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THE ROLE OF ACUTE-PHASE REACTANTS IN PATIENTS WITH RHEUMATOID ARTHRITIS

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Abstract

Radiographic evaluation is still the most important tool for assessing structural damage to joints and the skeleton. The progression of the radiographic damage to the joints in the hands and feet is an important and objective variable for assessing the disease's activity as well as predicting the outcomes of treatment.

In this study, radiographic assessment of the hand joints, acute phase reactants (ESR and CRP), and ACPA autoantibodies were used to assess the disease activity in RA patients treated with methotrexate therapy. Their roles as prognostic indicators of disease outcome were also examined.

The serum of 70 participants (35 in the untreated RA group and 35 in the control group) was tested using the ELISA method DIA-STATTM Anti-CCP (Axis-Shield Diagnostics). In the same participants, RF was determined using the agglutination test (Latex RF test). Patients were treated with methotrexate at an average dose of 10 mg once weekly. For clinical evaluation of disease activity in every patient's radiographic index (RI), sedimentation, CRP, and RF were analyzed at certain time intervals (baseline, after 6, 9, and 12 months).

The dynamic changes in the mean values of the RI score, sedimentation, CRP, and RF were used to assess RA. RI showed an increased radiographic progression of hand joint damage at time intervals between baseline and 9 months ($p = 0.0167$) and between baseline and 12 months ($p = 0.0089$). Statistical analysis showed statistically significant differences among the mean values of ESR in the four time intervals ($p = 0.00002$). Also, statistically significant differences were shown in the mean values of CRP in the four time intervals ($p = 0.0488$) (standard deviations showed great variations). At baseline, progression was seen in 3 (10%) patients, after 6 months in 13, and after 9 and 12 months RI progression was seen in 15. It was also observed that most patients had increased values of RF and CRP.

Despite the methotrexate therapy, progression of the radiographic damage followed, especially in patients with increased values of sedimentation, CRP, and RF with persistence of previous hand joint erosions, as predictors of the aggressive course of disease.

Keywords: Rheumatoid arthritis, Rheumatoid factor, Reactants of the acute phase.

Introduction

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), as reactants of the acute phase, serve as sensitive tools for objectifying and measuring the immune-mediated inflammatory response in rheumatoid arthritis (RA) while indirectly reflecting synovitis. Simultaneous tests, particularly for the reversible inflammatory variables ESR, CRP, and rheumatoid factor (RF), in combination with clinical and radiographic indicators of inflammatory synovitis, are recommended.

They enable it to determine which of these parameters appears to be most closely related to the other articular and radiographic markers of disease activity. Given the variable course of activity of the disease, serial measurements of ESR and CRP are the most suitable for a reliable assessment of RA [1].

The study's findings are paradoxical in terms of joint damage and inflammatory synovitis as represented by acute phase reactants.

Although acute phase reactants and radiographic progression are correlated, some studies suggest that erosion can still occur even when joint inflammation is suppressed [2].

On the other hand, ACPAs (anti-citrullinated protein antibodies autoantibodies) react with linear synthetic peptides that contain the unusual amino acid citrulline. They are present in 76% of RA patients. IgG class antibodies, with a relatively high affinity, predominate in RA patients.

The ELISA test based on these cyclic citrullinated peptides (CCP) has superior characteristics for RA detection, with varying degrees of sensitivity and specificity [2]. Depending on the population, the anti-CCP test's sensitivity ranges between 64% and 74%, while its specificity ranges between 90% and 99%.

The purpose of this study was to determine the disease activity in RA patients receiving methotrexate treatment by evaluating the hand joints radiographically, acute phase reactants (ESR and CRP), and ACPA autoantibodies, analysing their function as prognostic indicators of the course of the disease.

Sample description

The revised diagnostic criteria (RDC) for RA classification established by the American Association for Rheumatism (ARA) in 1987 were used to diagnose RA in study participants.

For a patient to be placed in the RA group, they should meet at least four of the suggested seven criteria. The duration of the fourth criteria should be at least six weeks. 35 RA patients (25 women and 10 men) and 35 other subjects (20 women and 15 men) who were healthy controls were all included in the study. Four time points were used for the assessments: the baseline (0 time), after 6, 9, and 12 months.

Along with non-steroidal anti-rheumatic drug therapy, immunomodulatory therapy using methotrexate (average dose of 10 mg once weekly) was suggested for the first time. The free interval from the time of entry into the study to the occurrence of the first erosion was measured in order to track the preventative effect of methotrexate therapy simultaneously.

Radiographic evaluation of the disease progression

Radiographic index (RI) as a parameter was analyzed in every patient, serving as a parameter for radiographic assessment of disease progression in the specified time intervals. With this rating were evaluated 29 joint surfaces for bone erosions and destructions and 27 joints for joint space narrowing on the hand and wrist joints.

The sum of the scores for erosions and the sum of the scores for joint space narrowing represents the total score (TS) of joint destruction. In total, 14 finger joints (5 metacarpal, 8 carpal, radio-carpal, and radio-ulnar) were evaluated. Each joint was evaluated for erosions, scoring from 0 to 5. The sum of the individually evaluated joints for erosions and destruction gives the cumulative score for joint damage in the hands and wrists.

On the other hand, the score for joint space narrowing was evaluated at 27 joints on each hand and wrist (14 joints on the fingers, 5 carpometacarpal, carpal, radio-carpal, and radio-ulnar joints). The joint space narrowing was scored on a scale of 0 to 4. The sum of the individual scores gives the cumulative score for joint space narrowing.

Clinical assessment of disease activity

An expert in the field of the subspecialty performed the clinical evaluation. The Disease Activity Score (DAS) 28 index was also used to assess the disease activity.

This index engages a mathematical formula to produce a singular composite quantitative score that includes morning stiffness, palpatory pain joints (maximum number 28), swollen joints (maximum number 28), Westergren ESR, and the patient's overall assessment of disease activity (0-100 mm VAS) (minutes). The DAS-28 index ranges from 0 to 10, and a score of 3.2 or less indicates low disease activation.

Inclusion criteria

- Patients with RA
- Age range: 18 to 65 years
- Newly diagnosed patients
- RA untreated patients

Exclusion criteria

- A history of autoimmune diseases, spleen, thyroid, liver, kidney, hematological, cardiovascular, neurological, or lung conditions
- Under 18 years old
- The existence of diseases like diabetes mellitus, severe infections, cancer, and febrile conditions
- The existence of diseases like vasculitis, mixed connective tissue disease, SLE, uric arthritis, and urine infections
- A history of blood transfusions and obesity
- Identification of baseline hyperglycemiaor elevated degradation products such as serum and urine creatinine, serum urea, arterial hypertension, and CBC disorder

Ethical considerations

All participants voluntarily participated in the study; hence, the ethical criteria for conducting this study were fulfilled.

Laboratory evaluation

For clinical evaluation of the disease, it was necessary to consider the following laboratory variables: complete blood count (CBC), differential blood count, reactants of the acute phase, ACPA antibodies, C-reactive protein (CRP), rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), alkaline phosphatase (AP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatine kinase (CK), lactate dehydrogenase (LDH), serum urea, and creatinine.

CRP was determined with the agglutination test (Latex CRP test) (BioSystem S.A. reagents& instruments Costa Brava 30, Barcelona (Spain). Reference serum values are <6 mg/L.

RF was determined with the agglutination test (Latex CRP test) (BioSystem S.A. reagents& instruments Costa Brava 30, Barcelona (Spain). Reference serum values are <30 IU/ml RF.

For the determination of ESR, the Westergren quantitative method was used, and normal values for men were 7-8 mm and for women, 11-16 mm.

ACPA antibodies were detected by the manufacturer, DIA-STAT™ Anti – CCP (Axis – Shield Diagnostics). The test is a semi-quantitative/qualitative ELISA test, based on the detection of IgG autoantibodies in human serum or plasma, directed towards synthetic cyclic citrullinated peptides (CCP) that comprise modified arginine residues. This test is a complementary tool for diagnosing patients with RA.

For data processing, statistical methods for measuring central tendency were used. For testing the significance of the differences among the more arithmetical means in the groups (independent samples), Freedman's analysis of variance was used. Testing the significance of differences between two arithmetical means (dependent samples) was done with the Wilcoxon matched pairs test. A P-value between 0.05 and 0.1 was considered statistically significant.

Results

Socio-demographic indicators of the study

The mean of the age was 56.68 years (± 6.79) (40-65 years) in the RA group, and 46.2 years (± 12.49) (29-65) in the healthy control group. Moreover, the mean of the disease duration was 43.97 (± 45.23) months, in the interval 6-48 of months.

Clinical evaluation of the RA patients

The clinical evaluation of the disease was assessed following the dynamics of the changes in the mean values of the RI score, ESR, CRP, and RF (*Table 1).*

The analysis made with the Wilcoxon test showed that differences in average joint space narrowing were statistically significant between baseline and 9 months ($p = 0.0288$), as well as between baseline and 12 months ($p = 0.0205$). Differences in average joint space narrowing were not statistically significant ($p > 0.05$). On the other hand, differences in the average number of erosive changes were statistically significant between baseline and after 9 months ($p = 0.0169$) as well as between baseline and after 12 months ($p = 0.0034$). Differences considering the average number of erosive changes between other measurement points were not statistically significant ($p > 0.05$). Differences in the average total score were statistically significant between baseline and 12 months ($p = 0.0167$) as well as between baseline and 18 months ($p = 0.0089$). Differences in the average number of the total score between other measurement points were not statistically significant ($p > 0.05$).

Fridman's analysis of variance showed no statistically significant differences between the mean values of ACPA (mean time intervals, $Fr\ c2 = 1.017$, $p = 0.3875$).

The c2 test showed that the number of patients in whom values of ACPA were negative increased over time but without statistically significant differences ($c2 = 1.99$, $df = 3$, $p = 0.573$) (Figure 1).

Specific time intervals of observed changes

Baseline observed changes

At baseline, RI changes were registered in 10% of patients. Changes in the score for joint space narrowing were observed in two patients, and changes in the score for erosion were observed in one patient. Elevated levelsof RF and CRP were observed in 2 patients, while levels decreased in 1 patient.

Changes observed after a six-month period

After 6 months from the beginning of treatment with methotrexate, it was registered that the score for joint space narrowing had progressed in 12 patients and the total score (TS) had progressed in 13 patients. Furthermore, 4 patients had negative levels of RF and CRP, while the others had elevated values.

Changes observed after a 9-month period

After 9 months of methotrexate treatment, 14 patients had progressed in their joint space narrowing score, and 15 patients had progressed in their TS score.Elevated levels of RF were found in 9 patients, and elevated levels of CRP were found in 6 patients.

Changes observed after a year

After 12 months from the beginning of treatment with methotrexate, the number of patients with scores for joint space narrowing and the erosive score was the same as in the previous control (after 9 months). Elevated RF values were registered in nine patients, and negative CRP levels were registered in 11 patients.

Table 1. Mean values of RF, ESR, and CRP in patients with RA

Time intervals	Baseline	6 months	9 months	12 months
RF JU/ml RF< 30JU/ml (neg)	195.5 ± 289.9	194.4 ± 366.1	89.3 ± 157.9	126 ± 311.7
ESR mm/h	59.9 ± 27.7	31.6 ±16.9	31.4 ±17.4	25.0 ±11.6
CRP mg/l CRP< 6 mg/l(neg)	26.3 ± 28.8	19.0 ± 24.0	10.6 ± 11.9	13.4 ± 22.1

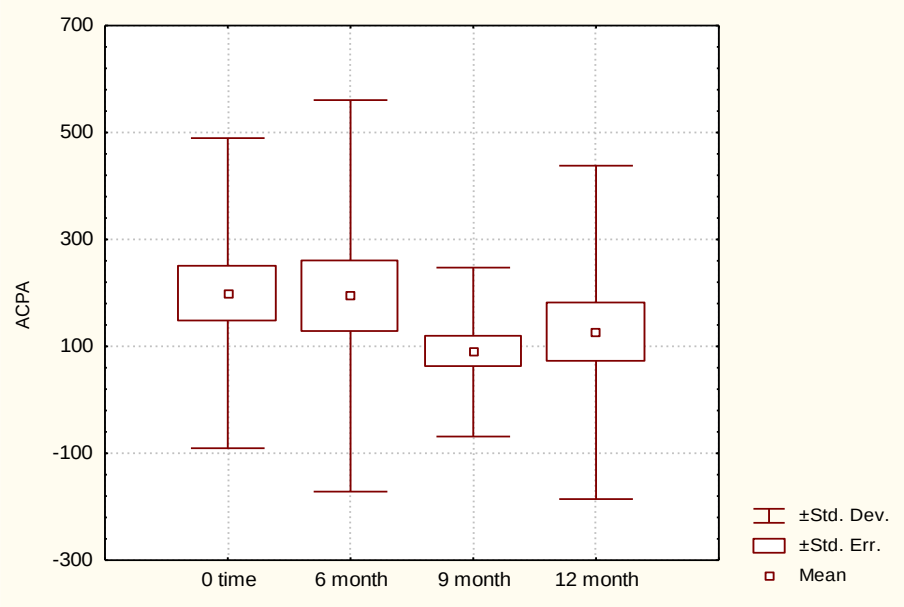

Figure 1.Mean values of ACPA in patients with RA

Discussion

By monitoring the dynamics of radiographic progression, acute phase reactants, and ACPA antibodies, the disease activity and therapeutic effect of methotrexate have been evaluated.

The statistical analysis of the progression of joint damage found statistically significant differences in the average number of erosive changes between baseline and after 9 months, as well as between baseline and 12 months (this was consistent with reports from the literature for slower radiographic progression over the course of 12 months and for faster progression after that [1].

The joint space narrowing showed statistically significant differences between baseline and after 9 months, as well as between baseline and after 12 months.

With statistical analysis, the overall score, which is the cumulative sum of the cores for sedimentation and joint space, also confirmed statistically significant differences at equal time intervals.

The rate of radiographic progression of joint damage has been reported in a variety of clinical studies, but the data are inconsistent. According to two studies, after one year of treatment, neither radiographic progression nor radiographic improvement were observed in the majority of the patients (absence of periarticular soft tissue swelling and juxta-articular osteoporosis) [2, 3].

Despite the majority of patients' clinical improvements, the other three studies found radiographic progression (without radiographic improvement) [4]. This could be compared to our group of RA patients as well as the findings from another study for more pronounced radiographic progression of the erosions after 6 and 9 months since the start of treatment in comparison to the first 6 months in early RA with linear progression of the erosions [5].

No statistically significant differences were found between ACPA in the four time intervals according to the statistical analysis (the standard deviations showed great variations). Some patients had ACPA levels that were extremely high.

The proportion of patients with negative ACPA levels increased over time, but the variations were not statistically significant. At the subsequent time intervals of RA activity, an increased progression of disease damage was only observed in patients with elevated ACPA values.

Several studies have found that, despite a decrease in inflammatory mediators, the radiographic progression of hand joint damage persists. Although there is a mutual dependence between inflammatory variables and acute phase reactants on the one side and radiographic joint damage on the other [6, 7], a recent study on experimental arthritis concepts has revealed a significant difference between inflammatory variables and joint destruction [8].

Although the cartilage and bone structures are not completely affected, they appear to only be present in the very early stages of the disease when the inflammation is active.Data indicate that the joint damage process, once started, is temporarily "autonomous" later, even though the inflammation could stop similarly in very early RA.

In contrast, the four-time interval follow-up of our patients revealed a higher progression of joint damage in patients with elevated RF and CRP levels at all time intervals.The elevated levels of acute phase reactants, sedimentation, CRP, and the rapid radiographic progression all reflect the chronic active course of RA [9].

The CRP parameter is a better predictor of radiographic progression than the erythrocyte sedimentation rate (ESR). This fact suggests that CRP has a stronger correlation with radiographic progression than Ritchie's articular index, the number of sensitive joints, or the number of swollen joints.

Additionally, it has been shown that serial CRP measurements correlate more strongly with radiographic progression than do sedimentation or articular indexes. With a tendency for greater progression in the already damaged joints and a smaller number of newly involved joints, radiographic progression is also observed in CRP levels that are normal.

Compared to sedimentation, which records changes in RA activity after a few weeks, CRP more accurately and quickly reflects changes in disease activity.

Conclusions

In daily clinical practice, ACPA antibodies are useful in the detection of early, untreated RA, excellent serologic markers in the prognosis and differential diagnosis of RA, and a definite indicator of the disease's aggressive course.

Acute-phase reactants allow the identification of high-risk groups for an aggressive disease course and illustrate which patients require an early and aggressive course of treatment.

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