

fat to inflammation: Old questions and new insights. *Febs Lett.* 2005; 579: 295–301.

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AB0242 EVALUATION OF VARIANTS IN MIR-146A, MIR-196A-2 AND MIR-499 AND THEIR ASSOCIATION WITH SUSCEPTIBILITY FOR RHEUMATOID ARTHRITIS AND ITS EXTRA-ARTICULAR MANIFESTATIONS

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Background: The miRNAs, small non-coding RNA, regulate the genetic expression to posttranscriptional level, inhibiting the translation. The role of miRNAs in the evolution of RA is not clear.

Objectives: To evaluate the variants rs 2910164G/C in *miR-146a*, rs11614913C/T in *miR-196a-2* and rs3746444A/G in *miR-499* and their association with susceptibility and severity to Rheumatoid arthritis (RA) and its extra-articular manifestations (EAM)

Methods: 133 cases with RA were included (ACR/EULAR criteria 2010) and 430 healthy controls. There were evaluated EAM (rheumatoid nodules [RN], Raynaud phenomenon [RP], cutaneous vasculitis [CV], episcleritis, scleritis, peripheral ulcerative keratitis [PUK], multiple mononeuritis [MM] and multiple polyneuritis [MP]) and levels of ESR, CRP, RF and CCP. It was performed genotyping of single nucleotide polymorphisms (SNPs) rs2910164G/C in *miR-146a*, rs11614913C/T of *miR-196a-2* and rs3746444A/G of *miR-499*. The descriptive and inferential statistical analysis was performed with the software SPSS and Finetti.

Results: Patients with RA, women 126 (94.7%); age Me 48.9 (IQR 40–58); patients with EAM 23 (17.2%; women 22 [95.6%]; RN 14 [60.8%], RP 4 [17.3%], CV 1 [4.3%], episcleritis 1 [4.3%], PUK 1 [4.3%], MM 1 [4.3%], MP 1 [4.3%]); ESR Me 37 (IQR 22–45), CRP Me 0.11 (IQR 0.03–0.27); positive RF 125 patients (93.9%, high positive 106 [79.7%], low positive 19 [14.3%]; EAM with high positive RF, 100%), positive CCP 70 (52.6%, high positive 48.9%, low positive 3.8%; EAM high positive 94.1%, negative 5.9%). The alleles and genotypic frequencies did not show statistically significant difference between cases and the healthy controls ($p > 0.05$). It was identified statistical difference between the patients with and without EAM in CPR ($p = 0.032$). The genotypic and allelic frequencies and association analysis of *miRNAs* in patients with and without EAM are shown in table 1

Table 1. Analysis of the genotypic and alleles frequencies of the SNPs rs2010164G-C from *miR-146a*, rs11614913C/T from *miR-196a-2* and rs3746444A/G from *miR-499* in patients with RA with and without EAM

Genotype	Patients without EAM		Patients with EAM		OR	CI 95%	p
rs2010164G/C	n	%	n	%			
GG	54	(49.1)	9	(39.1)	—	—	—
GC	47	(42.7)	11	(47.8)	1.40	0.54–3.68	0.49
CC	9	(8.2)	3	(13.0)	2.00	0.45–8.83	0.35
Allele							
G	155	(70.4)	29	(63.0)	—	—	—
C	65	(29.6)	17	(37.0)	1.34	0.72–2.71	0.32
rs11614913C/T							
CC	42	(38.2)	2	(8.7)	—	—	—
CT	55	(50.0)	14	(60.9)	5.34	1.15–24.81	0.02
TT	13	(11.8)	7	(30.4)	11.31	2.09–61.29	0.001
Allele							
C	139	(63.2)	18	(39.1)	—	—	—
T	81	(36.8)	28	(60.9)	2.67	1.39–5.12	0.002
rs3746444A/G							
AA	100	(90.9)	21	(91.3)	—	—	—
AG	9	(8.2)	2	(8.7)	1.06	0.25–5.26	0.94
GG	1	(0.9)	0	(0.0)	1.56	0.06–39.6	0.65
Allele							
A	209	(95.0)	44	(95.6)	—	—	—
G	11	(5.0)	2	(4.4)	0.86	0.28–4.83	1.03

O: Odds Ratio, CI: confidence interval, EAM: extraarticular manifestations

Conclusions: None of the evaluated variants in *miRNAs* are associated with susceptibility for RA, however, the SNP rs11614913C/T located in *miR-196a-2* is associated with EAM.

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AB0243 SERUM LEVELS OF ANGIOGENIC AND PROINFLAMMATORY CYTOKINES TO DISCRIMINATE BETWEEN 6 SETS OF REMISSION CRITERIA IN RA

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Background: The ideal definition of remission in RA remains to be agreed. Angiogenic factors and proinflammatory cytokines are key in RA pathogenesis.

Objectives: The aim of this study was to analyse serum levels differences of angiogenic and inflammatory biomarkers between SDAI, CDAI, ACR, DAS28 and sonographic remission in patients with (RA).

Methods: We selected patients with RA in clinical remission (DAS28-ESR < 2.6 for > 6 months). PDUS of knees and hands was performed. Serum levels of biomarkers of inflammation/angiogenesis were determined by Quantibody® Human Array. Patients were classified according to 6 sets of remission criteria: SDAI (< 3.3), CDAI (< 2.8), ACR, DAS28-ESR (< 2.6), Doppler (score Doppler = 0) and UdAS (ultrasound defined active synovitis: no joints with SH ≥ 2 + PD)

Results: 60 patients with RA were collected. 76% female, aged (mean) 53 years; disease duration 110 months. 47 (76%) csDMARDs, and 27 (45%) biological therapies. At baseline, 67% of patients had PD signal and 48% fulfilled criteria for previously defined UdAS. Although patients in sonographic remission had lower levels of inflammatory biomarkers such as IL-6, IL-17 or IL-23, no significant differences were found between the 6 sets of remission criteria. Angiogenic biomarkers such as CXCL6 (0.039), ENA78 (0.007), SDF1 (0.047) and VEGF-R1 (0.025) were significantly lower in patients fulfilling CDAI remission. Patients with no PD signal (0.009) and no UdAS (0.006) had significantly lower levels of bFGF.

Conclusions: RA patients in CDAI remission had significantly-lower levels of angiogenic cytokines. However, no differences in serum levels of proinflammatory cytokines were found between the 6 sets of remission criteria.

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AB0244 MICROWAVE RADIOMETRY-DERIVED THERMAL CHANGES OF SMALL JOINTS AS POTENTIAL ADDITIONAL BIOMARKER IN RHEUMATOID ARTHRITIS: A PROSPECTIVE STUDY

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Background: Microwave Radiometry (MR) is a rapid, non-invasive method that detects in-depth tissue temperatures. Using joint ultrasound as reference method, in a proof-of-concept study, we have found that an increased temperature at the knee joint detected by MR in the absence of relevant clinical signs reflects the presence of subclinical synovial inflammation in rheumatoid arthritis (RA) (1).

Objectives: To test the hypothesis that temperature of small joints assessed by MR correlates to global disease activity levels in RA, a disease in which small joints are primarily affected.

Methods: Ten patients with active, untreated RA underwent clinical and laboratory assessments, joint ultrasound and MR of hand and foot small joints (RTM 01 RES microwave computer based system, Bolton, UK) at baseline, as well as 15, 30 and 90 days after treatment onset. Twenty aged-matched healthy individuals served as controls.

Results: Using 1248 separate MR-derived recordings from RA patients we created several thermo-scores involving different small joint combinations and compared them with clinical and ultrasound data. The best performing thermo-score involved the sum of temperatures of 16 small joints (2nd-5th metacarpal and proximal inter-phalangeal joints, bilaterally). This thermo-score correlated positively to DAS28 disease activity score ($p = 0.001$), tender joint count ($p = 0.002$), swollen joint count ($p = 0.001$), patient's visual analogue scale ($p < 0.001$), CRP

($p=0.040$), but not ESR levels, as well as to the standard Ultrasound Score of 7 joints ($p\leq 0.025$) (2). The MR-derived thermo-score could also discriminate patients in high [mean (SD) 9.2 (5.6)], moderate [mean (SD) 7.1 (3.5)] and low disease activity/remission [mean (SD) 4.2 (1.8)] ($p=0.015$), or aged-matched healthy subjects [mean (SD) 5.0 (1.7)] ($p=0.002$). Moreover, individual changes from baseline to follow-up end mirrored the corresponding DAS28 changes in 7/10 patients.

Conclusions: Increased in-depth temperatures of small joints detected by MR, which are indicative of local inflammation, may serve as an additional biomarker in RA. Optimization of MR equipment and technique may result in an objective measurement of RA disease activity in clinical practice.

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AB0245 DISTRICT DIFFERENCES BETWEEN THE SEXES OF PREDICTIVE VALUE OF MATRIX METALLOPROTEINASE-3 AT BASELINE REGARDING CHANGES IN MODIFIED TOTAL SHARP SCORE AT 1 YEAR IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Background: Matrix metalloproteinase (MMP)-3, also known as stromelysin-1, is expressed in inflamed synovium of patients with rheumatoid arthritis (RA). It degrades components of articular cartilage, such as proteoglycans. In Japan MMP-3 has been used as a clinical biomarker of joint destruction and its predictive value for radiographic progression has been reported.

Objectives: We aimed to confirm a relation between baseline MMP-3 and radiographic progression at 1 year and to examine the association of the MMP-3 level with ultrasonography (US) findings.

Methods: A total of 259 (213 women) consecutive patients with RA were enrolled. We collected baseline data, that included the patient's age, sex, disease duration, use of glucocorticoid or disease modifying antirheumatic drugs, Disease Activity Score-28, and modified total Sharp score (mTSS); MMP-3 and, C reactive protein levels; rheumatoid factor or anti-citrullinated peptide antibody status; and the power doppler score (PD) of US assessment of digits and wrists. Baseline MMP-3 level was analyzed in association with the baseline PD value and changes (Δ) in mTSS, erosion score (Δ ERN), joint space narrowing (Δ JSN) at 1 year from baseline by Pearson's correlation method. Correlations between Δ MMP-3 and Δ mTSS, or Δ PD were also analyzed. Multiple regression analysis was performed, with Δ mTSS as the outcome for baseline variables. Statistical analysis was performed separately by sex because the upper normal limits of MMP-3 differ between the sexes (men ≤ 121 ng/ml, women ≤ 59.7 ng/ml).

Results: There was a weak correlation between the baseline MMP-3 level and baseline PD score in men. There was also moderate correlations between baseline MMP-3 level and structural damage at 1 year only in men. There was no predictive value for baseline MMP-3 level in women in terms of structural damage at 1 year. Multiple regression analysis revealed that the baseline MMP-3 level correlated independently with the Δ mTSS only in men ($p=0.0031$), whereas in

Table 1

	Variables	Correlation coefficient	Confidence interval	p
Male patients				
Baseline MMP-3	Δ mTSS	0.501 ^a	[0.246, 0.691]	<0.001
	Δ ERN	0.336 ^b	[0.051, 0.571]	0.022
	Δ JSN	0.542 ^a	[0.299, 0.719]	<0.0001
Δ MMP-3	Baseline-PD	0.228 ^b	[-0.074, 0.492]	0.136
	Δ mTSS	-0.435 ^a	[-0.644, -0.165]	0.003
	Δ ERN	-0.325 ^b	[-0.562, -0.038]	0.028
	Δ JSN	-0.436 ^a	[-0.645, -0.167]	0.002
	Δ PD	0.134	[-0.170, 0.414]	0.387
Female patients				
Baseline MMP-3	Δ mTSS	0.0011	[-0.130, 0.132]	0.987
	Δ ERN	0.0188	[-0.113, 0.150]	0.780
	Δ JSN	-0.0148	[-0.146, 0.117]	0.826
Δ MMP-3	Baseline -PD	0.0985	[-0.040, 0.233]	0.163
	Δ mTSS	-0.0344	[-0.165, 0.098]	0.610
	Δ ERN	-0.0485	[-0.179, 0.083]	0.472
	Δ JSN	-0.0127	[-0.144, 0.119]	0.851
	Δ PD	0.134	[-0.0058, 0.270]	0.060

^aModerate correlation, ^bWeak correlation. Statistical analysis was performed using Pearson's correlation.

the women the baseline PD score was correlated independently with the Δ mTSS ($p=0.0003$).

Conclusions: The baseline MMP-3 level was a good predictor of deterioration of the mTSS at 1 year in male patients with RA, but not in female patients. On the other hand, the baseline PD score was a useful predictor of joint destruction in female patients with RA.

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AB0246 IMPACT OF TREAT TO TARGET STRATEGY WITH COMPLEMENTARY ULTRASOUND ON REAL WORLD RADIOGRAPHIC OUTCOMES IN EARLY RHEUMATOID ARTHRITIS OVER THE PAST DECADE

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Background: Treatment for rheumatoid arthritis (RA) has changed over the past decade. Early diagnosis and prompt aggressive treatment based on treat to target strategy, as well as complementary ultrasound have been adopted and proven to improve patient clinical and radiological outcomes in clinical trials.

Objectives: The aim of this study was to compare radiographic progression of early RA patients starting their first DMARD 10 years ago vs more recently in daily clinical practice.

Methods: We reviewed the medical records of consecutive patients with symptom of 3 years duration who fulfilled the 1987 ACR classification criteria or the 2010 ACR/EULAR classification criteria in a single center retrospectively. In the first cohort (2000s), 70 patients (55.3 \pm 13.3y.o, Female 77%) who were diagnosed with RA during 2003–2005 were included. In the second cohort (2010s), 71 patients (54.5 \pm 17.3y.o, Female 90%) who were diagnosed with RA during 2013–2015 were included. Radiographs of hands were assessed at baseline and one year after according to the van der Heijde modified Sharp score (range 0–280) without clinical information and chronological orders of radiographs in the individual patients.

Results: Mean changes in radiographic joint damage for joint space narrowing score, erosion score, total radiographic score were higher in 2000s than 2010s (0.92 \pm 2.70 vs 0.28 \pm 1.86; $p=0.010$, 0.54 \pm 1.35 vs 0.35 \pm 0.99; $p=0.390$, 1.45 \pm 3.54 vs 0.68 \pm 2.55; $p=0.015$, respectively). Radiographic progression defined as total radiographic score >0 and >5 were 31.4% vs 22.5% and 8.6% vs 8.5% between 2000s and 2010s ($p=0.230$ and $p=0.970$, respectively). Methotrexate (MTX) was frequently used for initial treatment in 2010s than 2000s (86% vs 55%, $p\leq 0.001$), and initial dose and maximum dose of MTX were higher in 2010s than 2000s (9.13 \pm 2.09 mg/week vs 4.67 \pm 1.54 mg/week; $p\leq 0.001$ and 12.04 \pm 3.73 mg/week vs 8.13 \pm 1.88 mg/week; $p\leq 0.001$, respectively). The mean duration from symptom onset to diagnosis was earlier in 2010s than 2000s (5.75 \pm 5.04 months vs 7.85 \pm 6.85 months, $p=0.001$). CRP at baseline and 1 year after were lower in 2010s than in 2000s (2.74 \pm 1.90 mg/dL vs 3.35 \pm 3.94 mg/dL; $p=0.001$ and 0.60 \pm 1.19 mg/dL vs 1.20 \pm 1.99 mg/dL; $p=0.03$ respectively). There were no significant differences in sex, age, positive rate of RF and ACPA, the Sharp score at baseline, steroid use, and biological agents use between two cohorts.

Conclusions: In recent 10 years, early diagnosis with complementary ultrasound and appropriate MTX use based on treat to target strategy led to prevent joint destruction of RA patients in daily clinical practice.

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AB0247 EVALUATION OF RHEUMATOID ARTHRITIS CASES WITH HIGH ANTI-CCP ANTIBODY LEVEL

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Background: Anti-cyclic citrullinated peptide antibodies (Anti-CCP Ab) are well-established serological markers that show high sensitivity and specificity in diagnosing early rheumatoid arthritis (RA). Furthermore, Anti-CCP Ab is reported to be associated with bone erosions of RA. Therefore, Anti-CCP Ab positive RA patient can be a candidate for intensive treatment.

Objectives: Upper measurement limit of Anti-CCP Ab increased recently up to 1200 units. High level of Anti-CCP Ab may be a predictor of the profound therapy for RA. To understand the importance of Anti-CCP Ab level, we evaluated RA patients with high titer Anti-CCP Ab in relationship to the other activity markers of RA and the intensity of the treatment for RA.

Methods: Total of 186 RA patients with Anti-CCP Ab higher than 30 units was included in this study. Baseline markers such as CRP, MMP-3, RF and anti-CCP Ab were measured at the entry of the study. Relationship among these markers were evaluated and examined using statistical significance for the single-factor ANOVA and the multiple comparisons. Among those cases 131 cases were treated conservatively with biologics and/or DMARDs and were followed up more than one year. We graded them from I to IV by the intensity of the treatment. Grade I: Biological agent. Grade II: Methotrexate (MTX) more than 12mg or combination with more than 3 DMARDs Grade III: MTX 6–11mg or combination