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ASSOCIATION BETWEEN OSTEOARTICULAR SCORES AND ACUTE PHASE REACTANT LEVELS IN RHEUMATOID ARTHRITIS

VEZA IZMEĐU OSTEOARTIKULARNIH INDEKSA I REAKTANATA AKUTNE FAZE KOD REUMATOIDNOG ARTRITISA

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Summary: The aim of this prospective control study was a quantitative evaluation of the activity of rheumatoid arthritis (RA) in certain time intervals, using articular indexes (set of 28 sensitive and 28 swollen joints), laboratory parameters (Hb, Hct, Er, Le and Plt) and acute phase reactants (ESR, RF, CRP); to determine which of the acute phase reactants is the most useful biochemical marker for the evaluation of disease activity in RA; to quantify the therapeutical and laboratory differences in certain time intervals in the group with and without immunomodulatory therapy with Methotrexate. Sixty patients with RA were included, 27 of who were treated with non-steroid antiinflammatory drugs (NSAIDs) and Methotrexate (MTX). The control group consisted of 33 patients treated only with NSAIDs because of irregular controls. In the first group of patients the disease activity was estimated at four time intervals, and in the control group of patients at three time intervals following the scores of the articular indexes, blood cell counts**,** ESR and CRP in every patient. In the first group of patients decreased activity of RA was found upon every following control with a consecutive decrease in mean values of the scores of articular indexes with statistically significant differences at the four time intervals. Considering laboratory parameters, there were statistically significant differences in the mean values of Hb, Er, Plt, ESR, (p=0.0462, p=0.0076, p= 0.0058, p= 0.0003). Mean

Kratak sadržaj: Cilj ovog istraživanja bio je da se izvrši kvantitativna procena reumatoidnog artritisa (RA) u određenim vremenskim intervalima pomoću osteoartikularnog indeksa (set od 28 osetljivih i otečenih zglobova), laboratorijskih parametara (Hb, Hct, Er, Le i PLT) i reaktanata akutne faze (Se, RF, CRP), da se utvrdi koji od reaktanata akutne faze bi bio najkorisniji marker za procenu aktivnosti bolesti kod dugoročnog praćenja RA pacijenata, kao i da se registruju i kvanificiraju kliničke i laboratorijske razlike u određenim vremenskim periodima u grupi pacijenata tretiranih imunomodulatornom terapijom sa metotreksatom i bez njega. Ispitano je 60 pacijenata sa RA (27 tretiranih kombinovanom upotrebom NSAIL i metotreksata, 33 pacijenata samo sa NSAIL). Isti su ispitivani u nekoliko vremenskih intervala. U prvoj grupi pacijenata registrovano je smanjenje aktivnosti RA sa progresivnim smanjenjem srednje vrednosti artikularnih indeksa u svim vremenskim intervalima. Postoje statistički značajne razlike u srednjim vrednostima Hb, Er, Thr, SE (p = 0.0462, p = 0.0076, p= 0.0058, p=0.0003). Srednje vrednosti CRP nisu pokazale statistiški značajne razlike, no broj pacijenata koji su bili CRP negativni se povećao (postojale su velike standardne devijacije). U grupi tretiranoj samo sa NSAIL, postojale su statistički značajne razlike srednjih vrednosti skorova artikularnih indeksa sa povećanjem nivoa pri svakoj

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values of CRP did not show statistically significant differences, but the number of patients who were CRP negative increased (there were great standard deviations). In the group of patients treated only with NSAIDs, there were statistically significant differences in the mean values of the scores of articular indexes with an increse at every following control (in favour of progression of the disease). There were no statistically significant differences considering blood cell counts, ESR and CRP (in favour of permanently active disease). In conclusion, CRP is the most useful marker for the prospective follow-up of patients with RA.

Keywords: rheumatoid arthritis, articular indexes, acute phase reactants

narednoj kontroli (u prilog progresije aktivnosti bolesti). Nisu utvrđene statistički značajne razlike u odnosu na hemogram, Se i CRP (u prilog postojanja aktivne bolesti). U zaključku, CRP je najkorisniji marker za procenu aktivnosti RA kod dugoročnog praćenja RA pacijenata.

Ključne reči: reumatoidni artritis, artikularni indeksi, reaktanti akutne faze

Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease with peripheral synovitis as the main characteristic, and with characteristically progressive and unpredictable evolution which results in the disturbance of joint function. Besides the joints, the disease affects multiple organs and systems. The quantitative approach to joint inflammation is of great importance in the clinical evaluation of the disease. With the aim of standardization of the clinical measurement of joint inflammation several articular indexes have been developed (1, 2).

Laboratory abnormalities which accompany systemic involvement are increased ESR, anemia, thrombocytosis and increased values of the liver function tests. The reason for anemia in RA is multifactorial. It is related to the degree of the activity of the disease and not with its duration, and is one of the indicators of the activity of RA. The degree of anemia in RA correlates with the activity of disease, especially with the degree of joint inflammation. Usually it is normocytic and normochromic, except when it is accompanied by other conditions such as bleeding, wrong diet, concomitant infections or hemolytic anemia (in a small number of patients antibodies are the reason), and most commonly is induced by drugs which suppress bone marrow formation. Iron deficiency could be a complication of anemia in RA. Iron replacement therapy could be disappointing with an inadequate therapeutic effect, because anemia in RA is due to an inhibition of the hemoglobin synthesis caused by inflammation. Thrombocytosis is a common finding in active RA. The degree of thrombocytosis could correlate with the number of involved joints with active synovitis as well as with the extraarticular manifestations of the disease. The mechanism of thrombocytosis is unknown. It has been suggested that the possible reason is increased intravascular coagulation which results in a compensatory increased production of platelets. Thrombocytosis in RA does not correlate with the neoplastic changes of the bone marrow. Thrombocytopenia in RA is a more rare finding, and could be caused by drug therapy or the Felty's syndrome. It is supposed that reasons for thrombocytopenia are production of the inhibitors of coagulation or more rarely hyperviscosity.

Other more often used indicators which reflect the disease activity are acute phase reactants, i.e. the determination of the ESR, which is increased depending on the activity of the disease, as well as determination of CRP as a better indicator of the activity and progression of disease in relation with the ESR (3–5).

The aim of this study is a quantitative evaluation of the activity of RA in certain periods of time, following the scores of two different articular indexes (set of 28 sensitive and set of 28 edematous, swollen joints), laboratory parameters (Hb, Hct, Er, Le, Plt) and the acute phase reactants (ESR and CRP) in patients treated with Methotrexate (MTX) versus the control group (without immunomodulatory drugs), and to determine which of the acute phase reactants is the most useful biochemical marker for the evaluation of the disease activity in RA.

Patients and Methods

In this prospective control study 60 patients with RA were followed. These patients fulfill the criteria for disease classification according to the American College of Rheumatology from 1987 (6). Twenty-seven patients were treated with non-steroid antiinflammatory drugs (NSAIDs) and Methotrexate (MTH), mean dose 7.5 mg once weekly. Mean age of the patients was 50.3 ± 8.9 years (33–72 years), mean duration of the disease was 3.1 ± 1.3 years (1–5 years). The control group consisted of 33 patients who were incidentally treated with NSAID because of the irregular controls, with a mean age of 55.4 ± 8.3 (37–73 years) and mean duration of the disease 4.3 ±2.4 years (1–9 years).

Criteria for inclusion. The study involved patients who suffer from rheumatoid arthritis, aged 18–73 years, newfound and till now not treated.

Criteria for exception from the research. All the patients with a disease or condition which can directly or indirectly influence a change in results were excepted from the research:

1. Patients with a previous medical record of diseases of the spleen, thyroid gland, hepatal damage, renal, hematologic, cardiovascular, neurotic and lung damage, autoimmune disease, AIDS, age<18 years.
2. Patients with diabetes mellitus, acute infections, malignant neoplasm, febrile conditions.
3. Patients treated with antibiotics and salycilate in periods under six (6) months before the beginning of the study.
4. Patients with hypertension arterialis, uric arthritis, uric infections, SLE, Sy Sjogren, mixed conjunction texture disease, vasculitis.
5. Patients treated with antihypertension, antidiabetic and cardiac therapy.
6. Patients with anamnesis of blood transfusion and overweight.
7. Hypersensitive to some of the medicines or their components.
8. Patients who together with these medicines take medicines from the base line.
9. Patients whose results show that in 0 spot there is glycemia, an increased level of degraded products: creatinine in serum and urine, urea in serum and a disorder of the hematologic and enzymic status.

All the patients took part in this study voluntarily, so the ethical criteria were fulfilled.

Clinical evaluation of the disease activity

Rheumatoid arthritis was quantitatively evaluated in every patient following the changes of the scores of articular indexes, laboratory measurements (complete blood cell count and acute phase reactants – ESR, RF, CRP) in certain periods of time. In the first group of patients RA was quantitatively evaluated at 4 time intervals: 0-time, after 1, after 2, and after 3 years. In the control group of patients the disease was quantitatively evaluated at 3 time intervals: 0-time, after 1 year and after 2 years.

For a quantitative evaluation of the joint inflammation two different articular indexes were used: a set of 28 palpation painful, sensitive and a set of 28 edematous, swollen joints. These articular indexes evaluate each set of 28 joints with scoring from 0 to 1 separately for joint sensitivity and the joint edema. Their sum is the cumulative index of joint inflammation which varies between 0 and 28 (7–10).

Laboratory assessment

At the determined time intervals in every patient a complete blood analysis was done (blood cell count with differential)**,** acute phase reactants and ESR (mm/1 hour) were determined according to the Westergren method with reference values 4–10; CRP was determined using immunonephelometry, with reference values 0.0–0.6 mg/L. Values >6 mg/L signify positive CRP. Rheumatoid factor was detected with Latex, RF test, values >8 mg/L in serum. Liver function tests: AST, ALT, AP, LDH, CPK. Serum and urine creatinine.

Table I Quantitative evaluation of the activity of RA in patients treated with Methotrexate and in control patients (without Methotrexate).

	Methotrexate group				NSAIDS+Methotrexate group		
Time intervals	0-Time	After 1 year	After 2 years	After 3 years	0-Time	After 1 year	After 2 years
Mean values of the set of 28 painful joints	13.9 ± 5. 6	8.2 ± 5.5	5.5 ± 5.3	6.8 ± 5.5	4.0 ± 5.3	15.8 ± 5.4	17.6 ± 4.2
Mean values of the set of 28 swollen joints	6.6 ± 3.2	3.5 ± 3.0	2.7 ± 2.6	3.4 ± 2.2	8.4 ± 3.0	8.9 ± 3.8	8.9 ± 2.8
Mean values of ESR	78.5 ± 30.7	47.3 ± 28.1	37.4 ±19.3	36.7±24.1	58.8 ± 16.9	69 ± 14.4	65.6 ± 21.7
Mean values of CRP	30.9 ± 47.2	14.4 ± 21.9	8.4 ± 9.0	26.5 ± 51.4	32.3 ± 15.4	41.5 ± 16.8	49.9 ± 16.3
Mean values of PLT	310.5 ±106.3	273.9 ± 85.6	237.2 ± 77.2	239.4 ± 62.8			

Statistical analysis

In the processing and analysis of data from the study the following methods were used: analysis of the structure of the numerical data with measures of central tendency (mean values) and measures of dispersion (standard deviation); analysis of the relations between attributive series was made with x[test; determination of significance among three or more arithmetical means in the groups (dependant samples) was made using Freedman's two-directional analysis of variance.

Results

Quantitative evaluation of the activity of RA in patients treated with MTX is shown in *Table I*.

Friedman's two-directional analysis of variance showed statistically significant differences among mean values of the score in the set of 28 sensitive joints at the 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 edematous joints (Fr χ^2=10.262, p=0.00006) in favour of a decrease in the score of these articular indexes at every following control, as a result of decreased joint inflammation.

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

Among the mean values of CRP at four time intervals there were no statistically significant differences (Fr χ^2=2.094, p=0.1056); standard deviations showed great variations. Analysis with χ^2 test showed that the number of patients in who the values of CRP were negative increased during the course of time, and the differences were statistically significant (χ^2=17.35, df=3 p=0.00059).

Friedman's two-directional analysis of variance showed statistically significant differences among the mean values (Fr χ^2=4.418, p=0.0058), in favour of correction of thrombocytosis (*Figure 1*).

Quantitative evaluation of the activity of RA in the control group (without MTX) is shown in *Table I*. Friedman's two-directional analysis showed that there are statistically significant differences among mean values of the score in the set of 28 painful, sensitive joints (Fr χ^2=4.214, p=0.0176), in favour of an increase in the values at every following control; considering the mean values of the score in the set of 28 swollen, edematous joints, statistical analysis did not show any statistically significant differences (Fr χ^2=0.242, p=0.7851). They were at all times almost identical, which speaks in favour of constant activity of the disease. There were also no statistically significant differences in ESR at all three time intervals (Fr χ^2=2,807, p=0.0625), in favour of constantly increased high values and active disease (*Figure 2*). Finally, there were no statistically significant differences in the mean values of CRP at the three time intervals (standard deviations showed great variations).

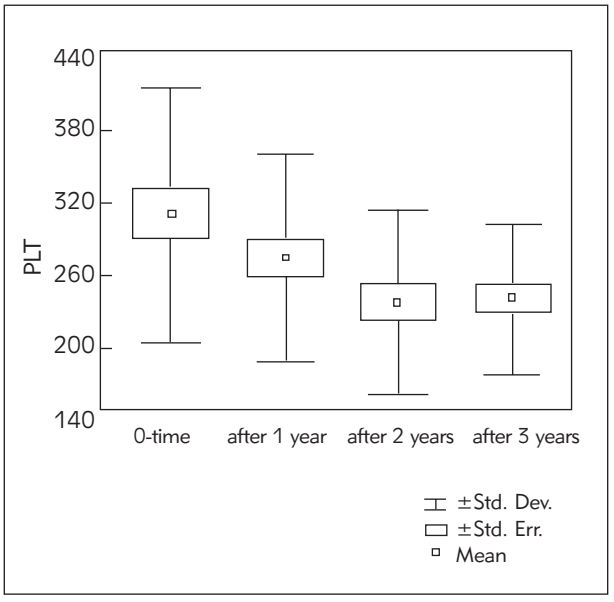

Figure 1 Mean values of PLT in patients treated with Methotrexate.

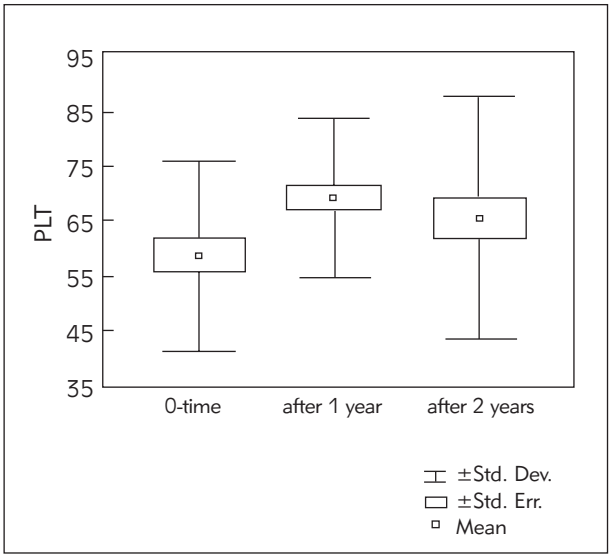

Figure 2 Mean values of ESR in patients of the control group.

Analysis with χ^2 test showed that the number of patients in whom the values of CRP were negative did not change in the course of time, so the differences were not statistically significant (χ^2=0.57 df = χ^2 p=0.752). Also, there were no statistically significant differences among the mean values of Hb (Fr χ^2=1.82, p=0.165), Er (Fr χ^2= 0.020, p=0.997), Le (Fr χ^2=0.319, p=0.727), Hct (Fr χ^2=1.085, p=0.341)

and mean values of Plt (Fr χ^2=0.257, p=0.773) at the three time intervals. All parameters in this group of patients showed increased activity of rheumatoid arthritis and progression of the disease.

Discussion

Evaluation of the disease activity in RA is of great importance in everyday practice, as well as for clinical investigations. The disease expression varies significantly among patients, but also in the same patient. Considering the heterogeneous presentation of the disease and variable course among different individuals, it is impossible to evaluate the disease activity on the basis of one variable/measure.

In the previous decades numerous measurements were used in clinical investigations for the quantification of different aspects of disease and for a more complete evaluation of the disease activity in RA, among which are clinical evaluation of the inflammation with articular indexes (11), laboratory measurements (for detection of anemia and thrombocytosis as parameters which show increased disease activity), as well as biochemical parameters which indirectly reflect synovitis i.e. acute phase reactants. ESR and CRP are sensitive indicators for measurement of the immune-mediated inflammatory response. All these measurements are standardized and have potential for the quantification of disease. Considering the variability of all these measurements, for a reliable evaluation of the activity of RA, it is important to individually monitor each one of them in certain periods of time (12, 13).

A great number of rheumatologists believe that MTX is the drug of choice, the most convenient for long-term treatment of RA. Many clinical doctors think that MTX is superior in comparison with other DMARDs drugs. Inhibition of the DNA synthesis and the inhibitory effect on cell proliferation, on the activity of lymphocytes and neutrophils, as well as the suppressive activity of cytokines are the most important mechanisms of MTX in the treatment of RA. It has an impact on the modification of the course the disease, improves the signs and symptoms of inflammatory synovitis, prevents and decreases the rate of progression of joint erosions, which all contributes to the maintenance of the functional status. Early treatment of RA with MTX is of great importance aiming to reach the maximal efficacy of treatment, and eventually to reach remission of disease and better therapeutic response to treatment.

The results of this study are similar to those of a clinical study of early RA considering the mean values of the set of 28 palpation painful, sensitive and the set of 28 swollen, edematous joints, reactants of the acute phase, as well as the laboratory parameters. Differences are due to variations in the number of patients and the disease activity at the beginning of the study (14). Following all the previously exposed 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 is unpredictable, progressive and individual, versus the group of patients treated with MTX, in whom suppression of the disease was achieved, clinically expressed with a decrease in the mean values of the scores of the two articular indexes, with laboratory parameters (correction of anemia and thromocytosis), as well as the acute phase reactants (with a decrease in the values of ESR at the following controls and increase in the number of patients who were CRP negative).

There are other studies which confirm the association of these two parameters, but they are cut-off studies and with a smaller number of patients (15, 16). They also emphasize the benefit of CRP as the most useful biochemical marker in the evaluation of activity of the disease.

Nowadays most rheumatologists strongly recommend early introduction of MTX in the treatment of RA. However, even early treatment with MTX does not stop the total progression of the disease in certain patients, and what is more important the term early is defined discussible (17, 18).

Quantitative evaluation of the disease activity with the shown measurements enables assessment of the actual condition of the patient and also helps clinical doctors to be more effective in the modification of the therapeutical access. In conclusion, CRP is the most useful marker in the prospective follow-up of patients with RA.

References

1. Pincus T, Strand V, Koch G, Amara I, Crawford B, Wolfe F, et al. An index of the three core data set patient questionnaire measures distinguishes efficacy of active treatment from that of placebo as effectively as the American College of Rheumatology 20% response criteria (ACR20) or the Disease Activity Score (DAS) in a rheumatoid arthritis clinical trial. Arthritis Rheum 2003; 48: 625–30.
2. Pincus T, Amara I, Koch GG. Continuous indices of core data set measures in rheumatoid arthritis clinical trials: lower responses to placebo than seen with categorical responses with the American College of Rheumatology 20% criteria. Arthritis Rheum 2005; 52: 1031–6.
3. Buchbinder R, Bombardier C, Yeung M, Tugwell P. Which outcome measures should be used in rheumatoid arthritis clinical trials? Clinical and quality-of-life measures' responsiveness to treatment in a randomized controlled trial. Arthritis Rheum 1995; 38: 1568–80.
4. Ranganath VK, Elashoff DA, Khanna D, Park G, Peter JB, Paulus HE. Age adjustment corrects for apparent differences in erythrocyte sedimentation rate and C-reactive protein values at the onset of seropositive rheumatoid arthritis in younger and older patients. J Rheumatol 2005; 32: 1040–2.
5. Wolfe F. Comparative usefulness of C-reactive protein and erythrocyte sedimentation rate in patients with rheumatoid arthritis. J Rheumatol 1997; 24: 1477– 85.
6. Arnett FC, Edworthy Sm, Bloch Da, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988; 31: 315–24.
7. Van Gestel AM, Prevoo MLL, Van't Hof MA, Van Rijswijk MH, Van de Putte LBA, Van Riel PLCM. Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Arthritis Rheum 1996; 39: 34–40.
8. Prevoo ML, Van't Hof MA, Kuper NH, Van Leeuwen MA, Van de Putte LB, Van Riel PL. Modified disease activity scores that include 28-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis. Arthritis Rheum 1995; 38: 44–8.
9. Balsa A, Carmona L, González-Álvaro I, Belmonte MA, Tina X, Sanmartí R. Value of DAS-28 and DAS 28-3 as compared to ACR-defined remission in rheumatoid arthritis. J Rheumatol 2004; 31: 40–6.
10. Prevoo MLL, Van Gestel AM, Van't Hof MA, Van Rijswijk MH, Van de Putte LBA, Van Riel PLCM. Remission in a prospective study of patients with rheumatoid arthritis. American Rheumatology Association preliminary remission criteria in relation to the disease activity score. Br J Rheumatol 1996; 35: 1101–5.
11. Smolen JS, Breedveld FC, Eberl G, Jones I, Leeming M, Wylie GL, et al. Validity and reliability of the twenty-eight-joint count for the assessment of rheumatoid arthritis activity. Arthritis Rheum 1995; 38: 38–43.
12. Hassell AB, Davis MJ, Fowler PD, Clarke S, Fisher J, Shadforth MF, et al. The relationship between serial measures of disease activity and outcome in rheumatoid arthritis. Q J Med 1993; 86: 601–7.
13. Anderson JJ, Chernoff MC. Sensitivity to change of rheumatoid arthritis clinical trial outcome measures. J Rheumatol 1993; 20: 535–7.
14. Nell VP, Machold KP, Eberl G, Stamm TA, Uffmann M, Smolen JS. Benefit of very early referral and very early therapy with disease-modifying anti-rheumatic drugs in patients with early rheumatoid arthritis. Rheumatology 2004; 43: 906–14.
15. Kadir Y, Saliha K, Meltem AM, Gurhan G, Mahir U, Kazim S. Associations between Acute Phase Reactant Levels and Disease Activity Score (DAS28) in Patients with Rheumatoid Arthritis. Annals of Clinical & Laboratory Science 2004; 34: 423–26.
16. Matsui T, Kuga Y, Kaneko A, Nishino J, Eto Y, Chiba N, et al. Disease Activity Score 28 (DAS28) using C-reactive protein underestimates disease activity and overestimates EULAR response criteria compared with DAS28 using erythrocyte sedimentation rate in a large observational cohort of rheumatoid arthritis patients in Japan. Ann Rheum Dis 2007; 66: 1221–6.
17. Van der Heide A, Jacobs JW, Bijlsma JW, Heurkens AH, Van Booma-Frankfort C, Van der Veen MJ, et al. The effectiveness of early treatment with »second-line« antirheumatic drugs. A randomized, controlled trial. Ann Intern Med 1996; 124: 699–707.
18. Hider SL, Buckley C, Silman AJ, Symmons DP, Bruce IN. Factors influencing response to disease modifying antirheumatic drugs in patients with rheumatoid arthritis. J Rheumatol 2005; 32: 11–16.

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