Figure 1: Time until First transition to Good and No EULAR Response (DAS28-ESR)

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SAT0071 RHEUMATOID ARTHRITIS (RA) REGISTRY IN AKITA PREFECTURE, WHERE AGING IS THE MOST ADVANCED IN JAPAN

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Background: The rate of aging (percentage of population aged 65 years and over) in Akita Prefecture is 33.8% (26.6% for the whole of Japan), the highest throughout Japan. The Akita Orthopaedic Group on Rheumatoid Arthritis (AORA) was established in 2010. Since then, patients have been enrolled every year to prepare the registry.

Objectives: To compare patient characteristics as well as clinical effectiveness between the treatments with and without use of methotrexate (MTX) and a biological (BIO) using the data of the AORA registry.

Methods: The subjects were 2,016 patients enrolled in the Akita registry in 2015. The subjects included 403 men and 1,613 women. According to the use of MTX and BIO, 2,016 patients were divided into the group treated with no use of MTX or BIO (group A), that treated with BIO, but no use of MTX (group B), that treated with MTX, but no use of BIO (group C), and that treated with MTX and BIO (group D).

Results: The subjects were grouped into group A (n=673), B (n=153), C (n=805), and D (n=385). MTX was used in 59.0% and BIO was used in 26.7% of all patients. The mean ages were 69.6 years (group A), 65.7 years (group B), 65.6 years (group C), and 62.6 years (group D). The aging rates were 67.9% (group A), 55.6% (group B), 56.8% (group C), and 48.3% (group D), which shows that aging was more advanced in group A.

The rates of patients with a complication of hypertension, diabetes, respiratory disease, cerebrovascular disease, heart disease or malignant tumour were 52.0% (group A), 54.2% (group B), 45.5% (group C), and 40.8% (group D). The incidence of complication was the lowest in group D.

The rates of patients who received one or more of conventional synthetic disease-modifying antirheumatic drugs (cs DMARDs) other than MTX were 79.0% (group A), 42.5% (group B), 39.9% (group C), and 19.2% (group D). Although bucillamine and salazosulfapyridine were frequently used in any group, concomitant use of tacrolimus was remarkable in group A and C, while that of iguratimod was remarkable in groups C and D. The rate of use of a prednisolone (PSL), was significantly higher in group B. The dose of PSL was significantly higher in group A. In regard to BIO, three drugs of etanercept, tocilizumab, and abatacept accounted for 90% in group B. In group D, etanercept and tocilizumab were also frequently used, followed by infliximab, adalimumab, golimumab and abatacept. In DAS28ESR, the rate of combined low disease activity and remission was significantly higher in group D. The mean values of C-reactive protein (CRP) (mg/dL) were 0.61 (group A), 0.52 (group B), 0.47 (group C), and 0.35 (group D), which shows that the mean value was significantly higher in group A than group D. The mean values of matrix metalloproteinase 3 (MMP3) (ng/dL) were 119.0 (group A), 130.6 (group B), 100.7 (group C), and 88.9 (group D), which shows that the mean value was significantly higher in group A and B than group C and D.

Conclusions: Using the AORA registry, we compared patient characteristics as well as clinical effectiveness between the treatments with and without use of MTX and BIO. Since in group A, neither MTX nor BIO could be used in most patients, one had to practically rely on PSL. The study suggests that remission needs to be achieved prior to increase in complication due to aging.

References:

- [1] Population census in Japan, 2015.

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SAT0072 DOSE REDUCTION OF BARICITINIB IN PATIENTS WITH RHEUMATOID ARTHRITIS ACHIEVING SUSTAINED DISEASE CONTROL: RESULTS OF A PROSPECTIVE STUDY

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Background: In patients (pts) with active rheumatoid arthritis (RA) and inadequate response (IR) to DMARDs, ph3 studies demonstrated efficacy of baricitinib (bari) (2mg and 4mg). Larger, more rapid treatment effects were observed for bari 4mg. **Objectives:** To investigate the effects of bari dose step-down in pts who achieved sustained disease control with bari 4mg.

Methods: Pts with RA who completed a bari ph3 study could enter a long-term extension (LTE) study. In the LTE, pts who received bari 4mg for ≥ 15 months and who achieved sustained low disease activity ([LDA]-CDAI score ≤ 10) or remission (CDAI ≤ 2.8) at 2 consecutive visits ≥ 3 months apart were re-randomised in a blinded manner to continue bari 4mg or step down to 2mg. Patients could rescue (to bari 4mg) if CDAI > 10 . Efficacy and safety were assessed through 48 weeks (wks) following re-randomisation.

Results: Among pts who achieved sustained disease control with bari 4mg, dose reduction to 2mg resulted in significant increases in disease activity at 12, 24, and 48 wks; however, the majority of pts in both groups maintained the state of LDA

Abstract SAT0072 – Table 1

Pts originating from RA-BEAM, RA-BUILD, RA-BEACON Combined†						
Week 12		Week 24		Week 48		
Continued bari 4 mg N=396	Stepped down to bari 2 mg N=394	Continued bari 4 mg N=353	Stepped down to bari 2 mg N=358	Continued bari 4 mg N=245	Stepped down to bari 2 mg N=245	
Efficacy measure						
NRI after rescue or for missing data						
CDAI LDA ≤ 10	359/396 (90.7)	326/393 (83.0)**	309/353 (87.5)	269/357 (75.4)***	198/245 (80.8)	167/245 (68.2)**
CDAI remission ≤ 2.8	158/396 (39.9)	143/393 (36.4)	149/353 (42.2)	127/357 (35.6)	99/245 (40.4)	82/245 (33.5)
NRI only for missing data (observed data used after rescue)						
CDAI LDA ≤ 10	359/396 (90.7)	326/393 (83.0)**	314/353 (89.0)	289/357 (81.0)**	212/245 (86.5)	196/245 (80.0)
CDAI remission ≤ 2.8	158/396 (39.9)	143/393 (36.4)	150/353 (42.5)	133/357 (37.3)	103/245 (42.0)	90/245 (36.7)
Safety measure						
Wks 0-48						
n [EAIR/100 PYE]	Continued bari 4mg N=396		Stepped down to bari 2mg N=394			
SDEAE	225 [70.5]		196 [65.4]			
Infection	99 [31.0]		70 [23.3]			
SAE	23 [7.2]		23 [7.7]			
Serious infection	8 [2.5]		4 [1.3]			
AE $\rightarrow$ discontinuation	9 [2.8]		11 [3.6]			

Efficacy and safety data are n/N (%), and n [EAIR/100 PYE], respectively. †RA-BEAM = MTX-IR pts; RA-BUILD = csDMARD-IR pts; RA-BEACON = bDMARD-IR pts; EAIR = exposure-adjusted incidence rate; NRI = nonresponder imputation; PYE = patient-years of exposure; SDEAE = step-down emergent adverse event. **p ≤ 0.01 , ***p ≤ 0.001 vs. continued bari 4mg.

or remission. Rescue rates were 7.3% for bari 4mg, 17.1% for bari 2mg. Most rescued patients could regain LDA or remission. Dose reduction was associated with a lower rate of non-serious infections; rates of SAEs and AEs leading to discontinuation were similar across groups.

Conclusions: These data indicate that 4mg once daily was the most efficacious dose of bari for pts with RA; increases in disease activity were consistently seen with dose reduction from 4mg to 2mg in well-controlled pts. However, after step-down most pts could maintain LDA or remission, or recapture control with return to 4mg if needed. Attempted dose taper may be a reasonable consideration for some pts following induction of sustained disease control with bari 4mg.

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SAT0073 MIR-186-5P TARGETING IL-33 GENE AS BIOMARKER TO PREDICT SUBCLINICAL ATHEROSCLEROSIS IN PATIENTS WITH EARLY RHEUMATOID ARTHRITIS

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Background: Patients with rheumatoid arthritis (RA) die prematurely compared with the general population, primarily because of cardiovascular diseases (CVD). Interleukin-33 (IL-33) is a member of the IL-1 cytokine family which was important in the pathogenesis of RA and development of CVD. Blood IL-33 protein was not detectable in most subjects, even in RA patients. Thus, the usability of IL-33 as a biomarker for CVD is limited. MicroRNAs (miRNAs) are small non-coding RNAs that function as post-transcriptional regulators of gene expression.

Objectives: This study was to ascertain if dysregulated miRNAs targeting IL-33 gene in early RA (ERA) patients were associated with subclinical atherosclerosis in ERA patients.

Methods: 76 ERA patients were recruited in this cross-sectional study. Potential miRNAs binding to 3'UTR of the IL-33 gene were predicted by miRanda (www.microRNA.org). 10 miRNAs with highest possibility targeting functional sites of IL-33 gene were quantified in cell free plasma samples using a 2^{-ΔCt} method. Caenorhabditis elegans miR-39 (cel-miR-39) was used as spike-in control. The results were then log transferred. Carotid plaque (CP) was measured and identified at bilateral common carotid artery, bulb, and proximal internal carotid artery using a high-resolution B mode ultrasound. Receiver-operating characteristic curve (ROC) analysis was performed to determine the discriminating power of the miRNA for the presence of CP.

Results: CPs were identified in 26/76 (34%) subjects (CP+ group). Subjects in the CP+ group were older [58±10 vs 48±11 years old, $p=0.001$], predominantly male [48 (42.3%) vs 43 (14.0%), $p=0.006$], with a higher C-reactive protein (CRP) level [24.9±25.0 vs 11.8±13.7 mg/dL, $p=0.018$] and higher cardiovascular risk [Framingham risk score (FRS): 12.8±11.6 vs 5.7±6.8, $p=0.008$] (Table 1). All miRNAs were detected in >80% of subjects in both group. Plasma level of miR-186-5p in the CP+ group was significantly higher than that in the CP-group [log miRNA: 3.28±3.21 vs 2.58±1.13 $p=0.008$]. It was still significant after adjusting age, sex, plasma CRP and FRS ($p=0.030$) (Table 1). Using multivariate logistic regression, miRNA-186-5p was an independent predictor of the presence of carotid plaque (OR: 1.919, 95% CI=1.096–3.361, $p=0.023$) after adjustment of FRS and CRP level. [Area under the ROC (AUC) 0.66, 95% CI: 0.60–0.80 $p=0.024$].

Conclusions: miR-186-5p was an independent predictor for presence of subclinical atherosclerosis and may serve as a novel biomarker for risk stratification in ERA patients with mild to moderate cardiovascular risk.

Table 1 - Characteristics of patients with and without carotid plaque

	Carotid Plaque		<i>p</i>	<i>p</i> *
	Absence (n=50)	Presence (n=26)		
Age	48 ± 11	58 ± 10	0.001	
Gender, male	43 14.0%	15 42.3%	0.006	
CRP, mg/dL	11.8 ± 13.7	24.9 ± 25.0	0.018	
Framingham Risk Score	5.7 ± 6.8	12.8 ± 11.6	0.008	
log miRNA				
miR_9_5p	0.39 ± 0.99	0.26 ± 0.36	0.809	0.225
miR_382_5p	0.87 ± 0.88	0.94 ± 0.82	0.809	0.730
miR_377_3p	0.69 ± 0.61	0.94 ± 0.83	0.227	0.550
miR_590_3p	0.10 ± 0.20	0.33 ± 0.61	0.684	0.222
miR_499a_5p	0.11 ± 0.17	0.19 ± 0.29	0.809	0.406
miR_145_5p	2.43 ± 1.05	3.30 ± 1.82	0.227	0.091
miR_542_3p	0.08 ± 0.27	0.08 ± 0.14	0.373	0.886
miR_186_5p	2.58 ± 1.13	3.28 ± 1.21	0.008	0.030
miR_214_3p	0.41 ± 0.66	0.61 ± 0.65	0.091	0.085
miR_496	0.14 ± 0.32	0.17 ± 0.25	0.809	0.546

*Multivariate analysis adjusted with age, sex, plasma CRP and FRS

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SAT0074 PERSISTENCE WITH METFORMIN TREATMENT AND ONSET OF RHEUMATOID ARTHRITIS

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Background: Several studies have suggested that metformin, an oral hypoglycemic agent, possess an anti-inflammatory property and may have a role in the treatment of rheumatoid arthritis (RA)^{1,2}, but little is known on its preventive effects.

Objectives: To examine the association between persistence with metformin and the onset of RA.

Methods: Using the computerized medical database of a large health organization in Israel (Maccabi Healthcare Services, MHS) we have identified incident RA cases among new users of metformin between 1998 and 2014. Included were patients aged 18 or above with one year of follow up before and after the therapy initiation. RA was defined according to physician diagnoses. Participants were followed until the earliest of the following dates: onset of RA, leaving MHS, death, end of follow up (1.1.2016). Persistence with metformin was assessed by calculating the mean proportion of follow-up days covered (PDC) with metformin during the study period.

Results: A total of 113,749 eligible patients were included. During the study follow up period (794,386 person-years) we identified 600 incident cases (incidence rate of 75 cases per 100,000 PY). The incidence of RA in women (111 per 100,000 PY) was higher compared to men (42 per 100,000 PY). In a multivariable model, persistence with metformin (PDC≥80%) was associated with lower risk of RA (hazard ratio (HR) 0.66; 95% confidence interval (CI) 0.53–0.82) compared to non-persistent participants (PDC<20%). Figure 1 shows the hazard function according to persistence with metformin treatment. Similar risk reduction was observed among men but did not reach statistical significance (HR=0.85; 95% CI 0.54–1.32).

Hazard Function according to persistence with metformin treatment

Conclusions: In the present study, we observed an association between high persistence to metformin therapy and reduced risk of developing RA in women.