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C-REACTIVE PROTEIN - THE MOST USEFUL REACTANT OF ACUTE PHASE IN RHEUMATOID ARTHRITIS

Dejan Spasovski[1,3], Emilija Sandevska[1,3], Ljindita Djemaili Jakupi [1,3], Ana Vasilevska[1,3] , Svetlana Krstevska-Balkanov[2,3], Aleksandra Pivkova-Veljanovska[2,3], Maja Jakimovska[3,3], Vladimir Mitreski[4,3], Nikola Chamurovski[4,3], Kujtim Iseini [5,3]
[1]University Clinic for Rheumatology, [2]University Clinic for Hematology,
[3]University Institute of Radiology,
[4]PHI Institute of Lung Disease and Tuberculosis,
[5]PHE Hospital klinik Tetovo-Department of Internal Medicine,Clinical Center Mother Therese, Skopje, North Macedonia,
[3]Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, North Macedonia

Abstract

The aim of the study was to determine the most useful biochemical marker of the acute phase reactants for the evaluation of disease activity in rheumatoid arthritis (RA).

Sixty patients with RA were included, 27 of whom were treated with non-steroid anti-inflammatory drugs (NSAIDs) and methotrexate (MTH).

The control group consisted of 33 patients treated only with NSAIDs due to irregular control. In the first group, disease activity was evaluated at four-week intervals and in the control group at three-week intervals, following the scores of the articular indices, complete blood count (CBC), elevated sedimentation rate (ESR), and C-reactive protein (CRP) in every patient.

In the first group of patients, decreased activity of RA was found in every subsequent control, with a consecutive decrease in the mean values of the scores of the articular indices and statistically significant differences in the four-time intervals.

Considering laboratory parameters, there were statistically significant differences in the mean values of haemoglobin (Hb), erythrocytes (Er), platelets (Plt), and ESR ($p=0.0462$, $p=0.0076$, $p= 0.0058$, $p= 0.0003$). The mean values of CRP did not show statistically significant differences, but the number of patients who were CRP negative increased (the standard deviation also increased). In the group of patients treated only with NSAIDs, there were statistically significant differences in the mean values of the scores of the articular indices, with increases in every subsequent control (in favor ofdisease progression).

There were no statistically significant differences considering CBC, ESR, and CRP (in favor of a permanently active disease).

CRP is the most useful marker in the prospective evaluation of patients with rheumatoid arthritis.

Keywords: rheumatoid arthritis, articular indices, reactants of the acute phase

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease with peripheral synovitis and a progressive and unpredictable evolution, eventually leading to joint failure. Apart from the joints, many other organs and systems are also affected by this disease. For the assessment of the condition, the quantification of joint inflammation is crucial. In order to standardize the clinical measurement of joint inflammation, several articular indices were developed [1,2].

Systemic involvement is accompanied by laboratory abnormalities such as an increased erythrocyte sedimentation rate (ESR), anemia, thrombocytosis, and elevated values of the liver function tests.

The cause of anaemia in RA is multifactorial. In fact, as one of the indicators of RA activity, it is related to the degree of disease activity but not its duration. The degree of anemia in RA correlates with the disease activity, especially with the degree of joint inflammation.

The anaemia is typically normocytic and normochromic, unless it is accompanied by other disorders such as bleeding, an unhealthy diet, concurrent infection, or hemolytic anemia (due to antibodies in some patients), which is most commonly caused by drugs that suppress bone marrow. As well, iron deficiency could cause anemia in RA.

Iron replacement therapy could be disappointing with an inadequate therapeutic effect because anemia in RA is caused by the inhibition of hemoglobin synthesis due to inflammation [2].

Another common finding inactive RA isthrombocytosis. Its degreecorrelates with the number of involved joints with active synovitis as well as with the extra-articular disease manifestations.It is supposed that increased intravascular coagulation with compensatory increased platelet production could be a possible mechanism for its occurrence.

Otherwise, thrombocytopenia in RA is a rare finding that could be caused by drug therapy or be found in Felty's syndrome. The cause for thrombocytopenia in RA could be inhibitors of coagulation or, more rarely, hyperviscosity.

Other indicators that are often used are the reactants of the acute phase such as ESR, which increases depending on the disease activity, as well as CRP, which is a better indicator of the disease activity and progression[1].

The objective of this study was to compare patients receiving methotrexate (MTX) versus a control group (without immunomodulatory drugs) and to quantify RA activity over time by comparing the results of two different articular indices(a set of 28 sensitive joints and a set of 28 swollen joints), laboratory parameters (hemoglobin (Hb),hematocrit (Hct),number ofred blood cells (Er), number of white blood cells(WBC), number of thrombocytes (Plt)), and reactants of the acute phase (ESR and C-reactive protein (CRP)).

Materials and Methods

Sample description

In this prospective control study, 60 patients with RA were included. These patients met the disease classification criteria established by the American College of Rheumatology in 1987 [2].

Twenty-seven patients were treated withnon-steroidal anti-inflammatory drugs(NSAIDs) and MTH, with a mean dose of 7.5 mg once weekly.

Inclusion criteria

- Patients with RA
- Age range: 18 to 73 years
- Newly diagnosed patients
- RA untreated patients

Exclusion criteria

- A history of autoimmune diseases, spleen, thyroid, liver, kidney, hematological, cardiovascular, neurological,lung conditions,human immunodeficiency virus (HIV), diabetes mellitus, malignant disease, febrile conditions, arterial hypertension
- Under 18 years old
- The existence of diseases like vasculitis, mixed connective tissue disease, systemic lupus erythematosus (SLE), uric arthritis, and urine infections
- A history of blood transfusions and obesity
- Identification of baseline hyperglycemia or elevated degradation products such as serum and urine creatinine, serum urea, and arterial hypertension
- Patients who were treated with antibiotics and salicylates within six months of the study's start
- Patients who take drugs from the basic line
- Patients treated with antihypertensive, anti-diabetic, and cardiac therapies
- Patients who are hypersensitive to some drugs or their components

Ethical considerations

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

Clinical evaluation of disease activity

RA was quantitatively evaluated in every patient according to the changes in the articular indices score, complete blood count (CBC), and reactants of the acute phase (ESR, rheumatoid factor (RF), and CRP) in certain time intervals.

In the first group of patients, RA was quantitatively evaluated at 4-time intervals: at baseline, after 1, 2, and 3 years. In the control group of patients, the disease was quantitatively evaluated at 3 time intervals: baseline, after 1 year, and after 2 years.

For the quantitative evaluation of the joint inflammation, two different articular indices were used: a set of 28 palpation-painful, sensitive joints and a set of 28 edematous, swollen joints.

These articular indices evaluate a set of 28 joints, with scores ranging from 0 to 1 separately for joint sensitivity and joint edema. Their total produces a cumulative index of joint inflammation ranging from 0 to 28 [2].

Laboratory assessment

Every patient was evaluated at determined time intervals for complete blood analysis (CBC with differential), reactants of the acute phase (ESR (mm/hour) according to the Westergren method with reference values 4/10), and CRP determined with the immunonephelometric method with reference values 0.0–0.6 mg/l.

Values > 6 mg/l signify a positive CRP. Rheumatoid factor (RF) was detected with a latex RF test, with reference values > 8 mg/l in serum. Liver function tests, such asaspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), creatine phosphokinase (CPK), and creatinine in serum and urine, were also measured.

Statistical analysis

Data analysis was done with the statistical package Statistica 7.0.For data processing, statistical methods for measuring central tendency were used. For testing the significance of the differences among the more arithmetical means of 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

Patients' mean age was 50.3 ± 8.9 years (range 33–72 years), and their mean disease duration was 3.1 ± 1.3 years (range 1-5 years). The control group consisted of 33 patients who were incidentally treated with NSAIDs due to irregular control, with a mean age of 55.4 ± 8.3 years (range 37–73 years) and a mean disease duration of 4.3 ± 2.4 years (range 1-9 years).

Freedman's two-directional analysis of variance

Freedman's two-directional analysis of variance showed statistically significant differences among mean values of the score on the set of 28 tender joints (DAS28 sensitivity) in four-time intervals (Fr χ^2=12.205, p=0.000001), as well as among mean values of the articular index on the set of 28 tender and swollen joints (Fr χ^2=10.262, p=0,00006) in favor of a decrease of the articular indices score in every subsequent control due to the decreased joint inflammation.

There were statistically significant differences among mean values of ESR in all four time intervals (Fr χ^2=15.161, p=0.0003) in favor of decreased mean values of ESR in the subsequent controls.

Among the mean values of CRP in the four time intervals, there were no statistically significant differences (Fr χ^2=2.094, p=0.1056); standard deviations showed great variations.

The analysis of the χ^2 test revealed that patients with negative CRP levels increased over time, and the differences were statistically significant (χ^2=17.35, df=3, p=0.00059).

Freedman's two-directional analysis of variance showed statistically significant differences among mean levels of **Hb** (Fr χ^2=2.756, p=0.0462), mean levels of **Er** (Fr χ^2=4.199, p=0.0076), with increases in the mean levels of Hb and Er in the subsequent controls.

Among the mean levels of **Hct** in this group, there was no statistical increase in the four-time intervals (Fr χ^2=4.353, p=0.0063) in favor of correction of anemia. Differences in the mean levels of **WBC** were not significant (Fr χ^2=0.6807, p=0.5658).

Considering platelets, Freedman's two-directional analysis of variance showed statistically significant differences among mean levels (Fr χ^2=4.418, p=0.0058), in favor of correction of thrombocytosis (*Figure 1*).

Freedman's two-directional analysis showed that there were statistically significant differences among the mean values of the score in the set of **28 painful, tender joints** (Fr χ^2=4.214, p=0.0176), in favor of elevated values in every subsequent control. Considering the mean values of the score in the set of **28 swollen joints**, the statistical analysis showed no statistically significant differences (Fr χ^2=0.242, p=0.7851); they were almost identical in all time intervals, which spoke in favor of constant disease activity.

There were no statistically significant differences in **ESR** in all three time intervals (Fr χ^2=2.807, p=0.0625), in favor of constantly increased high levels and disease activity (*Figure 2*).

Also, there were no statistically significant differences in the mean levels of **CRP** in the three time intervals (standard deviations showed great variations).The χ^2 test analysis showed that patients in whom the CRP values were negative did not change within the course of time, so the differences were not statistically significant (χ^2=0.57, df =2, p=0.752).

There were no statistically significant differences among mean levels of Hb (Fr χ^2=1.82, p=0.165), mean levels of Er (Fr χ^2= 0.020, p=0.997), mean levels of WBC (Fr χ^2=0.319, p=0.727), mean levels of Hct (Fr χ^2=1.085, p=0.341) and mean levels of Plt (Fr χ^2=0.257, p=0.773) in the three-time intervals.

To sum up, all parameters in this group of patients showed increased activity of RA and disease progression.

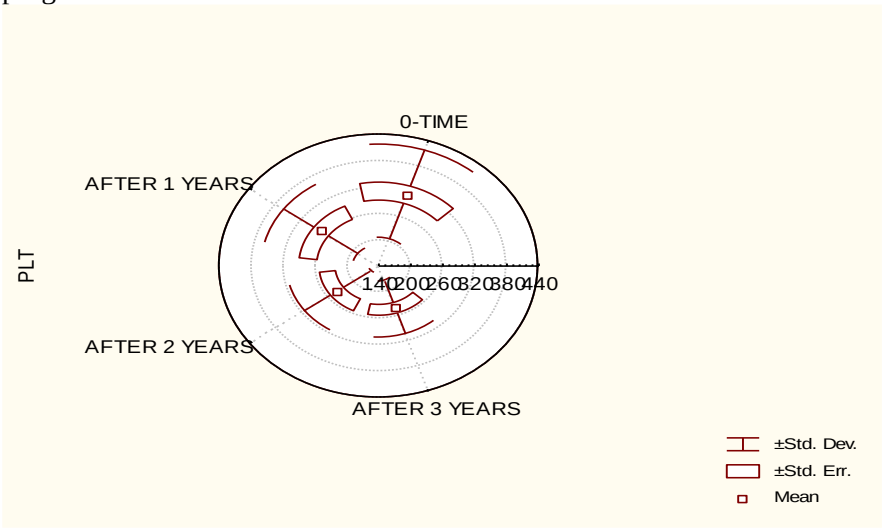

Figure 1. Mean values of PLT in patients treated with Methotrexate

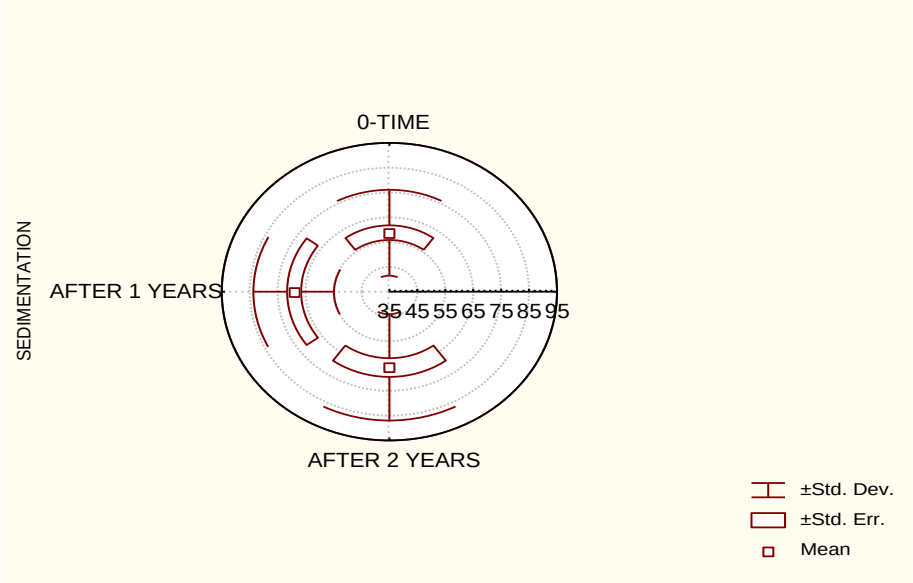

Figure 2. Mean values of ESR in patients in the control group

Discussion

RA disease activity evaluation is very important in everyday practice and in clinical investigations. The disease presentation varies significantly among patients as well as within the same patient.

Considering the heterogeneous presentation of the disease and the variable course among different individuals, it is impossible to evaluate the disease activity on the basis of one variable/measure. Several measurements were used in clinical investigations in previous decades for the quantification of various aspects of disease and for a more complete evaluation of disease activity, such as the clinical evaluation of inflammation with articular indices [3].

Laboratory measurements are also made for the detection of anemia and thrombocytosis as parameters that show increased disease activity, as well as biochemical parameters that indirectly reflect synovitis, such as reactants of the acute phase. ESR and CRP are sensitive indicators for measuring the immune-mediated inflammatory response. All these measurements are standardized and have the potential for disease quantification.

Considering the variability of all of these measurements for the reliable evaluation of the RA activity, individual monitoring of each and every patient is important at certain time intervals [4].

A large number of rheumatologists think that MTX is the drug of choice and most convenient for long-term treatment of RA. Manyclinicians think that MTX is superior in comparison with other DMARDs.

The most important mechanisms of action of MTX in the treatment of RA are the inhibition of DNA synthesis, the inhibitory effect on cell proliferation, the activity of lymphocytes and neutrophils, and the suppressive activity of cytokines.

It has an impact on the modification of the course of the disease, improves the signs and symptoms of the inflammatory synovitis, and prevents and decreases the rate of joint erosion progression, all of which contribute to function maintenance.Early treatment of RA with MTX is of great importance for achieving maximal treatment efficacy, disease remission, and a better treatment response [5].

The results of this study are similar to other studies discussing earlyRA, considering the mean values of the set of 28 painful, tender joints and the set of 28 swollen joints, as well as laboratory parameters.

The differences were due to variations in the number of patients and disease activity at the beginning of the study. Following all the previous measurements in patients of the control group who were incidentally treated with NSAIDs, it was possible to evaluate the natural course of the disease, which was unpredictable,progressive, and individual.

There are other studies that confirm the association between these two parameters, but they are cut-off studies with a smaller number of patients, emphasizing the benefit of CRP as the most useful biochemical marker in the evaluation of disease activity [6–8].

Nowadays, the majority of rheumatologists strongly recommend the early introduction of MTX in the treatment of RA. However, even early MTX treatment cannot stop complete disease progression in some patients, and the term "early" is debatable. [9–11].

Quantitative evaluation of disease activity by these measurements enables assessment of the actual patient's condition and also helps clinicians be more effective in treatment modification.

Conclusions

The most valuable marker for the prospective follow-up of RA patients is CRP

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