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Original article

# Acute-phase response, clinical measures and disease activity in ankylosing spondylitis

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**Abstract**

*Objective*: The evaluation of disease activity in ankylosing spondylitis (AS) is sometimes difficult. In this study we assessed acute-phase reactants (APR) and immune response status (humoral and cellular) in active and inactive untreated AS patients categorized according to different activation/remission criteria.
*Methods*: Patients with AS were categorized into three groups as active and inactive according to ASsessment in Ankylosing Spondylitis (ASAS) International Working Group remission/partial remission criteria, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) less than 4 or equal or more than 4 and peripheral joint involvement present or absent. Health Assessment Questionnaire—Spondyloarthropathies (HAQ-S), Daugados Articular Index and Bath Ankylosing Spondylitis Functional Index were performed. Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), immunoglobulin A, G and M, and complements C3 and C4, interferon-gamma, interleukin-4 and alpha-1-antitrypsin (AAT), alpha-2-macroglobulin, ceruloplasmin, haptoglobin, and transferrin were measured. Immunophenotypic analysis by flow cytometry was performed (CD45, CD3, CD4, CD8, $CD4^+/CD8^+$ T cell ratio, CD19, CD16, CD56, CD23, CD25 and CD30 were assayed).
*Results*: Patients with peripheral involvement had higher ESR and CRP levels. According to ASAS criteria patients in remission had significantly lower values of disease activity and functional limitation measures, and AAT was the only APR significantly lower in remission/partial remission group. Lymphocyte subpopulations did not show significant correlation with clinical parameters or APR.
*Conclusions*: Our results showed weak a relation between APR and disease activity in AS; however, APR should not be disregarded in the evaluation of disease and/or response to the treatment, which was supported by the new research on biologic agents infliximab and etanercept in AS. The ASAS remission/partial remission criteria may discriminate patients' clinical activity status and AAT may be a good indicator of disease activity in AS.


*Keywords:* Ankylosing spondylitis; Lymphocyte subtypes; Immunophenotyping; Acute-phase reactant; Alpha-1-antitrypsin; Cytokine; T helper

## 1. Introduction

The evaluation of disease activity in ankylosing spondylitis (AS) is very difficult due to the lack of a comprehensive relationship between laboratory variables (acute-phase reactants), or clinical variables and imaging with disease process [1–4]. ASsessment in Ankylosing Spondylitis (ASAS) International Working Group has defined acute-phase reactants as an extra domain for disease-modifying anti-rheumatic drugs (DMARDs) core sets [5]. In recent studies with some of the non-steroid anti-inflammatory drugs (NSAIDs) and anti-tumor necrosis factor (TNF) therapies, acute-phase reactants have been proposed as an outcome instrument [6,7]. On the other hand, levels of commonly used acute-phase reactants—erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP)—are elevated in only a limited number of patients with AS [3,5,8,9].

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In this study, we investigated whether acute-phase reactants, immune response status (humoral and cellular) and lymphocyte subtypes were related to disease activity. We performed this research by examining the difference in these parameters within subgroups of patients classified according to different activation criteria.

## 2. Methods

Twenty-seven patients fulfilling the modified New York criteria for AS were recruited [10]. Patients were examined by the same researcher after obtaining the written informed consent, and clinical examination and measurements of functional ability and disease activity were carried out. Duration of morning stiffness and peripheral joint involvement was noted. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [11], modified version (spondyloarthropathies) of the Health Assessment Questionnaire (HAQ-S), Daugados Articular Index, and Bath Ankylosing Spondylitis Functional Index were carried out [12–14]. Patient's global assessment of disease activity and pain in the last two days was measured on a 0-100 mm visual analogue scale (VAS-global).

Patients were analyzed in subgroups: first, peripheral joint involvement present or absent, second, active and inactive according to the ASAS remission/partial remission criteria [15], and third, BASDAI score $\geq$4 or less than 4. Peripheral arthritis was defined as presence of at least one swollen joint.

### 2.1. Blood sampling

The collected blood samples were centrifuged and stored frozen at −80 °C for analysis. The serum levels of CRP, immunoglobulins (Ig) A, G and M, and complements $C_3$ and $C_4$, acute-phase proteins alpha-1-antitrypsin (AAT), alpha-2-macroglobulin (A2M), ceruloplasmin (Cp), haptoglobin (Hp), and transferrin (Tf) were determined by a standard turbidometric technique, using Schiappaerelli Biosystems Instrument (Schiappaerelli Biosystems, BV, ENI Diagnostic Division, Woerden, The Netherlands). Erythrocyte sedimentation rate was measured using the Westergreen method.

### 2.2. Immunologic analysis

Blood samples were analyzed within 1 h for immunophenotypic analysis. After the immunophenotypic analysis, percentage of lymphocyte subpopulations cell ratio and $CD4^+$ to $CD8^+$ T cell ratio was calculated.

### 2.3. Cytokine evaluations

Interferon-gamma (IFN-$\gamma$) and interleukin (IL)-4 levels were studied by ELISA using cytokine kits (Biosource, CA, USA). Results were expressed in pg/ml.

### 2.4. Statistical analysis

Comparisons between subgroups were performed using a non-parametric test (Mann–Whitney $U$ test). Spearman rank correlation was used to examine relationship between parameters. A two-tailed $p$ value of less than 0.05 was considered statistically significant.

## 3. Results

Patients had mean disease duration of 11.4 ± 8.4 years, five patients were newly diagnosed and all were drug free (no current usage of DMARDs or regular full dose NSAIDs except analgesics and irregular low-dose NSAIDs) at least for past 2 months. Twenty-one of the patients were male and six were female. Comparison of the parameters between patient subgroups is shown in Table 1. Patients with peripheral joint involvement had significantly higher ESR and CRP levels. According to ASAS criteria, patients in remission had significantly lower values of disease activity and functional limitation measures, and AAT was the only parameter of acute-phase response which was significantly lower in remission/partial remission group.

### 3.1. Relationship between biological and clinical parameters

Functional scores (BASFI, HAQ-S, DAI), BASDAI and patient's global assessment of disease activity (VAS) correlated with each other to different degrees ($r = 0.51$, $p = 0.007$ to $r = 0.83$ $p < 0.0001$). Alpha-1-antitrypsin was the only acute-phase response parameter correlated with these clinical scores (BASDAI $r = 0.54$, $p = 0.005$; VAS-global $r = 0.48$, $p = 0.015$; BASFI $r = 0.46$, $p = 0.022$; HAQ-S $r = 0.41$, $p = 0.043$). Total IgA levels correlated with BASDAI ($r = 0.44$, $p = 0.02$), BASFI ($r = 0.39$, $p = 0.046$) and HAQ-S ($r = 0.38$, $p = 0.046$). Distribution of lymphocyte subpopulations did not show significant correlation with clinical parameters or acute-phase reactants.

## 4. Discussion

In rheumatology practice, the measurement of acute-phase proteins can be a powerful clinical assessment tool for detecting, diagnosing, and monitoring inflammatory diseases. In AS only 50–70% of patients with active disease have an increased level of CRP and a raised ESR, and measurement of the levels of these acute-phase reactants has been suggested to have limited value in determining disease activity [3,4,8,9,16]. Patients with AS may only have axial involvement in varied severity but may also have peripheral joint involvement and extraspinal manifestations as enthesitis, uveitis and inflammation of gastrointestinal tract. This diverse clinical symptomatology makes evaluation of disease activity in AS difficult and still there is no "gold standard" for disease activity in AS.

In this study, we showed that CRP and ESR levels changed according to the presence of peripheral joint involvement, and