogen peptides α36–50„ α563–583, α580–600, α621–635, β36–52, β60–74, β62–81 (with citrullination in positions 72 and 74, respectively), α-enolase 5–21 (CEP-1), peptides 1, 5, Z1, Z2 and Bla26 from hnRNP, and histone 4 peptides 14–34 and 31–50. Cutoffs were established in relation to healthy controls. Backward stepwise regression was used to investigate what factors determined Larsen Dale index, DAS28, and duration of remission after steroid treatment. Independent factors were anti-CCP2, IgM RF, IgA RF, CIC, number of ACPA peptide reactivities, and number of ACPA reactivities in IC, all measured both in serum and paired SF.

Results: A considerable proportion of anti-CCP2 negative patients had multiple ACPA in SF, and in IC fractions. High DAS28 associated with reactivity against 7/19 peptides in serum and 9/19 in SF. High Larsen score associated with number of specific ACPA in SF IC and with CIC in SF. DAS28 levels associated with IgM RF in SF and with CIC in SF, and steroid response duration with number of specific ACPA in serum and in SF IC.

Conclusions: We found ACPA in SF, and especially in the IC fraction of SF, in a sizeable fraction of anti-CCP2 negative patients. Number of peptide-specific ACPA (but not anti-CCP2 levels) associated with radiological destruction and length of remission after intra-articular steroid therapy. Our data do not support a role for any unique ACPA specificity in RA pathogenesis. Instead, the number of individual ACPA specificities may be important.

Disclosure of Interest: None declared

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FRI0086 EFFICACY AND SAFETY DATA BASED ON HISTORICAL OR PRE-EXISTING CONDITIONS AT BASELINE FOR PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS WHO WERE TREATED WITH BARICITINIB

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Background: Patients (pts) with rheumatoid arthritis (RA) often experience comorbidities that may affect efficacy and safety when treated with different drugs.[1] Baricitinib (BARI) is a selective inhibitor of Janus kinase[2,3] 1 and 2 that improves disease activity in pts with RA with an acceptable safety profile.[4–6]

Objectives: To investigate the effect of selected comorbidities on safety and efficacy outcomes in pts treated with BARI.

Methods: Pts were selected for this post hoc analysis on the basis of historical or ongoing conditions defined by Medical Dictionary for Regulatory Activities and divided by the following comorbidity subgroups: depression, osteoporosis, hepatic disorders, and previous cardiovascular events. Efficacy outcomes included 20% and 50% improvement in American College of Rheumatology 20 Response (ACR20) and American College of Rheumatology 50 Response (ACR50) criteria, respectively; the proportion of pts who achieved a Disease Activity Score for 28-joint count using high-sensitivity C-reactive protein (DAS28-hsCRP) score ≤3.2; and change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) at week 12. Pts who had an inadequate response (IR) to conventional disease-modifying antirheumatic drugs (cDMARDS) from 5 studies with BARI 4 mg and placebo (PBO) were included in efficacy analyses (N=1684) and safety analyses (N=1683). The interaction of comorbidity by treatment was analysed using logistic regression or analysis of variance modelling. Interaction tests were performed within each comorbidity subgroup, and the effect size in pts with and without the comorbidity was analysed.

Results: Pts in the efficacy set had similar baseline demographic and disease-activity characteristics across treatments within each comorbidity subgroup. The presence of a comorbid condition did not affect the incidence of treatment-emergent adverse events (TEAEs), serious adverse events (AE), discontinuations, or deaths caused by AEs for BARI 4 mg vs PBO (Table 1). The most common TEAEs across the subgroups for BARI and PBO were nasopharyngitis and upper respiratory tract infection. For cDMARD-IR pts, change from baseline for each comorbidity subgroup for ACR20, ACR50, DAS28-hsCRP ≤3.2 response, and HAQ-DI was higher for BARI 4 mg compared with PBO. Within each comorbidity subgroup, BARI responses compared with PBO were similar (interaction $P > 0.1$) (Table 2).

Table 1: Adverse Events Reported by Selected Comorbidity up to Week 16

Baricitinib 4 mg n (%)	Depression (N=64)	Osteoporosis (N=113)	CV Event (N=350)	Hepatic Event (N=222)	Overall (N=802)
Any TEAE	45 (70.3)	70 (61.9)	227 (64.9)	152 (68.5)	495 (61.7)
Serious AE	0	9 (8.0)	14 (4.0)	8 (3.6)	25 (3.1)
Discon due to AEs	1 (1.6)	7 (6.2)	14 (4.0)	9 (4.1)	25 (3.1)
Deaths	0	0	0	0	0
Placebo	**(N=69)**	**(N=134)**	**(N=381)**	**N=202**	**(N=881)**
Any TEAE	57 (82.6)	91 (67.9)	228 (59.8)	119 (58.9)	494 (56.1)
Serious AE	6 (8.7)	9 (6.7)	16 (4.2)	5 (2.5)	31 (3.5)
Discon due to AEs	3 (4.3)	9 (6.7)	12 (3.1)	6 (3.0)	24 (2.7)
Deaths	1 (1.4)	1 (0.7)	1 (0.3)	0	1 (0.1)

Abbreviations: AE=adverse event; CV=cardiovascular; Discon=discontinuations; TEAE=treatment-emergent adverse event.

Table 2: Efficacy Outcomes Reported by Selected Subgroup at Week 12

Baricitinib 4 mg	Depression (N=64)	Osteoporosis (N=113)	CV Event (N=350)	Hepatic Event (N=222)	Overall (N=803)
ACR20, NRI, n (%)	38 (59.4)	74 (65.5)	239 (68.3)	149 (67.1)	542 (67.5)
ACR50, NRI, n (%)	22 (34.4)	46 (40.7)	143 (40.9)	90 (40.5)	330 (41.4)
DAS-hsCRP≤3.2, mLOCF, n (%)	20 (31.3)	53 (46.9)	157 (44.9)	95 (42.8)	352 (43.8)
ΔHAQ-DI,mLOCF* N-Obs, LSM (SE)	63,-0.46 (0.14)	111,-0.36 (0.07)	347, -0.54 (0.04)	219 -0.58 (0.08)	792, -0.53 (0.03)
Placebo	(N=69)	(N=134)	(N=381)	(N=202)	(N=881)
ACR20, NRI, n (%)	22 (31.9)	43 (32.1)	155 (40.7)	75 (37.1)	345 (39.2)
ACR50, NRI, n (%)	6 (8.7)	16 (11.9)	55 (14.4)	23 (11.4)	127 (14.4)
DAS28-hsCRP ≤3.2, mLOCF, n (%)	9 (13.0)	17 (12.7)	60 (15.7)	26 (12.9)	146 (18.2)
ΔHAQ-DI, mLOCF* N-Obs, LSM (SE)	68, -0.20 (0.13)	131, -0.08 (0.07)	374 -0.27 (0.04)	201, -0.28 (0.08)	868, -0.25 (0.03)

Abbreviations: ACR20 = 20% improvement in American College of Rheumatology 20 Response criteria; ACR50 = 50% improvement in American College of Rheumatology 50 Response criteria; CV = cardiovascular; DAS28-hsCRP = Disease Activity Score for 28-joint count using high-sensitivity C-reactive protein; HAQ-DI = Health Assessment Questionnaire-Disability Index (patient-reported questionnaire with 24 questions in 8 domains: dressing/grooming, arising, eating, walking, hygiene, reach, grip, and activities); LSM = least squares mean; mLOCF = modified last observation carried forward; N-obs = number of patients in the analysis; NRI = nonresponder imputation; SE = standard error
*LSM and SE were calculated using analysis of variance model.

Conclusions: Treatment with BARI 4 mg showed similar effect in selected comorbidity subgroups with depression, osteoporosis, cardiovascular events, and hepatic impairment for efficacy and safety. No trends were noted for pts in each comorbidity subgroup for increased risk of events after treatment with BARI 4 mg compared with PBO.

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FRI0087 LOW RATES OF RADIOGRAPHIC PROGRESSION OF STRUCTURAL JOINT DAMAGE OVER 2 YEARS OF BARICITINIB TREATMENT IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: In ph3 studies, baricitinib (bari) inhibited progression of radiographic joint damage for up to 1 year in patients (pts) with active rheumatoid arthritis (RA) who were DMARD-naïve or who had an inadequate response to conventional synthetic DMARDs (csDMARD-IR).

Objectives: To evaluate radiographic progression of structural joint damage in pts with RA over 2 years of treatment.

Methods: Upon completion of a bari ph 3 study, pts could enter a long-term extension (LTE) study, in which they continued to receive the same bari dose as in the original ph3 study. At 52 wks, DMARD-naïve pts receiving methotrexate (MTX) or combination therapy (bari 4mg + MTX) were switched to bari 4mg monotherapy; MTX-IR pts receiving adalimumab (ADA) were switched to bari

4mg on background MTX. At 24 wks, csDMARD-IR pts receiving placebo (PBO) were switched to 4mg on background csDMARD. Radiographs at baseline, year 1 and year 2 were scored using the van der Heijde modified total sharp score (mTSS). Data are least squares mean change from baseline using mixed model repeated measures on observed data.

Results: Of all pts randomised, 82.5% entered the LTE, and 87.6% of those could be entered in this analysis. At year 2, progression was significantly lower with initial bari (including monotherapy) vs. initial MTX in DMARD-naïve pts. In MTX/csDMARD-IR pts, progression with initial bari was significantly lower than initial PBO, and similar to initial ADA.

	1 year (52 weeks)			2 years (100 weeks)		
DMARD-naïve	MTX N=136	Bari 4 mg mono N=120	Bari 4 mg + MTX N=150	MTX → Bari 4 mg mono† N=136	Bari 4 mg mono N=117	Bari 4 mg + MTX → Bari 4 mg mono† N=150
Change in (Δ) mTSS	1.62	1.14	0.37***	1.97	1.35	0.61***
Δ mTSS ≤0.5, n (%)	85 (63)	89 (74)*	126 (84)***	77 (57)	83 (71)*	120 (80)***
	1 year (52 weeks)			2 years (100 weeks)		
MTX-IR	PBO → Bari 4 mg¶ N=358	Bari 4 mg N=380	ADA‡ N=260	PBO → Bari 4 mg¶ N=357	Bari 4 mg N=376	ADA → Bari 4 mg‡ N=260
Δ mTSS	1.64	0.81***	0.81**	2.20	1.13***	1.14**
Δ mTSS ≤0.5, n (%)	228 (64)	287 (76)***	196 (75)**	212 (59)	269 (72)***	190 (73)***
	1 year (48 weeks)			2 years (96 weeks)		
csDMARD-IR	PBO → Bari 4 mg§ N=143	Bari 2 mg N=157	Bari 4 mg N=144	PBO → Bari 4 mg§ N=153	Bari 2 mg N=163	Bari 4 mg N=149
Δ mTSS	1.09	0.70	0.44*	1.42	0.98	0.68*
Δ mTSS ≤0.5, n (%)	104 (73)	125 (80)	120 (83)*	105 (69)	119 (73)	122 (82)**

Missing scores at 2 years were imputed using linear extrapolation based on data collected between 1 and 2 years; Time point=time from randomisation in originator study; N=number of pts with non-missing baseline and non-missing postbaseline mTSS data.
†Pts switched to bari 4mg at entry to LTE (at Week 52).
¶Pts switched to bari 4mg at rescue or at Week 24.
‡Pts switched to bari 4mg at rescue or at entry to LTE (at Week 52).
§Pts switched to bari 4mg at rescue or at entry to LTE (at Week 24). Comparisons analysed using MMRM.
*p≤0.05, **p≤0.01, ***p≤0.001 vs. PBO or MTX.

Conclusions: Treatment with once-daily oral bari resulted in low rates of radiographic progression for up to 2 years. Pts starting with bari showed progression that was significantly less than those starting with PBO or MTX, and comparable to those starting with ADA. The most robust benefit was seen with the 4mg dose.

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FRI0088 SYNOVIAL PATHOBIOLOGY CORRELATES WITH DIAGNOSTIC SUBGROUPS IN EARLY INFLAMMATORY ARTHRITIS: RESULTS FROM THE PATHOBIOLOGY OF EARLY ARTHRITIS COHORT (PEAC)

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Background: Application of the 2010 ACR/EULAR Criteria for RA to early inflammatory arthritis cohorts permits an enhanced sensitivity for diagnosis compared to the historic 1987 ACR criteria but risks loss of diagnostic specificity. Heterogeneity in RA synovial pathobiology is well recognised with differences in qualitative and quantitative degree of immune cell infiltration, whether such heterogeneity correlates with classification criteria in early inflammatory arthritis is unknown, offering the potential to refine early diagnostic criteria.

Objectives: The aim of this study was to examine in a cohort of therapy naïve, early inflammatory arthritis patients whether synovial immune cell infiltration differed significantly between diagnostic categories of early inflammatory arthritis (ACR/EULAR 2010 vs ACR 1987 vs undifferentiated).

Methods: A total of 200 consecutive DMARD naïve early arthritis patients (disease duration <1 year) recruited as part of the multicentre PEAC study at Barts Health NHS Trust were categorised according to the following criteria: i. RA 1987 ACR, ii. RA 2010 ACR/EULAR, and iii. Undifferentiated Arthritis (UA). All patients underwent a baseline synovial biopsy of a clinically active joint along with collection of demographic data. Following H&E staining, degree of synovitis was assessed. Sections underwent immumohistochemical 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 three 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: 166/200 samples were suitable for analysis. 115 patients were classified as RA1987, 16 patients as RA 2010 ACR/EULAR and 35 as UA. 80% of synovial samples were collected from small joints (wrist, MCP, PIP). Although there were no significant differences in disease duration between diagnostic subgroups, patients classified as RA1987 criteria had significantly higher levels of CRP, tender and swollen joints, DAS28 and sero positivity for ACPA and RF. When patients were stratified into pathotypes, a numerically higher proportion of patients within the RA1987 group were categorised as lymphoid. Further, patients within the RA 1987 group had a significantly higher synovitis score and degree of immune cell infiltration.

N=166	RA1987 (115)	RA2010 (16)	UA (35)	P value
Fibroid 47 (%)	27 (23.5%)	6 (37.5%)	14 (40%)	
Myeloid 57 (%)	38 (33%)	5 (31.2%)	14 (40%)	0.10
Lymphoid 62 (%)	50 (43.5%)	5 (31.2%)	7 (20%)	
CD3 T cells	3.19	1.21	0.60	<0.001
CD20 B cells	2.88	0.80	0.75	<0.05
CD68L macrophages	3.60	1.86	1.34	<0.001
CD68SL macrophages	3.60	2.18	1.79	<0.05
CD138 Plasma Cells	2.85	1.06	0.73	<0.05
Synovitis Score	6.17	3.26	3.24	<0.001

Conclusions: Stratifying patients according to baseline clinical diagnosis translates into differences in synovial pathobiology. The capacity to refine early clinical classification criteria through application of synovial pathobiological markers offers the potential to predict disease outcome and stratify therapeutic intervention.

Disclosure of Interest: None declared

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FRI0089 EFFECT OF STARTING DOSE OF BARICITINIB IN ACHIEVING SUSTAINED LOW DISEASE ACTIVITY

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Background: In Phase 3 studies, baricitinib (bari) treatment with 2 different doses (2 mg and 4 mg once daily) demonstrated significant improvements across multiple measures of disease activity in patients (pts) with active RA and an inadequate response (IR) to conventional synthetic (cs) DMARDs (RA-BUILD[1]) or biologic (b) DMARDs (RA-BEACON[2]).

Objectives: To determine the effect of starting dose of bari on achieving and sustaining low disease activity (LDA).

Methods: RA-BUILD and RA-BEACON trials were 24 week (wk), placebo (PBO) controlled studies. Pts completing the studies on bari treatment could enter a long-term extension (LTE) study, RA-BEYOND, continuing blinded treatment with the same dose, while pts on PBO switched to bari 4 mg. This post hoc analysis assessed disease activity in pts who achieved CDAI ≤10 at ≥1 visit (LDA) or at ≥2 consecutive visits (sustained LDA) within the originating study (24 wks) and continued into the LTE. The length of time required by pts to achieve LDA was determined by the incidence rate (percent pts responding per month) for each group.

Results: Treatment with bari 2 mg and 4 mg, when compared to PBO, resulted in higher rates of LDA and sustained LDA, as well as higher incidence rates (shorter time to achieve LDA/sustained LDA) within 24 wks of each originating study. Across studies, treatment with bari 4 mg demonstrated higher incidence rates when compared to bari 2 mg, both in achieving LDA and sustained LDA, indicating that these pts reached the desired LDA state faster. Incidence rates were lower in all treatment groups in bDMARD-IR pts compared with csDMARD-IR pts.

Conclusions: The most robust benefit in terms of achieving LDA and sustained LDA was observed with bari 4 mg treatment, which required shorter time to response, than treatment with 2 mg. This was observed in both the short (24 wks) and in the long-term in pts with IR to csDMARDs or bDMARDs.

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