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THE RELEVANCE OF PREDICTING RHEUMATOID ARTHRITIS SEVERITY: FACILITATING EARLY TREATMENT IN POOR PROGNOSIS AND PROGNOSTIC LABORATORY MARKERS OF JOINT DAMAGE

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Abstract

Simultaneous testing especially of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and rheumatoid factor (RF), which are reversible measures of inflammation, together with clinical variables of inflammatory synovitis are recommended for evaluation of disease activity. In this study 35 patients (pts) with early RA were included, while 35 pts were in the healthy control group. Pts were treated with Methotrexate at an average dose of 10 mg once weekly.

RA was evaluated following the dynamics of changes of the mean values of ESR, CRP and RF. Statistical analysis showed statistically significant differences among mean values of ESR in the four time intervals (p=0.00002). Regarding CRP, there were statistically significant differences among mean values in all four time intervals (p=0.0428) (standard deviations were with great variations). There were no statistically significant differences of RF in the four time intervals (p=0.573). We found high values of CRP and RF in most of the patients. In spite of the therapy with Methotrexate, disease progression continues especially in patients with elevated values of ESR, CRP and RF, which are shown as predictors for aggressive course of disease. This enables selection of high risk groups of patients for aggressive course of disease and points to the need of early and aggressive treatment.

Keywords: rheumatoid arthritis, reactants of the acute phase, rheumatoid factor

Introduction

RA is a chronic systemic inflammatory disease with mainly joint manifestation. In the course of the disease every synovial joint could be affected, but the most affected are small hand joints. Chronic synovitis usually is the reason for irreversible destructive changes of the joint cartilage and subchondral bone [1-7].

Reactants of the acute phase like ESR and CRP indirectly reflect synovitis, but at the same time they are sensitive tools which enable objectivization and measurement of immune-mediated inflammatory response in RA. Simultaneous testing especially of ESR, CRP and RF (that are reversible measures of inflammation) together with clinical variables of inflammatory synovitis are recommended for evaluation of disease activity. Considering the changeable course of the disease, for credible evaluation of RA the most appropriate are serial measurements of ESR and CRP (timely integrated) [8].

Reports from studies are paradoxical in terms of joint damage and inflammatory synovitis expressed with the reactants of the acute phase. Although there is a correlation between radiographic progression and the reactants of the acute phase, some studies have shown that progression of the erosion continues despite suppression of the joint inflammation [9].

From laboratory tests, anemia and thrombocytopenia also reflect the inflammation in RA. Rheumatoid factor (IgM-RF) is a serological indicator included in ARA criteria for RA and represents anti-immunoglobulin antibody that directly acts on Fc fragment of immunoglobulin G. RF is detected in 75-80% of patients. High titer of RF is associated with foudroyant course of disease.. However, from

clinical point of view, one could not predict the disease outcome in individual patients with early RA [10].

Aim

The aim of this study was to evaluate the activity of RA with radiographic assessment of hand joints, reactants of the acute phase (ESR, CRP) and rheumatoid factor (RF) and they were analyzed as prognostic markers for disease outcome in patients with RA, treated with Methotrexate.

Material and methods

In patients included in the study the disease diagnosis was made upon the revised diagnostic criteria

for classification of RA proposed by the European League against Rheumatism (EULAR), and the American Association for Rheumatism (ARA).

In order to include patients in the RA group they should satisfy at least 4 of the proposed 7 criteria. The criteria from 1 to 4 should be present at least 6 weeks.

The study included 35 pts (28 women, 7 men) with RA and 35 pts (18 women, 17 men) as a healthy control group. The mean age in the group with RA was 56.68 years (± 6.79) (40-65 years), while in the healthy control group 46.2 years (± 12.49) (9-65). The mean disease duration from the beginning expressed in months was 43.97 (± 45.23) months, in the interval 6-168 months. Examinations were made in several time points - in 0 time, 6, 9 and 12 months. For the first time immunomodulatory therapy with Methotrexate was indicated (average dose of 10 mg once weekly, in addition to the non-steroidal antirheumatic therapy.

None of the patients included in the study had previous or actual history of disease.

Clinical evaluation of disease activity

Clinical evaluation was made by a subspecialist in the field. Disease activity was evaluated by using DAS 28 index (Disease Activity Score - DAS 28). The Index uses mathematical formula to obtain unique composite quantitative score which consists of palpatory pain joints (maximal number 28), swollen joints (maximal number 28), Westergren ESR and patient's global assessment for disease activity [0–100 mm Visual Analogue Scale - VAS], as well as morning stiffness [minutes].

DAS 28 index is ranged between 0-10, and the score < 3.2 qualifies the disease as low active.

Inclusion criteria:

The study included patients with RA, aged 18-65 years, newly diagnosed and untreated for RA.

Exclusion criteria:

The study did not include all patients with diseases or conditions that could directly or indirectly affect the results, such as:

1. Pts with previous history of diseases of the spleen, thyroid gland, liver, kidney, hematological, cardiovascular, neurological, lung disorders, autoimmune diseases, aged <18 years.
2. Pts with diabetes, acute infections, malignant diseases, febrile conditions.
3. Pts with uric arthritis, urine infections, SLE, mixed connective tissue disease, vasculitis.
4. Pts with history of blood transfusion, as well as overweight.
5. Pts treated with drugs from the basic line.
6. Pts that in 0-time were detected with hyperglycemia, or elevated degradation products like serum and urine creatinine, serum urea, arterial hypertension, CBC disorder and enzymes disorder.

All participants voluntarily participated in the study, so the ethical criteria for making this study were fulfilled.

Laboratory evaluation

For clinical evaluation of the disease, it was necessary to take into account 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. reagent & instruments Costa Brava 30, Barcelona (Spain). Reference values were <6 mg/L CRP in serum.

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

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

ACPA antibodies were determined by the manufacturer DIA-STAT^{TM}Anti – CCP (Axis – Shield Diagnostics). The test is a semi-quantitative/qualitative ELISA test, based on detection of IgG autoantibodies in human serum or plasma, directed towards synthetic cyclic citrullinated peptides (CCP) that comprise modified arginine residues. Calculation and interpretation of the results for quantitative protocol is estimated from the absorbent value (optic density) from positive and negative control, as well as for every sample.

Absorbent value	**Interpretation of the results**
<0.95	negative
≥0.95≤1.0	borderline
From the absorbent value	positive

Statistical analysis

Data analysis was made with the statistical package Statistica 7.0.

The following statistical methods were used for data analyses: for testing significance of the differences among more arithmetical means in the groups (independent samples) Freedman's analysis of variance was used; for testing significance of differences between two arithmetical means (dependent samples) Wilcoxon Matched Pairs Test was used. P-value between 0.05 and 0.1 was considered to be statistically significant.

Results

RA was evaluated following the dynamics of changes of the mean values of RI score, mean values of ESR, CRP and RF (Table 1).

Table 1. Radiographic index in patients with RA with mean values of tight joint space, erosive score and total score

Time intervals in RA up to 1 year	Mean values of RF JU/ml RF< 30JU/ml (neg)	Mean values of CRP mg/l CRP< 6 mg/l (neg)
0 time	195.5 ± 289.9	26.3 ± 28.8
After 6 months	194.4 ± 366.1	19.0 ± 24.0
After 9 months	89.3 ± 157.9	10.6 ± 11.9
After 12 months	126 ± 311.7	13.4 ± 22.1

1. Wilcoxon matched pairs test showed statistically significant differences in mean values of ESR in time intervals between 0 time and 6 months (p=0.,00014); between 0 time and 9 months (p=0.00014); 0 time and 12 months (p=0.00010). Friedman's analysis of variance showed statistically significant differences among mean values of ESR in the four time intervals - Frχ^2 = 19.485 p=0.00002 (Table 1). In regards to ESR, we noticed a consecutive decrease in the values in every other control in certain time intervals in most of the patients.
2. Friedman's analysis of variance showed that there were statistically significant differences among mean values of CRP in the four time intervals - Fr χ^2 = 2.804 p = 0.0428 (standard deviations showed great variations). Analysis with χ2 test showed that the number of pts in whom the CRP values were negative increased within the course of the time, and the differences were statistically significant (χ2 = 11.35 df = 3 p = 0.0099) (Figure 1).
3. Friedman's analysis of variance showed that there were no statistically significant differences among mean values of RF in the four time intervals - Fr χ^2 = 1.017 p = 0.3875 (standard deviations showed great differences).
Analysis with χ2 test showed that the number of pts in whom RF values were negative increased within the course of time, but the differences were not statistically significant (χ2 = 1.99 df = 3 p = 0.573).
4. Friedman's analysis of variance showed that there were no statistically significant differences among mean values of hemoglobin - Fr (χ2x2= 1.715 p=0.1677), mean values of erythrocytes - Fr (χ2 = 0.872 p=0.4578), mean values of leukocytes – Fr (χ2= 1.0276 p=0.4751), among mean values of hematocrit - Fr (χ2= 1.1028 p= 0.3509) in the four time intervals in the group of patients with RA.

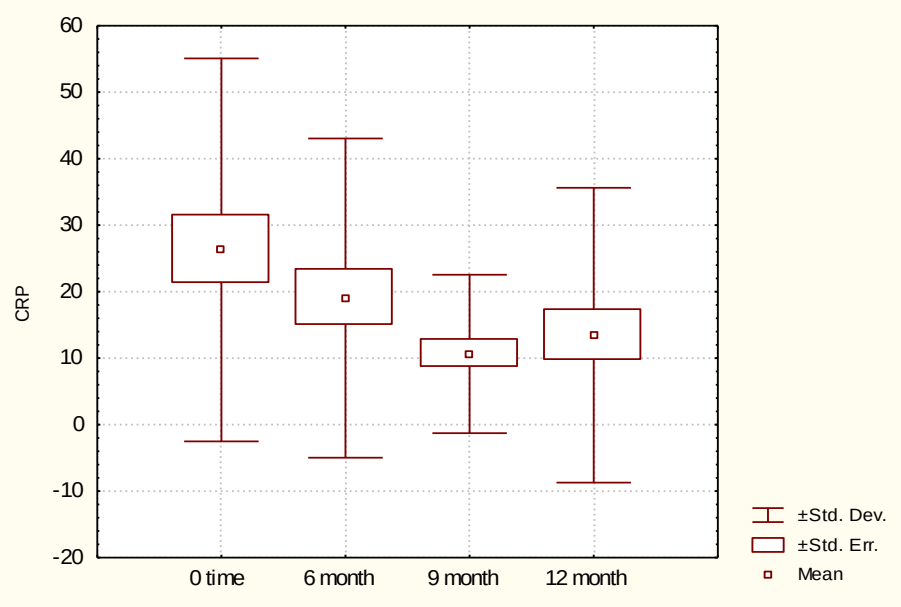

Figure 1. Mean values of CRP in patients with RA

Discussion

The results obtained in this study by following the dynamics of changes of the acute phase reactants made it possible for us to evaluate disease activity and treatment efficacy from administration of Methotrexate [11-15].

The statistical analysis showed statistically significant differences among mean values of CRP in all four time intervals. Distribution of pts according to CRP values over and bellow 6 mg/l showed that

the number of pts in whom CRP values were negative increased over time, but, however some pts had elevated CRP values (standard deviations showed great variations). Decrease in the values of CRP in the consecutive controls in the four time intervals confirmed the report from other studies for CRP sensitivity in terms of joint inflammation. Statistical analysis showed that there were no statistically significant differences among mean values of RF in the four time intervals (standard deviations showed great variations). Some patients had enormously high values of RF. According to the values of RF, patients were distributed over and bellow 30 JU/ml. The number of patients in whom values of RF were negative had increased over time, but differences were not statistically significant. In those patients with high values of RF we noticed a greater progression of the joint damage during the follow-up period of RA activity.

The Methotrexate therapy achieved clinical suppression of RA after 6 months from the beginning of treatment. In the consecutive time intervals of follow-up of patients we could confirm the reports from several studies that there was a mutual correlation between variables of inflammation and reactants of the acute phase [16,17].

Many clinical studies have reported that it is very difficult to assess which factors are the most significant predictors for treatment outcome and that difficulties are due to the different definitions of disease outcomes from therapy and examinations of different disease predictors in different clinical studies. Also, there are different approaches to RA treatment with DMARDs alone or in combination with several DMARDs [18-21].

Studies dealing with disease activity as a predictor for treatment outcome are inconsistent in their reports. Some studies consider that inflammatory markers manifested in the beginning of the disease (RA) when therapy was started have no predictive significance in the treatment outcome.

On the contrary, recent studies report that positive RF is a predictor of disease activity and radiographic progression, i.e. a high value of RF is a predictor of consecutive joint damage [22]. This is in agreement with our findings.

Other studies suggest that RF status is not a predictor of treatment outcome [23]. In one study patients with very early stage of the disease and intensive therapy, positive RF in the beginning of the study proved to be prognostically significant for treatment outcome [10]. This was also confirmed in our study..

In some studies RF is an indicator of disease seriousness, while other clinical variables measured in the beginning of the disease that evaluate disease activity by counting of inflammatory joints as well as the acute phase reactants vary in their influence in later joint damage [24].

Chronically active disease – RA is a reflection of elevated values of CRP and ESR [25-26]. The superiority of CRP in regards to ESR as a predictor for radiographic progression shows a greater correlation of CRP than of the number of sensitive joints. Superiority of CRP in regards to ESR could be explained with better sensitivity of CRP compared to inflammation. Also, CRP compared to ESR is resistant to the influence of gender, age, anemia and other serum proteins. Combination of CRP and ESR has no additive predictive value.

CRP is the best indicator for detectible damage because it is a direct and sensitive marker that gives rapid answer of the changes of the inflammatory synovitis compared to ESR, which is an indirect marker of inflammation. CRP more precisely and in shorter time reflects the changes in disease activity compared to ESR that registers the changes in RA activity after few weeks.

Conclusion

In despite of therapy with Methotrexate, disease progression continues especially in patients with elevated values of ESR, CRP and RF, which are shown to be predictors for aggressive course of the disease. This enables selection of high-risk groups of patients for aggressive course of disease, and points to the need of early and aggressive treatment.

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