Rheumatoid arthritis - prognosis, predictors and outcome

AB0189 RAID COMPOSITE INDEX IN THE EVALUATION OF RA PATIENTS RECEIVING BIOLOGICAL TREATMENT: HUR-BIO REAL-LIFE RESULTS

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Background: Rheumatoid Arthritis Impact of Disease (RAID) is a composite index. There are seven domains of this index (pain, function, fatigue, sleep disturbance, physical wellbeing, psychological/emotional well-being and coping). Daily activity in last week is evaluated. This score, is reccommended to be used in clinical trials to measure the effect of RA.
Objectives: The aim of this study is to examine the relationship between RAID composite index and other indexes.
Methods: This study was carried out from the HUR-BIO reserved database since August, 2016. In addition to the demographic characteristics of the patients, DAS-28, HAQ-DI, pain, fatigue, Patient global Assesment (PGA), Tender joint counts (TJC), swollen joint counts (SJC), CRP and ESR are recorded. Since 2015, a RAID form is filled for our patients. While this composite scale was being created, Gazi University Turkey carried out Turkish validation, in the original study. RAID composite index includes 7 questions, each scored from 0 to 10, 0 being the best score while 10 points is worst. The relationship between RAID composite index and other indexes were studied with Spearman correlation test.
Results: HUR-BIO database containts 1235 RA patients as of August 2016. A RAID form was filled for 149 of these patients before initiating biological agent. 124 patients (83.2%) were female. Mean age was 49±13 years and mean disease duration was 7.8±7.2 years. Positive ACPA and RF ratios were detected as 48/104 (45.7%) and 78/137 (56.9%) respectively. 77.9% of our patients had education of high school or less. RAID average score was detected as 6.72 (1.98). In female patients RAID disease activity was significantly higher than in men [RAID 6.8 (2.0) vs. 5.9 (1.6), p=0.038]. There was no significant difference among RF, CCP positive patients and auto antibody-negative patients in terms of RAID disease activity. [RAID for RF + vs -; 6.75 (2.05) vs 6.68 (1.86), p=0.82, RAID for CCP + vs -; 6.74 (1.96) vs 6.98 (1.82), p=0.52]. RAID disease activity measurements were correlated moderately acute phase reactants, it was very weak. In table, it is grouped by level of education and re-evaluated. In those with an education higher than college, rising parameters were seen in good level of correlation. [RAID vs Pain, r =0.65, p<0.005; RAID vs PGA, r =0.68, p<0.005].

Table 1. Correlation of RAID composite index according to education level

	RAID Query			
	RAID Total Score n: 149	Lower than High School n: 92	High School and Beyond n: 57	College and Beyond n: 33
DAS-28	0.28*	0.25*	0.42*	0.44*
HAQ-DI	0.49*	0.47*	0.50*	0.54*
Pain	0.51*	0.56*	0.58*	0.65*
Fatigue	0.45*	0.35*	0.52*	0.49*
PGA	0.50*	0.52*	0.59*	0.68*
TJC	0.27*	0.20*	0.30*	0.32
SJC	0.16*	0.06	0.29*	0.25
CRP	0.05	0.09	0.04	0.17
ESR	0.01	-0.01	0.12	0.20

DAS-28: Disease Activity Score, HAQ-DI: The Health assessment questionnaire disability index, PGA: Patient global Assesment, TJC: Tender joint counts, SJC: Swollen joint counts, CRP: C-Reactive Protein, ESR: Sedimentation. *p<0.005.

Conclusions: RAID has low correlation with other composite index such as DAS-28 score. RAID also has moderate correlation with pain, fatigue ad PGA VAS. On the other hand, patient with high education level had better perception for those patient reported composite index. RAID can be used confidently in these selected cases.
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AB0190 ASSESSMENT OF PLASMA MICRO-RNA 155 IN RHEUMATOID ARTHRITIS

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Background: Several observations have indicated that Epigenetics now play a role in the pathogenesis of many diseases including Rheumatological and Immunological disorders such as Rheumatoid Arthritis.(RA). Unlike the genetic code, the epigenome is altered by endogenous (e.g. hormonal) and environmental (e.g. diet, exercise) factors and changes with age. There are three main and interrelated mechanisms: DNA methylation, post-translational modification of histone proteins and non-coding RNA which includes Micro RNA (miR).
Objectives: 1. To determine the level of miR- 155 in plasma of RA patients.
2. To determine the potential value of miR-155 as molecular biomarker for diagnosis, prognosis of disease outcome, and prediction of therapeutic response in RA patients, and to test the relation miR-155 and serum levels of Matrix Metalloproteinase 3.(MMP)
Methods: The study group consisted of 50 female RA patients in active disease and 25 controls of matched age and sex. Disease duration of 1 to 10 years and age range from 20 to 45 years old. They underwent detailed history taking including questionnaire for disability and health assessment scoring, clinical examination, radiological assessment by modified Sharp score. Routine laboratory investigations in addition to assessment of Plasma miR -155 expression levels and serum MMP-3 levels were done for all patients. Ten of the cases were resampled for miR-155 and MMP-3 after receiving treatment and entering disease remission (By DAS 28 score).
Results: Plasma miR–155 expression levels and serum MMP-3 titers were significantly higher in RA patients than in controls (mean 4.071 and 1, $p<0.001$, mean 323.7 and 84.5, $p<0.001$) respectively. MMP-3 titers in serum were significantly higher in erosive than in non-erosive arthritis (mean 366.9 and 163.4, $p<0.001$). There was a significant positive difference between serum MMP-3 levels in disease activity and remission (mean 630 and 380, $p<0.001$). Mean values of the clinical parameters of our study group: STLW score (37.44±15.90), HAQ score (56.86±16.69), ACR disability class (2.224±0.872), DAS 28 score (4.856±1.222), ESR (58.16±29.44), Sharp score (32.36±23.9), There was a significant positive correlation between serum MMP-3 and DAS 28 score and ESR (r=0.022, p_0.022 and r=0.013, p=0.013 respectively). There was a significant positive moderate correlation between Plasma miR-155 and serum MMP-3 ($r=0.596$, $p<0.001$). Correlation between Plasma miR-155 expression levels and HAQ (p=0.612, r=0.0744), with ESR (p=0.13, r=0.219) with DAS 28 score (p=0.187, r=0.192), with Sharp score (p=0.675, r=0.0797).
Conclusions: miR-155 is indeed related to the presence of Rheumatoid arthritis, though not directly related to disease activity like MMP-3. miR-155 significantly but moderately correlates with MMP-3 in blood, but whether it plays a role in the pathogenesis of the disease with or without directly influencing MMP-3 in the joint will require more work on both markers inside the synovial fluid, synovial tissue and the synovial fibroblasts. MMP-3 was re-established in our study as a marker of disease activity and predictor of erosive arthritis.
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AB0191 CLINICAL SIGNIFICANCE OF MULTIPLE AUTOANTIBODY SPECIFICITIES IN RHEUMATOID ARTHRITIS: THE ROLE OF ANTI-CITRULLINATED ALPHA ENOLASE AND ANTI-INTERFERON INDUCIBLE PROTEIN 16

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Background: Anti-cyclic citrullinated peptide (anti-CCP) auto-antibodies (auto-Abs) represent the current gold standard for the diagnosis of rheumatoid arthritis (RA). However, growing evidence suggests that a variety of other citrullinated or not citrullinated self-proteins may act as autoantigens and lead to the production of auto-Abs. The identification of the diagnostic and/or prognostic value of such novel auto-Abs is under intense investigation. We recently demonstrated that RA patients display a higher prevalence of auto-Abs against the interferon-inducible protein 16 (anti-IFI16) but these auto-Abs do not have a good diagnostic value (1). Recent data showed that auto-Abs against citrullinated alpha-enolase (anti-CEP1) are associated with erosive RA (2).
Objectives: The purpose of this study was to investigate the possible prognostic value of anti-CEP-1 and anti-IFI16 as well as the clinical implication of their association with anti-CCP in a cohort or RA patients.
Methods: Two hundred and fifty two RA patients were enrolled and serum samples were obtained. Auto-Abs were assessed as follows: anti-CCP EDIA 2nd generation ELISA kit (Eurodiagnostica); anti-CEP-1 IgG ELISA kit (Euroimmun). In a subgroup of 113 patients also anti-IFI16 auto-Abs were assessed with an in-house ELISA kit (1). Clinical and serological records of patients were collected and statistical analysis was performed with SPSS 21.0 software.
Results: One hundred and twenty patients (44%) displayed anti-CEP-1 auto-Abs and of these 97 patients (87%) also displayed anti-CCP. Logistic regression analysis revealed an association between both auto-Abs and RA-associated pulmonary disease (odds ratio-OR=2.9; 95% CI=1.06–7.9; p=0.04). We also confirmed that anti-CEP-1 are associated with erosive RA but of interest to a greater extent compared to anti-CCP (anti-CEP-1: OR=4.12; p=0.04; anti-CCP: OR=2.1; p=0.03). The analysis that included anti-IFI16 auto-Abs revealed that a small proportion of patients display all the three auto-Abs (9%) but

the triple positivity was significantly associated with male gender (OR=3.5; p=0.02), the presence of rheumatoid nodules (OR=5,3; p=0.015) and pulmonary involvement (OR=2.6; p=0.007). Anti-IFI16 auto-Abs were associated to male gender independently of the presence of the other two auto-Abs.

Conclusions: Our study demonstrated that anti-CEP-1 auto-Abs may participate to the development of RA-associated pulmonary manifestation together with anti-CCP and that the assessment of multiple auto-Abs in daily practice may help clinician to stratify RA patients at identify those at higher risk to develop extra-articular manifestations.

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AB0192 SERUM MEASURES OF TYPE I COLLAGEN DEGRADATION ARE SURROGATE MARKERS OF JOINT DESTRUCTION AND PROGRESSION; FIRST STEPS TOWARDS A PROGNOSTIC SCORE

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Background: Monitoring of patients with rheumatoid arthritis (RA) requires assessment of biomarkers reflecting disease activity and its progression. There is a need for non-invasive markers for frequent monitoring of disease severity and progression as well as response to therapy.

Objectives: Serological markers together with clinical parameters was tested in a multi-marker model to assess its ability to objectively predict progression of RA.

Methods: Current post-hoc analysis included RA patients from the biomarker substudy of the phase III clinical study LITHE investigating the safety and efficacy of tocilizumab[1–4]. Patients had moderate/severe, active RA. In addition, only patients of the placebo arm and with total sharp score (SHP) recorded at baseline (BL), week 24 (W24) and W52 were included. Progressors were defined as the delta from BL to W24 and W24 to W52. Biochemical markers reflecting tissue turnover (table) were assessed at BL and W16. Associations with structural progression (deltaSHP) were investigated by spearman's r, least squared multivariate and logistic regression. Covariates were CRP, sex, BMI, age, disease duration, DAS-ESR, no. prior DMARDs/aTNF use and SHP/BL. The data were divided into a training and confirmation set; 1) association between markers/W16 and deltaSHP/W52 (n=31 prog./42 non-prog.), 2) association between markers/BL and deltaSHP/W24 (n=33/48).

Results: *The training set.* Eight markers were correlated (R>0.2) with deltaSHP/W52. Of these C1M, PINP, ICTP and MMP3 were predictive for of progression (deltaSHP/W52>0) with ORs of 3.2 [1.3–8.0], 4.0 [1.4–12], 8.5 [2.4–31], and 2.5 [1.3–5.1]; all p<0.01, respectively. A logistic model for prediction of disease progression incorporating C1M, ICTP, disease duration and BMI demonstrated an AUC of 0.77 [0.66–0.86], p<0.01. The model correctly identified 72% of the progressors. textitThe confirmation set: The results were confirmed in the second dataset with an AUC of 0.75 [0.64–0.81], p<0.01. The model correctly identified 65% of the progressors.

Biochemical marker	Description	Biomarker of	Spearman correlation between DeltaSHP/W52 and baseline biochemical marker R>0.2
C1M	MMP-mediated type I collagen degradation	Connective tissue destruction	**0.377**
C2M	MMP-mediated type II collagen degradation	Cartilage degradation	0.088
C3M	MMP-mediated type III collagen degradation	Connective tissue destruction	**0.277**
C4M	MMP-mediated type IV collagen degradation	Basement membrane destruction	0.157
C6M	MMP-mediated type VI collagen degradation	Connective tissue destruction	0.175
CRP	C-reactive protein	Acute reactant	**0.354**
CRPM	C-reactive degradation	Tissue inflammation	**0.290**
CTX-I/OC	Ratio between cathepsin K-mediated type I collagen degradation and osteocalcin	Bone turnover balance (Bone resporption/formation)	0.063
Gender	-	-	0.090
HAQ	Health assessment questionnaire		-0.032
ICTP	MMP-mediated type I collagen degradation	Connective tissue destruction /bone degradation	**0.334**
MMP3	Matrix metalloproteinase 3	Joint inflammation	**0.226**
Pain (VAS)	-	-	0.073
Patient global score (VAS)	-	-	0.110
Physician global score (VAS)	-	-	0.051
PIIANP	Propeptide of type II collagen	Cartilage formation	-0.077
PINP	Propeptide of type I collagen	Connective tissue and bone formation	**0.217**
VCAM	MMP-mediated Versican degradation	Epithelial turnover	-0.054
VICM	MMP-mediated degradation of citrullinated vimentin	Macrophage activity	**0.232**

Conclusions: We demonstrated that a multi-marker model was able to pint-point, which patients were more likely to be structural progressors. Such first steps to build a progression model, rather than a score reflecting disease activity only, may enrich clinical studies with structurally active diseaese. Importantly, the markers with strongest influence were those associated with MMP-driven bone (ICTP) and connective tissue (C1M) remodelling.

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AB0193 MEDICAL ADHERENCE IN PATIENTS WITH TIGHTLY CONTROLLED RHEUMATOID ARTHRITIS

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Background: Medication adherence is very important in the treatment of rheumatoid arthritis (RA). However, medication adherence of the patients with RA was not optimal in many of the studies (1–2).

Objectives: The purpose of this study was to investigate the medication adherence in tightly controlled RA patients and reasons of non-adherence.

Methods: A total of 82 RA patients (65 women and 17 men) who followed regularly in our outpatient clinic were included. Socio-demographic features and medical history were collected. The eight-item Morisky scale (MMAS-8) was used to evaluate adherence to medication. Disease activity score (DAS28), health assessment questionnaire (HAQ), mini mental state examination (MMSE) test and Beck depression inventory (BDI) were evaluated.

Results: According to Morisky scale, 34.1%, 15.9% and 50% of our patients were categorized as low, moderate and high adherence, respectively. The most prevalent noticed barriers for adherence were forgetting medication, inadequate information about using instructions, side effects of medications (Table 1). Socio demographic features, duration of disease, type and number of drugs used per day, the route of drug administration, co-morbid diseases, body mass index, smoking and alcohol consumption were not found to be associated with medication adherence, whereas low MMSE and high BDI score were associated with low medication adherence (p=0.009 and p=0.011, respectively). We found that the disease activity was significantly higher in non-adherent cases (p=0.00) (Table 2).

Table 1. Barriers to medication adherence

Barriers	%
Forgetfulness	41.4%
Inadequate information	22%
Side effects of medications	17%
Fears about drug benefit	12.2%
Anxiety about side effects	4.8%
Cost of medications	2.6%

Table 2. Medication adherence and disease activity

DAS 28	Low adherence (Morisky <6)	Moderate adherence (Morisky 6–7)	High adherence (Morisky = 8)	Total
Remission (<2.6)	2 (5.6%)	5 (13.9%)	29 (80.6%)	36
Low disease activity (2.6–<3.2)	7 (36.8%)	3 (15.8%)	9 (47.4%)	19
Moderate disease activity (3.2–<5.1)	17 (68.0%)	5 (20%)	3 (12%)	25
High disease activity (≥5.1)	2 (100%)	0 (0%)	0 (0%)	2
Total	28	13	41	82

DAS: Disease activity score.

Conclusions: Our RA patients who were closely followed had 50% high medication adherence. This rate is quite high compared to other studies using MMAS-8. It should be kept in mind that tight control and adequate communication increase medication adherence but different parameters may also be effective. Assessing cognitive disorders and emotional problems of the patient will be beneficial for improving adherence and controlling disease activity.

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