Biomarkers in Remission According to Different Criteria in Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** Remission is the primary aim in the treatment of patients with rheumatoid arthritis (RA). In this study, we aimed to evaluate biomarker profiles of patients in remission by different criteria and compare these profiles with controls.

Methods. Serum levels of calprotectin, interleukin 6 (IL-6), type II collagen helical peptide, C-terminal crosslinking telopeptide of type I collagen generated by matrix metalloproteinases (ICTP), matrix metalloproteinase 3 (MMP-3), resistin, and leptin were measured by ELISA in 80 patients. The patients were in Disease Activity Score at 28 joints with erythrocyte sedimentation rate (DAS28-ESR) remission, and had these characteristics: female/male 54/26, mean age 51.4 ± 12.1 years, mean disease duration 11.4 ± 8.1 years, rheumatoid factor positivity 68.7% (n = 55), anticyclic citrullinated peptide positivity 60.7% (n = 48). These patients were also evaluated for the American College of Rheumatology/European League Against Rheumatism (Boolean) and Simple Disease Activity Index (SDAI) remissions. Additionally, 80 age-, sex-, and comorbidity-matched individuals without rheumatic diseases were included in the study as controls.

Results. At recruitment of 80 patients in DAS28 remission, 33 patients (41.2%) were found in Boolean remission and 39 patients (48.7%) were in SDAI remission. Serum MMP-3, ICTP, resistin, and IL-6 levels of the 80 patients in DAS28 remission were statistically significantly higher than the controls. Patients in Boolean and SDAI remissions had significantly higher serum ICTP, resistin, and IL-6 levels in comparison with the controls.

Conclusion. The 3 commonly used remission criteria of RA are almost similar with regard to patients' biomarker levels. Biomarker profiles of patients may provide complementary information to clinical evaluation of remission and may help to determine the patients under the risk of progression. (J Rheumatol First Release October 15 2015; doi:10.3899/jrheum.150478)

Key Indexing Terms:
RHEUMATOID ARTHRITIS BIOMARKERS REMISSION CRITERIA

Regularly assessing disease activity in patients with rheumatoid arthritis (RA) to guide treatment decisions toward achieving remission or at least low disease activity state is extremely important[1,2,3].

RA disease activity assessment is an important concept in the evaluation of patients. Various composite indices have been developed to measure disease activity. However, there is no single definition that could include all aspects of RA activity. Further, some individual variables of composite indices, such as patient's global assessment (PtGA) and tender joint count (TJC), may be influenced by noninflammatory pain sources[4]. Rheumatoid factor (RF) and/or anticyclic citrullinated peptide (anti-CCP) positivity might help to predict severe disease course and rapid radiographic progression. However, it is not likely to predict the course and the results of RA in seronegative patients. For these reasons, the need for reliable, specific, and objective markers to determine disease activity and remission is ongoing.

Cytokines are important components of inflammatory response in RA. As a key cytokine, interleukin 6 (IL-6) takes part in the production of acute-phase reactants, chemotaxis[5], synovial proliferation[6], and osteoclast maturation and activation[7].

Adipokines are thought to be responsible in the pathogenesis of joint damage[8]. Resistin significantly increases cyclooxygenase 2 activity in macrophages, and when a resistin antibody is administered, this effect disappears[9]. Leptin plays a role in obesity, the regulation of metabolism, hypothalamic-pituitary function, cardiovascular and urinary systems, activation of the sympathetic system, hematopoiesis, and immunity[10]. Calprotectin is a neutrophil granulocytes' cytosolic protein. It

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is released during leukocytes activation and increased in the sera of patients with severe inflammatory disease[11].

Matrix metalloproteinase 3 (MMP-3) is involved in cartilage tissue destruction and bone erosion[12]. Detection of cartilage and bone degradation products in systemic circulation has been indicated as a potential way to determine joint damage and disease activity[13,14]. Type II collagen helical peptide (HELIX-II) and C-terminal crosslinking telopeptide of type I collagen generated by MMP (ICTP) are products of collagen degradation and are shown to be reliable predictors of radiographic progression in RA[15,16,17]. In our study, our purpose was to find the differences in inflammatory and destruction biomarker profiles of patients in remission according to different composite indices and comparing these profiles with age-, sex-, and comorbidity-matched controls who did not have rheumatic diseases.

MATERIALS AND METHODS

Our study was carried out in 2012–2013 with the sequential recruitment of patients who have been followed up since 2002 in our rheumatology outpatient clinic. The study group included 80 patients with RA in 28-joint Disease Activity Score with erythrocyte sedimentation rate (DAS28-ESR) remission out of 480 patients with RA who were fulfilling the 1987 American College of Rheumatology (ACR) RA classification criteria. As a case-control study, the control group included 80 subjects who did not have any rheumatic diseases and matched with patients in terms of age, sex, and comorbidities. Our study was approved by the local ethics committee and all participants gave written informed consent prior to the enrollment.

Evaluations were done of the TJC, swollen joint count (28 joints), PtGA, physician's global assessment, visual analog scale for pain (0–100 mm), Health Assessment Questionnaire scores, and laboratory data. Patients were evaluated according to 3 different remission criteria — DAS28-ESR, Boolean, and the Simple Disease Activity Index (SDAI) — to detect whether they were in remission by different criteria.

Peripheral venous blood was taken from each patient and healthy controls, and serum was separated and stored at –80°C. Serum levels of these substances were measured by ELISA in patients and controls according to the manufacturer's instructions: calprotectin (Eastbiopharm; ng/ml), IL-6 (Assaypro; pg/ml; minimum detectable dose typically ~0.008 ng/ml, intraassay and interassay coefficients of variation were 4.9% and 7.3%, respectively), HELIX-II (Eastbiopharm; ng/ml), ICTP (USCN Life Science Inc.; ng/ml), MMP-3 (Aviscera Bioscience; pg/ml; standard range 1.24–80 ng/ml, sensitivity 0.31 ng/ml, intraassay precision 4–6%, interassay precision 8–12%), resistin (Assaypro; ng/ml; minimum detectable level typically ~0.2 ng/ml, intraassay and interassay coefficients of variation 4.5% and 7.0%, respectively), and leptin (Assaypro; ng/ml; minimum detectable level typically ~0.12 ng/ml, intraassay and interassay coefficients of variation 4.7% and 7.0%, respectively). During experiments, Pasteur-brand LP 35 model microplate washer was used. Readings were made with BioTek-brand ELX-800 model microplate reader.

Statistics. Statistical analyses were performed using the SPSS 16.0 program. Demographic and clinical data were given as mean ± SD. If the distribution was not normal, median values were given for the variables. For parametric data analysis, the Student t test was used to compare the average of 2 populations. One-way ANOVA test was used for more than 2 populations. Nonparametric data were analyzed using the Mann-Whitney U test. For correlation analysis, the Pearson correlation coefficient was used. To identify significant difference, p value was < 0.05.

RESULTS

Eighty patients with RA in DAS28-ESR remission and 80 controls were included in our study. The demographic and disease-related characteristics of the patients are summarized in Table 1. In both groups, there were 54 women, and mean age was 51.4 ± 12.1 years in the study group and 51.2 ± 11.7 years in controls. Mean disease duration was 11.4 ± 8.1 years, and 68.7% (n = 55) and 60.7% (n = 48) of patients were seropositive for RF and anti-CCP, respectively. There was no statistical difference in the sex (p = 1.00), age (p = 0.11), and body mass index (26.9 ± 4.5 kg/m^2 in patients and 28.1 ± 4.6 kg/m^2 in controls, p = 0.88) of the study and control groups.

Eleven patients (13.7%) had raised C-reactive protein value (mean 0.56 ± 0.87 mg/dl), and mean ESR was 13.7 ± 7.9 mm/h. Thirty-three patients (41.2%) were receiving corticosteroids, 21 (26.2%) were receiving biological agents [alone or in combination with disease-modifying antirheumatic drugs (DMARD)], and 59 were receiving only DMARD (32 were receiving > 1 DMARD and 27 were receiving 1 DMARD). None of our patients were being treated with tocilizumab (TCZ) as a biologic agent.

In the study group, which included 80 patients with DAS28 remission, mean MMP-3, ICTP, resistin, and IL-6 levels were determined to be significantly higher than in the control group (35.0 ± 28.0 vs 23.2 ± 19.3 ng/ml, p = 0.003; 5.0 ± 2.0 vs 2.9 ± 1.8 ng/ml, p = 0.0001; 51.6 ± 28.6 vs 36.9 ± 17.7 ng/ml, p = 0.0001; and 26.7 ± 34.8 vs 5.9 ± 3.1 pg/ml, p = 0.0001, respectively; Table 2). Thirty-three of 80 patients (41.2%) were in Boolean remission and 39 of 80 patients (48.7%) were in SDAI remission. Patients in Boolean and

Table 1. Demographic and disease characteristics of patients. Values are mean ± SD unless otherwise specified.

Characteristics	Values
Female, n (%)	54 (67.5)
Age, yrs	51.4 ± 12.1
Disease duration, yrs	11.5 ± 8.1
Raised CRP, n (%)*	11 (13.7)
RF positivity, n (%)	55 (68.7)
Anti-CCP positivity, n (%)	48 (60.7)
ESR, mm/h**	13.7 ± 7.9
Corticosteroids, n (%)	33 (41.2)
DMARD, n (%)	59 (73.7)
Biological agents, n (%)	21 (26.2)
Extraarticular involvement, n (%)	24 (30)
Comorbidities, n (%)	40 (50)
HAQ	0.3 ± 0.4
PGA, 0–10	0.9 ± 0.8
PtGA, 0–10	1.9 ± 1.8
SJC, median (range)	0 (0–6)
TJC, median (range)	0 (0–4)

* CRP was measured as mg/dl and the cutoff was 0.5 mg /dl. ** ESR cutoff value was 20 mm/h. CRP: C-reactive protein; RF: rheumatoid factor; anti-CCP: anticyclic citrullinated peptide; ESR: erythrocyte sedimentation rate; DMARD: disease-modifying antirheumatic drugs; HAQ: Health Assessment Questionnaire; PGA: physician's global assessment; PtGA: patient's global assessment; SJC: swollen joint count; TJC: tender joint count.

Table 2. Serum biomarker levels of patients in DAS28-ESR, Boolean, and SDAI remissions compared with controls.

Serum Biomarkers	DAS28-ESR Remission Group, n = 80	Boolean Remission Group, n = 33	SDAI Remission Group, n = 39	Control Group, n = 80	p*	p**	p†
Calprotectin, ng/ml	134.4 ± 161.8	127.7 ± 186.9	118.0 ± 174.3	131.8 ± 171.7	0.920	0.911	0.714
MMP-3, ng/ml	35.0 ± 28.0	31.5 ± 24.3	30.5 ± 23.3	23.2 ± 19.3	0.003	0.061	0.074
ICTP, ng/ml	5.0 ± 2.0	4.9 ± 2.2	4.8 ± 2.1	2.9 ± 1.8	0.0001	0.0001	0.0001
HELIX-II, ng/ml	49.6 ± 50.9	43.2 ± 44.4	41.4 ± 41.4	51.5 ± 67.4	0.840	0.448	0.339
Resistin, ng/ml	51.6 ± 28.6	51.9 ± 35.6	53.3 ± 33.7	36.9 ± 17.7	0.0001	0.026	0.006
Leptin, ng/ml	8.8 ± 8.6	8.9 ± 9.7	9.2 ± 9.2	10.1 ± 11.1	0.41	0.580	0.680
IL-6, pg/ml	26.7 ± 34.8	23.8 ± 34.2	16.4 ± 24.7	5.9 ± 3.1	0.0001	0.005	0.013

* DAS28-ESR remission group versus control group. ** Boolean remission group versus control group. † SDAI remission group versus control group. DAS28: 28-joint Disease Activity Score; ESR: erythrocyte sedimentation rate; SDAI: Simple Disease Activity Index; MMP-3: matrix metalloproteinase 3; ICTP: C-terminal crosslinking telopeptide of type I collagen generated by MMP; HELIX-II: type II collagen helical peptide; IL-6: interleukin 6.

SDAI remissions had significantly higher serum ICTP, resistin, and IL-6 levels in comparison with the controls (Table 2).

There was no significant difference between biomarker levels of patients in Boolean remission and the ones in Boolean nonremission. However, SDAI nonremission patients had higher serum IL-6 levels than the patients in SDAI remission (36.7 ± 40.2 vs 16.4 ± 24.7 pg/ml, p = 0.008).

DISCUSSION

The primary aim of RA treatment is to achieve a state of remission[1]. Despite the development of many composite indices, a true assessment of a patient's overall disease activity and remission has been a challenge.

The lack of an objective, single variable that reflects all aspects of RA disease activity necessitates the use of composite scores. The evaluation of patients with RA for remission with different remission criteria revealed no consensus among these indices[18]. On the other hand, imaging techniques such as ultrasonography (US) and magnetic resonance imaging have entered the field of clinical evaluation assessed by several composite indices. A study from Spain, with patients with RA in DAS28-ESR remission for more than 6 months, showed that nearly half of these patients had US-defined active synovitis and also had significantly higher levels of several angiogenic biomarkers[19].

Because the criteria sets include components such as PtGA and TJC, which may be subjective and influenced by noninflammatory pain sources (fibromyalgia, depression, anxiety, and fatigue), a risk of overestimating RA activity with these conventional indices is possible[20,21]. For these reasons, multibiomarker scoring systems have been developed to complement clinical examination and indicate the different aspects of disease activity. Assessing RA activity according to the measurement of biomarkers may provide additional and more objective information about reliable remission combining with composite indices[22]. In our study, we investigated the biomarker profiles of patients with RA in remission according to different composite indices. We found that patients in Boolean remission and SDAI remission had similar biomarker profiles; ICTP, resistin, and IL-6 levels were significantly higher than the control group. Patients in remission according to the DAS28-ESR had higher MMP-3 levels than the controls, in addition to ICTP, resistin, and IL-6. This was the only discordance with the Boolean and SDAI remissions. In a study from South Africa, authors investigated serum MMP-3 in comparison with acute-phase proteins as a marker of disease activity and radiographic damage in early RA. They found significant correlation between MMP-3 and measures of disease activity, specifically SDAI[23]. Further, levels of other biomarkers, calprotectin, HELIX-II, and leptin were found to be similar with controls in the 3 remission groups. Previously, leptin has been proposed as a molecule predicting disease activity in RA[24,25]. Consistent with our results, Andrés Cerezo, *et al* showed normalization of calprotectin levels in patients with RA achieving remission after the initiation of conventional DMARD[26]. Further, significant correlations between the levels of calprotectin and the clinical evaluation of disease activity, and with the US scores, have been determined by Hammer, *et al*[27]. Garnero, *et al* investigated the effects of TCZ added to a stable dosage of methotrexate on biochemical markers of bone and cartilage in patients with moderate to severe RA. In that study, larger decreases in serum levels of HELIX-II, MMP-3, and ICTP have been detected in patients who achieved a good clinical response as assessed by the ACR50 improvement or DAS28 remission criteria[28].

In patients with RA in both Boolean and SDAI remission, higher ICTP, resistin, and IL-6 levels compared with controls were found, suggesting that the Boolean, the ACR/European League Against Rheumatism RA remission criteria, and the SDAI could determine patients with significantly suppressed inflammation. But it is not possible to say that the inflammatory activity is completely controlled. Hirata, *et al* examined the relationship between multibiomarker disease activity (MBDA) scores and conventional disease activity indices, and found a consistent trend of stronger association with DAS28 and a weaker association with the clinical disease

activity index[22]. They concluded that because biomarkers and clinical examination were indicative of different aspects of disease activity, they may complement each other and provide better information when used together. Van der Helm-van Mil, *et al* evaluated molecular and clinical remission in RA by assessing radiographic progression and indicated that in clinical remission, high MBDA scores showed an increased risk of disease progression. They also found that patients with RA in remission according to the MBDA score had favorable radiographic outcomes[29]. They concluded that the MBDA score provided complementary information to clinical assessments of remission.

Our study has some limitations. We determined serum levels of biomarkers at only a single visit. Assessment of biomarker serum levels at more than 1 visit would give us the chance to comment on our study results more clearly. The other limitation of our study is the lack of the patients' radiographic assessments. On the other hand, to our knowledge, ours is the first study investigating the relationship between different remission criteria and serum levels of biomarkers.

Several biomarker levels in patients with RA with remission are significantly higher than controls and similar with regard to the 3 most commonly used criteria sets (Boolean, SDAI, and DAS28-ESR). Biomarker profiles of patients may provide complementary information to clinical evaluation of remission and may help to determine patients at risk of progression.

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