The Role of Depression, Anxiety, Fatigue, and Fibromyalgia on the Evaluation of the Remission Status in Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To investigate the effect of depression, anxiety, fatigue, and fibromyalgia (FM) on the remission status in patients with rheumatoid arthritis (RA), defined according to the 28-joint count Disease Activity Score (DAS28)-erythrocyte sedimentation rate (ESR) and the Boolean-based new American College of Rheumatology/European League Against Rheumatism remission criteria.

Methods. The subjects were patients with RA who participated in a hospital-based observational cohort. Patients who met the DAS28-ESR remission criteria at their latest visit were invited to participate in our study. The patient groups fulfilling or not fulfilling the Boolean remission criteria were identified and compared with each other with regard to the presence of depression, anxiety, fatigue (0–50), and FM. The relationship between psychosocial factors and Simplified Disease Activity Index (SDAI) remission, which is the index-based definition of remission in RA, was also investigated.

Results. A total of 87 out of 428 patients (20%) with RA met the DAS28-ESR remission criteria and 32 (37%) of these also met the Boolean remission criteria, while 55 (63%) did not. Forty patients were also in SDAI remission. In the Boolean remission group, 2 patients had depression and 2 had anxiety ($p = 0.004$). In the Boolean nonremission group, 19 patients had depression and 13 had anxiety ($p = 0.04$). Continuous scales of anxiety (3.34 ± 3.76 vs 5.83 ± 4.70, $p = 0.012$) and depression (2.18 ± 2.75 vs 4.63 ± 4.10, $p = 0.001$) were also lower in the Boolean remission group in comparison with the nonremission group. Though FM syndrome was detected in only 1 patient of the Boolean remission group and in 7 patients of the Boolean nonremission group ($p = 0.249$), patients' polysymptomatic distress scores of FM in the Boolean remission group were significantly lower than those of the nonremission group (3.12 ± 3.25 vs 6.27 ± 5.19, $p = 0.001$). The mean fatigue scores were 9.5 ± 10.6 in the Boolean remission group and 16.8 ± 12.8 in the Boolean nonremission group ($p = 0.006$). In multivariate analysis, patient's global assessment (PtGA) and depression were found as the independent discriminators of Boolean-based definition. Similar relationships were also observed between psychosocial factors and SDAI remission.

Conclusion. In patients with RA who do not fulfill the Boolean remission criteria, to avoid overtreatment, assessment of anxiety, fatigue, FM, and especially depression must be considered if PtGA scores and disease activity variables are significantly different. (First Release Aug 1 2014; J Rheumatol 2014;41:1755–60; doi:10.3899/jrheum.131171)

Key Indexing Terms:

RHEUMATOID ARTHRITIS | REMISSION | DEPRESSION
ANXIETY | FATIGUE | FIBROMYALGIA

Clinical remission has been accepted as the ultimate target of treatment in patients with rheumatoid arthritis (RA)[1]. However, as there is no "gold standard" measure for remission; it is defined by several criteria to date[2]. In clinical practice, the composite indices are the techniques most widely used to assess remission, such as the disease activity score (DAS) and its derivative, more commonly used form of 28-joint count (DAS28)[3]. However, the validity of DAS28 for evaluating remission has been a matter of debate and DAS28 has been shown to allow for substantial residual disease activity in various studies[4,5,6]. From this point of view, the Boolean-based American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) criteria for remission were developed in 2011 to provide a uniform and clinically meaningful definition of remission in RA[7]. Boolean-based definition of remission criteria requires the number of swollen joint count (SJC) and tender joint count (TJC) to be ≤ 1, the value of C-reactive protein (CRP) to be ≤ 1 mg/dl, and the patient's global assessment (PtGA) to be ≤ 1/10.

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Simplified Disease Activity Index (SDAI), which provides the index-based definition of remission in RA clinical trials, is also produced by the ACR/EULAR Committee. SDAI is composed of TJC, SJC, CRP (mg/dl), PtGA, and physician's global assessment (PGA), and a patient with RA is defined as in remission when SDAI score is ≤ 3.3. Although the new remission criteria were developed and assessed using data from randomized clinical trials, observational studies have shown that the major factor for failing Boolean remission criteria is the PtGA, which often remains ≥ 1[8]. Further, an influence of patient-derived noninflammatory factors [fatigue, fibromyalgia (FM), etc.] on disease activity indices has been observed in several studies[8].

The PtGA is a criterion involved in all 3 indices: the DAS28, the SDAI, and the Boolean criteria. DAS28 is calculated according to a formula that requires multiplying PtGA by 0.014. A patient with no tender or swollen joints and an erythrocyte sedimentation rate (ESR) at ≤ 5 mm/h will still be in DAS28 remission whatever the PtGA is, even if it is 10. SDAI, the index-based definition of remission, is a summative score, and other variables of index can compensate slight elevations of PtGA[9]. However, in Boolean remission, PtGA must be ≤ 1 as the other variables of definition. A study by Aletaha, *et al* indicated that in remission, the SDAI is more stringent on the PtGA scores than the DAS28. They showed that the SDAI allowed up to a PtGA score of 3 and the DAS28 allowed a maximum of 7 in remission[4].

It has been shown that anxiety and depression in patients with RA increase the rating of disease activity[10]. Further, noninflammatory pain skews the sensitivity and specificity of the PtGA concerning remission[11,12,13]. Khan, *et al* showed that concomitant FM syndrome (FMS) and/or osteoarthritis correlates with higher PtGA in RA patients. On the other hand, patients with RA and without concomitant FM rate their disease activity lower than the patients with concomitant FM[14].

The aim of our cross-sectional study was to identify patients with RA with DAS28-ESR remission, and to compare the patients who were in the Boolean remission to those who did not meet the Boolean-based remission criteria with regard to the presence of FM, depression, anxiety, and fatigue.

MATERIALS AND METHODS

The subjects were 428 patients with RA who had participated in our hospital-based observational study since 2002. Complete medical information had been collected biannually, including TJC and SJC, visual analog scale (VAS) scores for the PGA and PtGA, VAS pain (on 10-cm analog scales), Health Assessment Questionnaire scores, and laboratory data. Patients who met the DAS28-ESR criteria for remission (< 2.6) at their latest visit were included in our study and were divided into 2 groups: patients in remission and patients not in remission according to Boolean-based criteria. These 2 groups were compared with each other with regard to depression, FM, fatigue, and anxiety. Multivariate binary logistic regression analysis was used to determine independent predictors of Boolean remission in RA. The independent variables of the multivariate model were determined according to the results of univariate analysis. The variables that were statistically significantly related to Boolean remission ($p \leq 0.05$) in univariate analyses were included in the regression analysis.

The published ACR 2010 diagnostic FM criteria were used to diagnose FM, which is given as a polysymptomatic distress score ranging between 0–31. Further, case definition of FM is also made using widespread pain index (WPI) ≥ 7 and symptom severity (SS) scale score ≥ 5 or WPI 3–6 and SS scale score ≥ 9[15,16]. Fatigue was measured by the Multidimensional Assessment of Fatigue (MAF) scale. The MAF scale contains 16 items and measures 4 dimensions of fatigue: severity, distress, effect on activities of daily living, and timing. Each 100 mm VAS was changed into a 10-point numerical rating scale. Scores range from 1 (no fatigue) to 50 (severe fatigue)[17].

The Hospital Anxiety and Depression Scale (HADS) is a self-administered questionnaire with 2 subscales of 7 items each [range 0–21 (greatest dysfunction)], and was used to assess anxiety and depression status. A depression score ≥ 7 is indicative of the presence of depression, and an anxiety score ≥ 10 is indicative of the presence of anxiety[18].

We also evaluated the relationship between SDAI and scores of FM, depression, anxiety, and MAF.

As a suggested discriminator between DAS28 and Boolean remission, the relationship between PtGA with core variables and psychosocial factors was evaluated.

Our study was approved by the Marmara University School of Medicine Ethics Committee for Clinical and Laboratory Research, and all participants gave written informed consent.

Demographic and clinical variables were summarized using means or medians with SD for continuous data or proportions, and counts as categorical data for each group. Comparisons of each group were performed using the Student's t test or Mann-Whitney U test for continuous variables, and the chi-square test for categorical variables. In 2×2 analysis, if the numbers are < 5 in any cell, Fisher's exact test has been used. The relationships of continuous variables were also investigated with Pearson's correlation coefficient. Multivariate binary logistic regression model was used to search for the independent variables of Boolean remission in RA. Statistical analyses were performed by using the Software Statistical Package Sciences (SPSS) for Windows version 16.0.

RESULTS

Out of the 428 patients with RA, 87 (20%) fulfilled the DAS28-ESR remission criteria. The mean age of these 87 patients was 50.5 ± 1.2 years and 66% were women (Table 1). Thirty-two of the patients (37%) in DAS28-ESR remission were also in Boolean remission, while 55 (63%) did not meet the Boolean remission criteria. The demographic and disease-related features of these patients are summarized in Table 1. PtGA, PGA, and pain scores were higher in the Boolean nonremission patient group.

The patients in Boolean remission were compared with the non-Boolean remission cases in regard to depression, anxiety, FM, and fatigue. HADS scores in 2 patients (2.6%) in the Boolean remission group indicated depression and 2 indicated anxiety; while the numbers were 19 (35%) regarding depression and 13 (24%) regarding anxiety in the nonremission group ($p = 0.004$ and $p = 0.04$, respectively). Further, both continuous scales of anxiety (3.34 ± 3.76 vs 5.83 ± 4.70, $p = 0.012$) and depression (2.18 ± 2.75 vs 4.63 ± 4.10, $p = 0.001$) were lower in the Boolean remission group in comparison with the nonremission group. FM was

Table 1. Demographic and disease-related variables of patients.

	DAS28-ESR Remission, n = 87	Boolean Remission, n = 32	Boolean Nonremission, n = 55	p*
Female, n (%)	57 (66)	22 (68.8)	35 (63.6)	0.62
Age, yrs, mean ± SD	50.52 ± 1.23	50.93 ± 1.32	50.29 ± 1.18	0.81
RA duration, yrs, mean ± SD	11.06 ± 7.93	11.40 ± 8.09	10.87 ± 7.9	0.76
HAQ, mean ± SD	0.33 ± 0.43	0.24 ± 0.52	0.39 ± 0.36	0.141
TJC28, mean ± SD	0 ± 0.5	0 ± 0.2	0 ± 0.6	0.233
SJC28, mean ± SD	0 ± 0.9	0 ± 0.3	0 ± 1.1	0.807
ESR, mm/h, mean ± SD	13.95 ± 8.11	15.37 ± 8.32	13.07 ± 7.87	0.201
Anti-CCP positivity, n (%)	46 (52.7)	22 (66.8)	26 (47.3)	0.05
RF positivity, n (%)	58 (66.7)	23 (71.9)	35 (63.6)	0.432
VAS pain, mean ± SD	2.04 ± 1.94	0.56 ± 0.94	2.9 ± 1.85	0.000
PtGA, mean ± SD	1.93 ± 1.80	0.46 ± 0.84	2.79 ± 1.65	0.000
PGA, mean ± SD	0.85 ± 0.82	0.53 ± 0.71	1.03 ± 0.83	0.005
Steroid, n (%)[a]	33 (26.4)	8 (25)	25 (45.5)	0.05
DMARD, n (%)[a]	83 (95.4)	30 (93.8)	54 (98.2)	0.275
DMARD1, n (%)[a]	69 (79.3)	25 (78.1)	45 (81.8)	0.675
DMARD2, n (%)[a]	48 (55.2)	15 (46.9)	33 (60)	0.235
Biologic, n (%)[a]	33 (37.9)	9 (28.1)	14 (25.5)	0.785

[a] Current treatment; *remission vs nonremission. DAS28: 28-joint count Disease Activity Score; ESR: erythrocyte sedimentation rate; RA: rheumatoid arthritis; HAQ: Health Assessment Questionnaire; TJC28: 28-joint tender joint count; SJC28: 28-joint swollen joint count; anti-CCP: anticyclic citrullinated peptide antibodies; RF: rheumatoid factor; VAS: visual analog scale; PtGA: patient's global assessment; PGA: physician's global assessment; DMARD: disease-modifying antirheumatic drug; DMARD1: methotrexate, leflunomide; DMARD2: sulfasalazine, hydroxychloroquine.

detected only in 1 patient in the Boolean remission group and in 7 patients in the Boolean nonremission group (p = 0.249); the patients' polysymptomatic distress score of FM in the Boolean remission group were significantly lower than the nonremission group (3.12 ± 3.25 vs 6.27 ± 5.19, p = 0.001). Mean MAF scores were 9.5 ± 10.6 in the Boolean remission group and 16.8 ± 12.8 in the Boolean nonremission group (p = 0.006; Table 2).

Forty of the patients (46%) in DAS28-ESR remission were also in SDAI remission, while 47 (54%) did not meet the SDAI remission criteria. Similarly, we observed that patients in SDAI remission also had lower scores of FM, HADS, and MAF than the patients not in SDAI remission (Table 3).

In multivariate analysis, Boolean remission was recorded as dependent and age, sex, pain, PGA, PtGA, depression, anxiety, and MAF scores were recorded as independent variables. We found that among all variables, PtGA (p < 0.0001) and depression scores (p = 0.020) were the strongest predictors of not being in Boolean remission (Table 4).

The involvement of foot and ankle joints were also evaluated in both patients with Boolean remission and in the Boolean nonremission group, and no difference was observed (3/32 vs 2/55, p = 0.352).

Since the PtGA was pointed out as a major factor for failing Boolean remission criteria[8], we also investigated the relationship between disease variables and psychosocial factors. There was an excellent correlation between pain and PtGA (r = 0.956, p < 0.0001), while a fair-poor relationship was observed between PtGA and FM (r = 0.360, p = 0.001), MAF (r = 0.309, p = 0.004), anxiety (r = 0.224, p = 0.037), depression (r = 0.189, p = 0.08), and PGA (r = 0.216, p = 0.045). Similarly, we observed a fair to poor correlation between VAS pain and FM (r = 0.369, p < 0.0001), MAF (r = 0.374, p < 0.0001), anxiety (r = 0.275, p = 0.010), and depression (r = 0.219, p = 0.041). On the other hand, while TJC (r = 0.052, p = 0.630) and SJC (r = 0.083, p = 0.447) were not correlated with PtGA, there was a fair correlation between PGA with tender joints (r = 0.210, p = 0.054) and swollen joints (r = 0.275, p = 0.01). If all of the patients in our study have PtGA ≤ 1, 35 more patients would have been

Table 2. Noninflammatory pain sources of patients in remission and nonremission according to Boolean criteria.

	DAS28-ESR Remission, n = 87	Boolean Remission, n = 32	Boolean Nonremission, n = 55	p*
FM, mean ± SD	5.11 ± 4.8	3.12 ± 3.25	6.27 ± 5.19	0.001
Depression score, mean ± SD	3.73 ± 3.83	2.18 ± 2.75	4.63 ± 4.10	0.001
Anxiety score, mean ± SD	4.91 ± 4.52	3.34 ± 3.76	5.83 ± 4.70	0.012
MAF score, mean ± SD	14.1 ± 1.2	9.5 ± 10.6	16.8 ± 12.8	0.006

*remission vs nonremission. DAS28: 28-joint count Disease Activity Score; ESR: erythrocyte sedimentation rate; FM: fibromyalgia (new criteria; continuous scale); MAF: Multidimensional Assessment of Fatigue.

Table 3. Noninflammatory pain sources of patients in remission and nonremission according to SDAI criteria.

	DAS28-ESR Remission, n = 87	SDAI Remission, n = 40	SDAI Nonremission, n = 47	p*
FM, mean ± SD	5.11 ± 4.8	3.4 ± 3.46	6.57 ± 5.31	0.001
Depression score, mean ± SD	3.73 ± 3.83	2.8 ± 3.01	4.53 ± 4.28	0.03
Anxiety score, mean ± SD	4.91 ± 4.52	3.8 ± 4.04	5.87 ± 4.72	0.032
MAF score, mean ± SD	14.1 ± 1.2	10.71 ± 10.25	16.91 ± 12.88	0.016

* remission vs nonremission. DAS28: 28-joint count Disease Activity Score; ESR: erythrocyte sedimentation rate; SDAI: Simplified Disease Activity Index; FM: fibromyalgia (new criteria; continuous scale); MAF: Multidimensional Assessment of Fatigue.

Table 4. Binary logistic regression model of independent predictors for Boolean remission in RA.

Predictor Variable	B	OR (95% CI)	p
Depression score	0.225	1.3 (1.1–1.5)	0.019
PtGA	1.351	3.9 (2.1–7.1)	< 0.001

RA: rheumatoid arthritis; B: β value; PtGA: patient's global assessment.

classified as in Boolean remission and 21 patients would have been added to the SDAI remission group.

DISCUSSION

In our study, we showed that about two-thirds of patients with RA who achieved DAS28-ESR remission failed to meet the Boolean remission criteria. When we analyzed the influence of patients' mood, fatigue, and FM on remission, we observed that patients in Boolean remission were less affected by depression, anxiety, FM, and fatigue. Similar results have been observed when we analyzed the effects of non-RA polysymptomatic distress on the classification of patients in remission according to SDAI. Among the patients in DAS28-ESR remission, patients achieving Boolean remission had lower PtGA, PGA, and pain scores than did the patients in Boolean nonremission. Further, in multivariate analyses, the strongest independent predictors of Boolean remission were found to be PtGA and depression.

PtGA was previously proposed as a major factor for failing Boolean remission criteria[8,9]. Similarly, in our study, we found that PtGA was one of the strongest independent predictors of Boolean remission. When we analyzed the effect of core variables and psychosocial factors on the PtGA score, there was an excellent correlation between VAS pain and PtGA, while TJC and SJC were not correlated. Khan, *et al* found that pain was the single most important independent determinant of PtGA, followed by fatigue[14]. Studenic, *et al* also showed that pain is the most important determinant of the patient's perception of RA disease activity, while for the physician, it is mostly the joint swelling[19]. In our current study, we observed a comparable result with Studenic, *et al*'s findings in terms of relationship between PGA and SJC. Masri, *et al* indicated that the PtGA question used in clinical trials and in ACR/EULAR recommendations assessed not only RA activity, but also RA severity. Further, they found that the use of a "severity scale" instead of an "activity scale" increases the likelihood of an abnormal (> 1) PtGA score[8]. A rewording of the PtGA question should be investigated to see whether that improves the functioning of the global question as a measure of disease activity in RA[8,9].

It was shown previously that patients and physicians rate RA activity differently; we determined a weak correlation between PtGA and PGA[14]. In addition, the psychosocial factors, which were investigated in our study, were correlated fair to poor with both pain and PtGA. If the PtGA had been scored ≤ 1 by all patients in our study, there would be 35 and 21 more patients with RA in Boolean and SDAI remission, respectively. With these results, we also confirmed that the SDAI remission was more tolerant to isolated PtGA elevations, which was previously proposed by Studenic, *et al*[9]. On the other hand, PtGA as a measure of the ACR/EULAR Boolean-based definition of remission in RA is often not achieved despite detection of minimal disease activity or absence of inflammation. The discriminative ability of PtGA between the fulfillment of the TJC28 joints, SJC28 joints, and CRP remission criteria versus nonfulfillment of all 3 remaining criteria (at least one > 1) was analyzed by the receiver-operation characteristic curve, and PtGA distinguished the 2 groups with moderate accuracy. Further, the cutoff point of PtGA in differentiating the 2 conditions was set at 2 (74% sensitivity and 65% specificity)[13]. Thus, Boolean remission criteria may categorize a significant percentage of patients with clinically inactive disease as not in remission[20]. In light of all this information, when we apply Boolean criteria, if the score of PtGA is unfavorable with disease activity measurements, evaluation of psychosocial factors would be appropriate, and SDAI might be also preferable in these patients. Further studies are needed to determine whether the PtGA criterion is sufficient or should be modified to be more specific for disease activity.

Depression worsens symptom reporting in RA[21]. Barton, *et al* reported that PtGA increases in line with depressive symptoms while PGA remains constant[10]. Further, a study on the assessment of physical function in RA showed that patients with less pain and fewer depressive symptoms had

concordant assessments with their physicians[22]. In our study, depression was found to be an independent predictor of Boolean remission and this indicated that the presence of depression in patients with RA was an important obstacle when trying to reach Boolean remission. In concordance with our result, a study by Hider, *et al* showed that patients with persistent depression tended not to respond well to anti-tumor necrosis factor (TNF)-α agents with smaller reductions in DAS28. In addition, recognition and appropriate management of depression have been suggested to improve anti-TNF effectiveness[23].

A study by Kekow, *et al* explored the role of anxiety/depression on patient-reported outcomes. Authors concluded that the presence of anxiety even without depressive symptoms reduced improvement in patient-reported outcomes[24]. Similarly, we observed 4 times more anxious patients in the nonremission group compared to the Boolean remission group. Further, we observed significant difference in the mean MAF scores between Boolean remission and nonremission groups. Although high in patients with RA, fatigue was a highly prevalent symptom in noninflammatory conditions as well and was associated with perception of a more severe disease[10]. Moreover, no association of inflammatory process with fatigue was determined in the multivariate analysis by Wolfe, *et al*[25]. A study from the United Kingdom also found that fatigue was mainly linked to pain and depression while the association with disease activity was secondary[26]. In the study by Masri, *et al,* fatigue was found to be an important and contributing factor on the patient symptom severity score[8].

Studies have also shown that concomitant FM may be the reason for patients rating disease activity higher than did their physicians. FM was more prevalent among patients with RA than in the general population, and patients with RA and FM rate their disease activity higher than the other RA cases[27]. In our study, FM score has been found significantly lower in patients with Boolean remission. A higher number of RA cases with concomitant FM were determined among the Boolean nonremission group compared to the Boolean remission group.

It was shown that foot involvement in patients with DAS28 remission might be the weakness of this criteria. On the other hand, similar radiological and functional outcome predictions were recently determined between the remission definitions with 28-joint counts versus 38-joint counts that included the 10 metatarsophalangeal joints[28]. In Boolean remission criteria, evaluation of feet and ankles is preferable as a result of the possibility of missing actively involved joints in use of a 28-joint count. In our study, we evaluated our patients with 28 joints, but the patient records were evaluated retrospectively for feet involvement. No difference was determined between Boolean remission and nonremission groups in terms of foot and ankle joint involvement.

Our study has some limitations. First, in a cross-sectional study, we were unable to assess the effect of the selected variables on remission over time. Secondly, we used patient self-reported questionnaires for the evaluation of depression and anxiety instead of clinical diagnostic examination. However, questionnaires are a practical tool for screening depression and anxiety in a population, and are shown to be reliable[29].

Among patients fulfilling DAS28-ESR remission criteria but not Boolean remission criteria, the prevalence of depression, anxiety, and fatigue is increased. These measures, particularly PtGA and depression, are the likely contributors for the loss of concordance between DAS28-ESR and Boolean remission criteria.

A better cutoff point for PtGA, as proposed by Vermeer, *et al*, might increase the discriminatory power of the ACR/EULAR Boolean-based remission criteria[13]. In patients with RA who do not fulfill the Boolean remission criteria, assessment of anxiety, fatigue, FM, and especially depression must be considered as the separate pain sources from objective RA activity to avoid the probability of improperly targeted treatment.

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