Journal of Rheumatic Diseases
Vol. 21, No. 1, February, 2014
http://dx.doi.org/10.4078/jrd.2014.21.1.20

□ Original Article □

Clinical Characteristics of Patients with Rheumatoid Arthritis Who have Sustained High Erythrocyte Sedimentation Rates after Clinical Remission

Bon San Koo, Seokchan Hong, You Jae Kim, Yong-Gil Kim, Chang-Keun Lee, Bin Yoo

Division of Rheumatology, Department of Internal Medicine,
University of Ulsan College of Medicine, Asan Medical Center, Seoul, Korea

Objective. **The aim of this study is to determine the clinical characteristics of patients with rheumatoid arthritis (RA) sustaining high erythrocyte sedimentation rate (ESR) despite clinical remission.**

Methods. **This cross-sectional study involved 91 patients, who visited a tertiary medical center. Patients underwent laboratory tests and a physical examination by a rheumatologist. The disease activity score (DAS) was calculated and patients who were in remission (defined as DAS28-CRP <2.6) were selected. Patients were divided into two groups: those with high and low ESRs (≥40 and <40 mm/hr, respectively).**

Results. **DAS 28-CRP scores revealed that 61 of the 91 patients were in remission. Of these 61 patients, 15 and 46 were allocated to the high and low ESR groups, respectively. Compared to the low ESR group, the high ESR group had a longer disease duration (99.2±60.2 vs. 59.1±48.9 months), significantly higher white blood cell counts, and CRP levels, total modified Sharp radiographic joint scores, and erosion scores, as well as significantly lower hemoglobin, albumin and alanine aminotransferase levels.**

Conclusion. **Patients who have high ESRs despite their remission status may show progressive radiographic change. In such patients, additional treatments that decreases the inflammation and prevents radiological progression should be considered.**

Key Words. **Rheumatoid arthritis, Inflammation, Remission**

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease that causes joint destruction and functional disability (1). Although recent advances in new therapeutic strategies and the development of biological agents have improved the prognosis of RA, a subset of patients do not respond to these biological agents (2).

When dealing with patients with RA in both daily clinical practice and clinical trials, it is important to assess their disease activity and treatment response properly and accurately. The disease activity score (DAS), which combines information about swollen joints, tender joints, the acute phase response, and general health, is useful for this purpose (3). Laboratory markers such as the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels have also been used as markers of inflammation (4,5). ESR is determined by a common hematological test and is the rate with which red blood cells sediment over a period of one hour. While it is a useful marker for evaluating disease activity, it is a non-specific measure of inflammation. The ESR changes slowly in response to inflammation and is increased in pregnancy, anemia, and old age and is decreased in polycythemia, hereditary spherocytosis, and congestive heart failure. CRP is synthesized by the liver and increases rapidly in response to inflammation. It has recently become the preferred serological marker for evaluating acute disease activity in RA. The DAS of 28 joints (DAS28) that is based on ESR and CRP (DAS28-ESR and DAS28-CRP, respectively) can also be used to evaluate disease activity status. Two reports found that DAS28-CRP is a more useful measure of disease activity than DAS28-ESR (6,7).

Some patients with RA continuously show high ESRs despite being in clinical remission, having normal CRP levels, and

<Received : October 30, 2013, Revised : December 16, 2013, Accepted : January 3, 2014>
Corresponding to : Bin Yoo, Division of Rheumatology, Department of Internal Medicine, University of Ulsan College of Medicine, Asan Medical Center, 388-1, Pungnap-dong, Songpa-gu, Seoul 138-736, Korea. E-mail : byoo@amc.seoul.kr

pISSN: 2093-940X, eISSN: 2233-4718

lacking known causes of high ESRs such as hematological disease or pregnancy. To determine factors that affect high ESRs in such patients, the present cross-sectional study was performed using DAS28-CRP.

Materials and Methods

This cross-sectional study was performed in a rheumatology outpatient clinic at a tertiary care center between September 2011 and February 2012. The study was approved by the institutional review board of the Asan Medical Center. All consecutive subjects who visited the clinic during the 5 month study period and fulfilled the 1987 American College of Rheumatology criteria for RA (8) were considered for enrollment. Patients were excluded if they had acute infection (such as rhinitis, laryngopharyngitis, or pneumonia) or their RA was combined with other autoimmune diseases. As a result, 91 patients were enrolled. During their visit to the clinic, the clinical and demographic information and laboratory findings of each patient were recorded. Radiographs of both hands were also obtained.

Disease activity was assessed by calculating the DAS28-ESR and DAS28-CRP, which were based on the number of swollen and tender joints, the ESR, the CRP, and the patient's global assessment of health, which was measured by using a visual analog scale (VAS, 1～100 mm). Other disease activity indices, namely, the Simplified Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI), were also calculated. Functional status was measured by using the modified Health Assessment Questionnaire (HAQ).

To determine the radiological findings, radiographs of the hands (standard film in postero-anterior projection) were obtained during the visit of each patient and then interpreted by an experienced radiologist who was blinded to treatment assignment. Radiographic damage was assessed by using the modified Sharp score (9) but only the hands were included in this study.

If the DAS28-CRP score was <2.6, the patient was deemed to be in remission. The patients who were in remission were divided according to their ESR into those with high and low ESRs (≥ 40 and <40 mm/hr, respectively). The two groups were then compared in terms of clinical characteristics, laboratory findings, and the radiological findings of both hands.

To compare the two groups in terms of their baseline characteristics, the Mann-Whitney test, the chi-square test, or the logistic regression test were used. A p-value of <0.05 was considered to indicate statistical significance. All statistical analyses were performed by using Predictive Analytics Software 17.0 (SPSS, Chicago, IL, USA).

Results

In total, 91 patients were included in the study. The DAS28-CRP scores revealed that 61 of these patients were in remission. Of these 61 patients, 15 and 46 were allocated to the high and low ESR groups, respectively. Table 1 summarizes the clinical characteristics of these two groups. On average, the high and low ESR groups were 60.1±10.8 and

Table 1. Baseline characteristics, disease activity index, and radiological findings of patients in remission who were divided into high and low erythrocyte sedimentation rate groups

	Low ESR (N=46)	High ESR (N=15)	p-value
Age (years)*	60.1±10.8	62.7±9.2	NS
M:F ratio	12:34	4:11	NS
BMI (kg/m^2)	23.5±3.4	23.30±3.02	NS
Disease duration (months)	59.1±49	99.2±60.2	0.023
Seropositive RA	87%	100%	NS
Swelling joint count	0.2±0.6	0.4±0.8	NS
Tenderness joint count	0.3±0.6	0.4±0.6	NS
DAS28-ESR	2.3±0.6	3.4±0.4	0.000
DAS28-CRP	1.7±0.4	2.0±0.5	0.023
SDAI	2.7±2.6	3.4±2.6	NS
CDAI	2.4±2.6	2.6±2.3	NS
HAQ	0.3±0.4	0.3±0.4	NS
Erosion score, 0～160 scale*	4.2±7.5	12.2±11.0	0.005
Joint space narrowing score, 0～120 scale†	5.0±8.6	8.6±10.1	NS
Total modified Sharp score, 0～280 scale†	9.3±15.1	20.7±19.0	0.012

BMI: body mass index, CDAI: Clinical Disease Activity Index, CRP: C-reactive protein, DAS28: 28-joint Disease Activity Index, ESR: erythrocyte sedimentation rate, HAQ: Health Assessment Questionnaire, NS: not significant, RA: rheumatoid arthritis, SDAI: Simplified Disease Activity Index. *The data are shown as mean±SD or n. †The radiographic findings included the hands only.

62.7±9.2 years old, respectively. Females were the dominant gender in both groups. The high ESR group had a significantly longer disease duration (99.2±60.2 months) than the lower ESR group (59.1±49.0 months; p=0.023).

While the two groups did not differ significantly in terms of the SDAI and CDAI disease activity indices, the mean SDAI score of the high ESR group (3.4±2.6) was in the range of low disease activity, unlike that of the low ESR group (2.7±2.6), which was in the range of remission status. In addition, although the DAS28-CRP scores of both groups were in the range of remission status (DAS28-CRP <2.6), as would be expected given that this cutoff was used to identify the patients that were in remission, the high ESR group still had a significantly higher DAS28-CRP score than the low ESR group (2.0±0.5 vs. 1.7±0.4; p=0.023). Moreover, the high ESR group had significantly higher erosion and total modified Sharp scores (12.2±7.5 and 20.7±19.0, respectively) than the low ESR group (4.2±7.5 and 9.3±15.1, respectively; p=0.005 and 0.012, respectively). Erosion and total modified Sharp scores were adjusted for disease duration by which radiologic progression can be affected. Although total modified Sharp scores were not different (p=0.157), erosion scores were significantly different between the two groups (p=0.048). The two groups did not differ in terms of modified HAQ score, physician health assessment, patient pain assessment, or patient global assessment.

Some patients suffered from underlying diseases, including osteoarthritis, osteoporosis, compression fracture, hepatitis, hypertension, dyslipidemia, asthma, interstitial lung disease, chronic obstructive pulmonary disease, heart disease, and a history of tuberculosis and malignancy. However, the two groups did not differ in terms of the frequencies of these underlying diseases (Table 2).

In terms of laboratory findings, compared to the low ESR group, the high ESR group had significantly higher white blood cell counts and CRP levels, and significantly lower hemoglobin, albumin, alanine aminotransferase and protein levels (Table 3). Although all results were in the normal range, these slight differences in inflammatory markers suggested that the two groups differed subtly in terms of disease activity and that inflammation was progressing in the high ESR group.

At the time of their visit, the patients were prescribed with low-dose steroid and disease-modifying antirheumatic drugs such as methotrexate, leflunomide, cyclosporine, and TNF-

Table 2. Underlying diseases of patients in remission who were divided into high and low erythrocyte sedimentation rate groups

	Low ESR (N=46)	High ESR (N=15)	p-value
Osteoarthritis of knee	3	1	NS
Osteoporosis	10	2	NS
Compression fracture	2	0	NS
Hypertension	7	4	NS
Dyslipidemia	3	3	NS
Hepatitis B or C	1	1	NS
Asthma	2	0	NS
Chronic obstructive pulmonary disease	1	1	NS
Interstitial lung disease	3	1	NS
Heart failure	0	1	NS
History of tuberculosis	3	0	NS
History of malignancy	3	0	NS

CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, NS: not significant.

Table 3. Laboratory findings of patients in remission who were divided into high and low erythrocyte sedimentation rate groups

	Low ESR (N=46)	High ESR (N=15)	p-value
White blood cell count ($\times 10^3/\mu L$)*	6.6±2.2	8.4±3.2	0.036
Hemoglobin (g/dL)	12.9±1.3	12.1±1.3	0.046
Platelet count ($\times 10^3/\mu L$)	231.9±57.7	267.7±65.7	NS
ESR (mm/hr)	20.6±12.7	71.1±18.4	0.000
CRP (mg/dL)	0.3±0.3	0.7±0.8	0.001
Aspartate aminotransferase (IU/L)	26.5±7.4	22.6±4.8	NS
Alanine aminotransferase (IU/L)	21.0±8.6	15.4±3.7	0.004
Alkaline aminotransferase (IU/L)	68.8±19.9	78.8±22.7	NS
Bilirubin (mg/dL)	0.8±0.2	0.7±0.2	NS
Creatinine (mg/dL)	0.8±0.2	0.8±0.2	NS
Uric acid (mg/dL)	4.3±1.2	4.3±1.4	NS
Glucose (mg/dL)	98.2±16.1	101.4±29.2	NS
Cholesterol (mg/dL)	176.9±31.0	186.6±35.2	NS
Albumin (g/dL)	4.1±.03	3.9±0.2	0.023
Protein (g/dL)	7.0±0.7	7.3±0.5	0.035

CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, NS: not significant. *The data are shown as mean±SD.

inhibitors. The two groups did not differ significantly in terms of the frequency of use of these agents (data not shown).

Discussion

The present study suggested that patients with high ESR may have progressive radiographic change despite being in remission (as defined by a DAS28-CRP score <2.6). These results, along with laboratory findings including high ESR level, suggest that the inflammation in the high ESR group was ongoing, even though the patients were asymptomatic. Thus, it may be necessary to improve the treatment of these patients so that their high ESR status is corrected, thereby halting the radiological progression.

The present study also suggests that DAS28-CRP may not be suitable for defining remission accurately. Although it correlates well with DAS28-ESR, it may underestimate the disease activity and inappropriately elevate the proportion of patients who are considered to be in remission or to have weak disease activity.

The present study showed that the DAS28-ESR scores of the patients tended to be higher than their DAS28-CRP scores. Indeed, since the DAS28-ESR and CAS28-CRP values are not fully equivalent, Castrejón *et al.* and Inoue *et al.* proposed specific cutoff values of DAS28-CRP that correspond to the DAS28-ESR values for remission and low and high disease activity (6,7). Some rheumatologists have also suggested that DAS28-CRP is an attractive alternative to DAS28-ESR because it is more sensitive to short-term changes in disease activity (10) and because CRP responds faster to variations (7). In the present study, DAS28-CRP seemed to evaluate the disease status more accurately than DAS28-ESR because the DAS28-ESR scores of the patients in the high ESR group were too high relative to the symptoms of these patients. However, the DAS28-CRP scores could not identify the subtly higher inflammatory status of the patients in the high ESR group. A new disease activity index that can overcome these limitations is needed.

Radiographic damage increases throughout the course of RA (11). Moreover, it tends to occur early in the disease course and the progression is most rapid during the first 2 years (12). In our study, we found that the high ESR group had significantly higher erosion score than low ESR group. The disease duration may have contributed to higher erosion score in the high ESR group. However, disease durations of both groups were over 5 years and the erosion score showed a significant difference after adjusting disease duration. Therefore, higher erosion score in high ESR group may be due not only to the disease duration but also to other inflammatory conditions.

In terms of laboratory findings, the patients in the high ESR group had significantly lower alanine aminotransferase levels than the patients in the low ESR group. Alanine aminotransferase activity is the most specific and widely used screening test for the evaluation of hepatic disease. Low alanine aminotransferase levels may indicate a liver disease such as decreased liver function or malnutrition. In particular, since the active form of vitamin B (pyridoxal-5'-phosphate) serves as a coenzyme for transaminases, low alanine aminotransferase activity may be due to malnutrition-induced occult vitamin B6 deficiency (13). In addition, the vitamin B6 status of RA patients appears to associate with disease activity (14, 15). Thus, the lower alanine aminotransferase levels in the high ESR group (compared to the low ESR group) may also be related to their higher levels of chronic inflammation.

Heart failure can also contribute to high ESRs. Maradit-Kremers *et al.* showed that high ESRs associated with heart failure and anemia in patients with RA (16). However, ESR is a non-specific test that can be affected by many factors other than the acute phase response, including age, sex, the size, shape and number of erythrocytes, other plasma constituents (such as serum immunoglobulins and rheumatoid factor), various drugs such as salicylates, and even smoking (4,17). Therefore, it might be difficult to find the cause of high ESR.

The present study had some limitations. First, as mentioned above, ESR is a non-specific inflammatory marker that is affected by many factors such as age, sex, and other comorbidity (5,7,18). Second, the sample size was small. Third, the study is cross-sectional and data of follow-up will provide the information of disease activity.

This study showed that patients who have high ESR despite being in remission may have progressive radiographic change. Additional treatment that decreases inflammation and prevents radiological progression might be considered in these patients.

Summary

Patients with RA who have sustained high ESR despite clinical remission had more radiolgraphic change than low ESR patients. This result showed that high ESR patients with clinical remission may need more RA treatment to decrease inflammation.

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