FRI0122 PREDICTING FACTORS FOR DISAPPEARANCE OF ANTI-MUTATED CITRULLINATED VIMENTIN ANTIBODIES IN SERA FROM PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Mutated citrullinated vimentin (MCV) is one of the important targets of anti-citrullinated protein/peptide antibodies (ACPA) and is found in synovial fluid in patients with rheumatoid arthritis (RA). Serum anti-MCV antibody (anti-MCV) titer may be better correlated with RA disease activity and radiographic progression than anti-cyclic citrullinated peptide antibody (anti-CCP) titer.

Objectives: In the present study, we tried to determine the predicting factor of anti-MCV disappearance in sera from RA patients.

Methods: Both anti-MCV (ORGENTEC Diagnostika, Germany) and anti-CCP (MESACUP™-2 test CCP, MBL, Japan) in sera from 280 RA patients who met 2010 ACR/EULAR classification criteria in Kyoto University RA Management Alliance (KURAMA) cohort 2013 and 2014 were measured by ELISA. Then, we determined retrospectively the predicting factors of anti-MCV disappearance using multivariate logistic analysis.

Results: In 2013 cohort, anti-MCV and anti-CCP positivities were 64.6 and 84.6%, respectively. The majority (97.8%) of anti-MCV-positive patients was also anti-CCP-positive and there was significant correlation between anti-MCV and anti-CCP titers ($r=0.63$, $p<0.001$). In 2013 baseline, there was no difference in patients' age, gender and disease duration between anti-MCV-positive ($n=181$, 64.6%) and -negative ($n=99$, 35.4%) groups. DAS28, however, was higher in anti-MCV-positive group than in -negative group (3.08 ± 1.22 vs. 2.68 ± 1.07 , $p=0.011$), while anti-CCP-positive ($n=237$, 84.6%) and -negative ($n=43$, 15.4%) groups had no significant difference of DAS28. Of note, whereas anti-CCP positivity rate did not change during 2013 and 2014, anti-MCV changed to positive and to negative were recognized in 20 ($=7.2\%$) and 41 ($=14.6\%$, disappeared group) patients. So we next compared anti-MCV disappeared and sustained-positive groups ($n=140$, 50.0%). There was no difference in patients' age, gender, disease duration and DAS28 in 2013. While decrease of DAS28 from 2013 to 2014 ($=\Delta$ DAS28) in disappeared group was more apparent than that in sustained-positive group (-0.58 ± 1.1 vs. $+0.02\pm0.34$, $p=0.028$). Methotrexate monotherapy was rarer in disappeared group than in sustained-positive group (26.5% vs. 53.8%, $p=0.015$), while continuous use of biological disease modifying antirheumatic drug (bDMARD) was more frequent in disappeared than sustained-positive group (64.7% vs. 25.2%, $p<0.0001$). Also serum levels of KL-6, a serum marker of interstitial lung disease, were lower in disappeared than in sustained-positive group (255 ± 146 vs. 315 ± 183 , $p=0.006$). To clear the most effective factor in anti-MCV disappearance, we choose variables including anti-MCV titers in baseline, KL-6 levels, Δ DAS28 and bDMARD use, and performed multivariable analysis. Analysis showed that anti-MCV titers and bDMARD use, especially TNF inhibitor (Odds Ratio $=7.2$, $p<0.001$) were observed as the predicting factors of anti-MCV disappearance. On the other hand, no predicting factor for newly anti-MCV appearance was recognized in our cohort.

Conclusions: Anti-MCV, but not anti-CCP, can be disappeared in a year by continuous bDMARD use regardless of disease activity.

Disclosure of Interest: None declared

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FRI0123 DOES THE BODY MASS INDEX HAVE ANY INFLUENCE IN THE CHARACTERISTICS OF EARLY ARTHRITIS PATIENTS?

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Background: Obesity has been proposed as a risk factor to develop rheumatoid arthritis (RA) and it has been associated with a worse response to several disease modifying anti-rheumatic drugs (DMARDs).

Objectives: To study the differences in baseline characteristics according to the body mass index (BMI) of patients in the PEARL (Princesa Early Arthritis Register Longitudinal) study.

Methods: A total of 432 patients (69.1% female) of the PEARL cohort were included for this study. The register protocol comprises the collection of sociodemographic, disease-related and treatment data in five visits (baseline, 6, 12, 24 and 60 months). The local ethics and clinical research committee approved the protocol and all patients sign an informed consent prior to their inclusion. For this study it was analyzed the baseline visit data from the 304 (70.37%) patients that met ACR 1987 criteria for RA after 2 years of follow-up, as well as those considered undifferentiated arthritis (UA) since other diagnoses were excluded. The WHO definition for low, normal weight, overweight and obesity (BMI <18.5 , 18.5 – 25 , 25 – 30 or ≥ 30 kg/m² respectively) was applied. ACPA (anticitrullinated peptide antibodies) were assessed by enzyme immunoassay (CCP2 Eurodiagnostica). HLA-DRB1 genotype was determined in 219 patients

using specific HLADRB1 typing kits (Dynal RELI SSO). The presence of shared epitope (SE) was determined based on this genotyping. The statistical analysis was performed by using Stata 12.1. Chi-Square and Kruskal-Wallis tests were used for the bivariate analysis. A multivariate logistic regression was performed to determine which factors may be related to ACPA positivity, including BMI, age, sex, smoking habit, number of SE alleles and study level as independent variables.

Results: Patients were 54.9 years old [44.2–67.5] (median [p25–p75]); disease duration was 5.3 months [3–8.4]. Table 1 shows the main variables significantly associated to BMI. In addition, we observed less ACPA positivity with increasing BMI (57% low weight vs. 43% in obese [$p=0.08$]), as well as a lower frequency of SE in patients with a higher BMI. The multivariate analysis confirmed that being smoker (ever or current) and carrying SE alleles is associated with the presence of ACPA. Adjusted by these variables, overweight and obesity were associated with lower probability of suffering an ACPA positive disease (OR 0.49, $p=0.027$ and OR 0.39, $p=0.019$ respectively).

Table 1. Variables significantly different according to BMI

BMI	Age (years)	Sex (W/M)	Level of studies (N/P/Se/U; %)	HAQ	VAS pain	TJC28
Low weight	52.3 [22.2–64]	7/0	0/14.3/42.9/42.9	1.25 [0.9–2.2]	50 [26–75]	7 [2–19]
Normal weight	50 [38.6–64]	145/24	1.2/21.4/35.1/42.3	0.87 [0.4–1.4]	41 [20–61]	3 [0–7]
Overweight	57.9 [47–69.6]	120/45	8.5/35.4/32.9/23.2	0.87 [0.5–1.6]	49 [20–62]	3 [0–9]
Obesity	59 [50.7–69.8]	68/23	12/38.5/26.5/22.9	1.3 [0.7–1.9]	50 [36–65]	5 [2–12]
	$p\leq 0.001$	$p=0.01$	$p\leq 0.001$	$p=0.0018$	$p=0.031$	$p=0.047$

*HAQ: Health Assessment Questionnaire; VAS: visual analogic scale (mm); TJC28: tender joints count (28 joints); W: women; M: men; N: no studies; P: primary studies; Se: secondary studies; U: university studies.

Conclusions: In our early arthritis register, patients with a higher BMI have predominantly ACPA negative disease, a more intense perception of pain and higher disability. These findings should be validated in other populations.

Disclosure of Interest: None declared

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FRI0124 TEMPORARY INTERRUPTIONS OF STUDY DRUG DURING THE BARICITINIB PHASE 3 RHEUMATOID ARTHRITIS PROGRAM

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Background: Temporary interruption of RA therapy is common in clinical practice; therefore, rapid clearance and low immunogenicity may be useful DMARD attributes. Baricitinib (bari) is a non-biologic Janus kinase (JAK) 1/JAK2 selective inhibitor with a pharmacokinetic half-life in RA patients of approximately 13 hours. It has demonstrated improved clinical efficacy compared to MTX, adalimumab and placebo (pbo) with a satisfactory safety profile when administered once daily to RA patients in 4 completed Phase 3 studies.

Objectives: These analyses aimed to characterize temporary interruptions of study drug during these studies and explore the kinetics of RA symptoms during and following interruption.

Methods: During bari Phase 3 studies, investigators were required to document temporary interruptions of study drug, including timing, reason and duration, using electronic case report forms. In 2 studies, patients recorded RA symptoms (duration and severity of morning joint stiffness, worst tiredness and worst joint pain) daily for 12 weeks. Post hoc analyses investigated changes in these scores among patients randomized at least 7 days prior to interruption, having an interruption that lasted at least 3 days, and retreated.

Results: Across the 3 pbo-controlled studies, interruptions occurred in a larger proportion of patients with bari than pbo only in the biologic DMARD-inadequate responder (IR) study RA-BEACON. In the 2 active comparator-controlled studies, the lowest rates of interruption were in the bari monotherapy arm of the DMARD-naïve MTX-controlled RA-BEGIN study, and proportions were similar for bari and adalimumab in the MTX-IR study, RA-BEAM (Table 1). Adverse events (predominantly non-serious, mild or moderate infections, most commonly of the respiratory tract) were the most frequent reason for interruption. Few patients interrupted for the reason of abnormal laboratory results. Most interruptions lasted for 2 weeks or less; in RA-BEAM, interruptions appeared shorter in duration for bari than for adalimumab. Diary measures indicated modest symptom increases during interruption compared to the last pre-interruption value, with a return to pre-interruption values or better after resumption of study drug (Table 2).

Conclusions: Consistent with its pharmacologic properties, brief temporary interruptions of bari during Phase 3 studies were associated with minor increases in RA symptoms, which resolved following resumption of therapy. A small molecule with a short half-life may offer advantages over injectable biologic therapies with respect to drug interruption for clinical cause in RA patients.

Disclosure of Interest: P. Emery Consultant for: Pfizer, MSD, Abbvie, BMS, UCB, Roche, Novartis, Samsung, Sandoz, Eli Lilly and Company, Y. Tanaka Grant/research support from: Mitsubishi-Tanabe, Takeda, Daiichi-Sankyo, Chugai, Bristol-Myers, MSD, Astellas, Abbvie, Eisai, Speakers bureau: Abbvie, Chugai, Daiichi-Sankyo, Bristol-Myers, Mitsubishi-Tanabe, Astellas, Takeda, Pfizer, Teijin,

Table 1. Summary of temporary interruptions during completed bimec Phase 3 studies in RA**

	Study RA-BEAM (0-24/0-52, data up to rescue)			Study RA-BUILD (0-24, data up to rescue)		
	PBO (N=488)	BARI 4 mg (N=467)	ADA (N=330)	PBO (N=228)	BARI 2 mg (N=229)	BARI 4 mg (N=227)
Total number of dose interruptions, I	67	62/103	30 /46	32	24	40
Patients with ≥1 interruption, n (% of N)	54 (11.1)	50 (10.3)/75 (15.4)	28 (8.5)/40 (12.1)	29 (12.7)	21 (9.2)	34 (15.0)
Number of interruptions per interrupted patient, mean	1.2	1.2/1.4	1.1/1.2	1.1	1.1	1.2
Time from first dose to first interruption, mean, days	68.9	70.6/126.9	73.2/112.3	53.1	41.0	53.6
Duration of individual interruptions, mean (SD), days	11.7 (13.2)	11.4 (9.4)/15.1 (15.7)	19.4 (24.6)/23.1 (29.1)	11.6 (10.2)	12.3 (12.6)	10.7 (9.8)
Interruption duration categories, n (% of I)						
0-7 days	35 (52.2)	26 (41.9)/44 (42.7)	10 (33.3)/15 (32.6)	16 (50.0)	10 (41.7)	20 (50.0)
8-14 days	14 (20.9)	15 (24.2)/28 (25.2)	10 (33.3)/16 (34.8)	7 (21.9)	8 (33.3)	10 (25.0)
15-21 days	6 (9.0)	5 (8.1)/6 (5.8)	4 (13.3)/4 (8.7)	5 (15.6)	4 (16.7)	4 (10.0)
22-28 days	3 (4.5)	5 (8.1)/14 (13.6)	0/1 (2.2)	1 (3.1)	0 (0.0)	3 (7.5)
>28 days	5 (7.5)	4 (6.5)/13 (12.6)	5 (16.7)/10 (21.7)	3 (9.4)	2 (8.3)	3 (7.5)
Reason for interruptions, n (% of I)						
Adverse event	44 (9.0)	46 (9.4)/69 (14.0)	26 (7.9)/37 (11.2)	24 (10.5)	16 (7.6)	26 (11.5)
Abnormal lab result	10 (2.0)	3 (0.6)/6 (1.2)	0/0	4 (1.8)	5 (2.2)	6 (2.6)
Investigator decision	3 (0.6)	2 (0.4)/2 (0.4)	2 (0.6)/3 (0.9)	2 (0.9)	0	2 (0.9)

Abbreviations: ADA=adalimumab; BARI=bimec; n=number of interruptions in the specified category; N=number of patients in safety population; n=number of patients in the specified category; PBO=placebo.
*Interruptions are based on daily tablet study drug. **Temporary interruption is defined as a temporary withholding of study drug that is followed by resumption of study drug during the study.

Table 2. Summary of ePRO daily diary scores among patients retreated following study drug interruptions*

Mean (SD)	Placebo 25 (25)*				Bimec 54 (25)*			
	Study drug initiation†	Pre- interruption‡	Last during interruption‡	Post- interruption‡	Study drug initiation†	Pre- interruption‡	Last during interruption‡	Post- interruption‡
MJS Duration	106 (87)	118 (157)	128 (159)	116 (159)	160 (167)	137 (164)	135 (171)	121 (188)
MJS Severity	5.5 (2.1)	4.3 (2.0)	4.5 (2.0)	4.2 (1.9)	5.8 (2.0)	4.2 (2.2)	4.4 (2.2)	3.8 (2.1)
Worst Joint Pain	5.8 (1.7)	4.6 (2.0)	4.9 (2.0)	4.4 (1.9)	6.1 (2.0)	4.6 (2.2)	4.7 (2.1)	4.2 (2.1)
Worst Tiredness	5.5 (2.5)	4.7 (2.2)	4.7 (2.2)	4.1 (2.0)	5.5 (2.0)	4.7 (2.3)	4.9 (2.5)	4.2 (2.4)

Abbreviations: ePRO=electronic patient reported outcome; MJS=morning joint stiffness.
*Data presented are mean (SD). †Number of patients; ‡Number of patients without at least 3 diary entries during interruption. †For MJS severity, it is 26 (26). ‡Includes combined doses of bimec (2 mg and 4 mg). †Average of values obtained within the first 3 days following randomization. ‡Average of up to 3 most recent values obtained in the 7 days prior to interruption. †Average of 3 most recent values in the last 7 days of the interruption. ‡Average of last 3 available values obtained following interruption and prior to any subsequent interruption or Week 12 study visit.

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FRI0125 RHEUMATOID ARTHRITIS PATIENTS WITH ANTI-ACETYLATED PEPTIDE ANTIBODIES STARTING THEIR FIRST TUMOR-NECROSE-FACTOR-INHIBITOR TREATMENT SHOW GREATER RESPONSE

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Background: Anti-acetylated-peptide antibodies (AAPA) have recently been described in rheumatoid arthritis (RA) patients.[1] Patients that show multiple autoantibody positivity have a higher likelihood to flare when stopping biological treatment. The role of AAPA antibodies for response to Tumor-Necrose-Factor-inhibitor treatment (TNFi) has not been explored.

Objectives: To determine the prevalence and serological overlap of AAPA to rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) in a cohort of RA patients starting their TNFi-inhibitor, and to assess their relation of autoantibody status to response to therapy.

Methods: We measured AAPA by ELISA using 21 acetylated peptides derived from vimentin, as well as RF and ACPA. We evaluated the prevalence of autoantibodies, baseline characteristics of autoantibody positive and negative patients, and their association with a 50% response by the Simplified disease activity index (SDAI50), and with achieving of SDAI low disease activity or remission at 6 months after starting the first TNFi. Likelihood ratios were calculated from logistic regression analyses. To better determine differences in SDAI change over time General Estimated Equation analyses (GEE) was used.

Results: Among our 93 patients starting treatment on a TNFi (85% female, mean disease duration: 7.7±7 years mean SDAI20±13), 50% were positive for AAPA, 57% for ACPA and 61% for RF (for overlap of antibodies see figure). There were no significant differences in baseline characteristics found between AAPA positive and negative patients. 61% of patients reached LDA or REM and 33% achieved an SDAI50 response after 6 months of TNFi treatment. AAPA positive patients showed a likelihood ratio (LR+) of 5.3 (p=0.022) to achieve an SDAI50 response and 3.9 (p=0.048) to reach LDA/REM. In contrast, being RF or ACPA positive did not coincide with a higher likelihood of achieving SDAI50 (LR+ of 0.08; p=0.773 and 1.09; p=0.297, respectively) or LDA/REM (LR+ of 1.83; p=0.177 and 1.55; p=0.213). Relative changes upon treatment with TNFi in composite scores were neither different between RF+ vs. RF- patients, nor between ACPA+ vs ACPA-patients; however AAPA+ showed significantly higher relative changes in SDAI (p=0.021), CDAI (p=0.025) and DAS (p=0.022) compared to AAPA- patients. Of note, relative changes in CRP were similar between the groups.

GEE on up to 230 days of TNFi treatment or until change of treatment, showed no significant difference in SDAI courses comparing RF+ vs RF- or ACPA+ vs ACPA-

Figure 1. Overlap of RF, ACPA and AAPA positive patients.

patients; but for AAPA+ vs. AAPA- patients the difference in change in SDAI was significant (p=0.045) over time.

Conclusions: AAPA positivity, in contrast to RF and ACPA positivity, appears to have a tighter association with greater levels of response in patients who are initiating TNFi-treatment. Therefore, AAPA might add additional information to estimate the chances of RA patients for responding to TNF-inhibitors.

References:

[1] Juarez M, Bang H, Hammar F, et al. Identification of novel antiacetylated vimentin antibodies in patients with early inflammatory arthritis. Ann Rheum Dis 2016;75(6):1099–107.

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FRI0126 AIMING FOR REMISSION ACCORDING TO ANY OF THE RHEUMATOID ARTHRITIS DISEASE ACTIVITY INDICES IS MORE IMPORTANT FOR PHYSICAL FUNCTION THAN THE ACTUAL CHOICE OF INDEX: A LONGITUDINAL ANALYSIS IN A CLINICAL PRACTICE SETTING (METEOR COHORT)

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Background: The association between remission and disability in patients with rheumatoid arthritis (RA) has been established mainly in clinical trial cohorts and not in “real-life” patients. Moreover, only a limited number of remission definitions have been tested.

Objectives: To compare the association between different remission criteria and physical function in patients with RA followed in clinical practice.

Methods: Longitudinal data from the METEOR database were used. Fifteen definitions of remission were tested: ACR-EULAR boolean-based; Simplified Disease Activity Index (SDAI); Clinical Disease Activity Index (CDAI); Disease Activity Score (DAS) and 28-joint count DAS (DAS28), both with ESR/CRP, with 3/4 variables (3v/4v), and various cut-offs tested. Disability was measured by the Health Assessment Questionnaire (HAQ) and HAQ≤0.5 was defined as a good outcome. Associations were investigated using generalised estimating equations (GEE), using HAQ≤0.5 as dependent variable and the various remission criteria as independent variables. Potential confounding factors (age, body mass index, gender, rheumatoid factor positivity, erosions and biologic treatment) were also tested. Sensitivity analyses were performed using first visits only and using patients with no missing data for all definitions of remission.

Results: Data from 32,915 patients and 157,899 visits were available. The most stringent definition of remission (table 1) was the ACR-EULAR boolean definition (4.5%). The proportion of patients with HAQ≤0.5 among patients in remission

Table 1. Remission rates (%) and association with HAQ≤0.5

Remission definition	Remission rate	HAQ≤0.5 (%)		Adjusted OR (95%CI) for HAQ≤0.5 (GEE)
		Among patients in remission	Among patients in non-remission	
ACR-EULAR boolean	4.5	87.0	34.1	2.6 (2.3-2.9)
CDAI≤2.8	13.4	78.5	27.4	3.2 (2.9-3.5)
SDAI≤3.3	17.1	78.1	25.7	3.4 (3.0-3.7)
DAS-CRP<1.6	4v 38.6	59.1	19.3	3.2 (2.9-3.5)
	3v 39.1	56.4	20.7	2.8 (2.6-3.0)
DAS-ESR<1.6	4v 31.7	63.2	22.6	3.0 (2.7-3.2)
	3v 30.4	60.4	24.3	2.6 (2.4-2.8)
DAS28-CRP<2.6	4v 34.8	62.8	20.2	3.3 (3.0-3.6)
	3v 37.5	57.7	21.3	2.8 (2.6-3.0)
DAS28-ESR<2.6	4v 25.2	68.1	26.5	2.8 (2.6-3.1)
	3v 24.4	62.5	28.7	2.3 (2.2-2.5)
DAS28-CRP≤1.9*	4v 20.0	72.8	26.1	2.9 (2.7-3.2)
	3v 21.7	64.5	27.4	2.3 (2.2-2.5)
DAS28-ESR≤2.2*	4v 18.4	71.3	29.9	2.6 (2.4-2.8)
	3v 17.3	64.4	31.8	2.1 (1.9-2.2)

*Fleischmann 2015 (PMID: 25143522)