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RADIOGRAPHIC ASSESSMENT OF JOINT DAMAGE IN EARLY RHEUMATOID ARTHRITIS PATIENTS TREATED WITH METHOTREXATE

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Abstract

In rheumatoid arthritis (RA), progression of the radiographic damage of hand and feet joints is a significant and objective variable for evaluation of disease activity as well as measurement of treatment outcome**.** The aim of this study was to evaluate the RA activity with radiographic evaluation of hand joints in patients with early RA treated with Methotrexate by using acute phase reactants, as rheumathoid factor (RF), C-reactive protein (CRP) and DAS28 index of disease activity.

We tested 70 participants (35 control patients, 35 untreated RA patients). Patients were treated with Methotrexate at an average dose of 10 mg once weekly. For clinical evaluation of disease activity radiographic index (RI), sedimentation, CRP and RF in certain time intervals (0-time, after 6, 9 and 12 months) were analyzed in every patient.

RI showed an increased radiographic progression of hand joint damage in time intervals between 0-time and 9 months (p=0,0167) and between 0-time and 12 months (p=0.0089). The statistical analysis showed statistically significant differences among mean values of ESR in the four-time intervals (p=0.00002).

Keywords: rheumatoid factor, acute phase reactants, rheumatoid arthritis

Introduction

Every synovial joint could be involved in the early phase of RA. However, mainly affected are knuckle joints of the hand, metacarpophalangeal (MCP), proximal (PIP) and metatarsophalangeal (MTP) joints [1]. Progression of the radiographic damage of the hand and feet joints is a significant and objective variable for evaluation of disease activity as well as for measurement of treatment outcome [2].

Chronic synovitis usually is the reason for irreversible destructive changes of joint's cartilage and subchondral bone. Conventional anteroposterior radiograms of the hands and feet are used for detection of structural changes that lead to loss of the joint space and appearance of erosions, quantified with methods that should be reproducible and should enable dynamic follow-up of changes. Radiographic evaluation of joint damage is based on the standardized methods (1950) for evaluation of treatment outcome in RA [3].

In the last few decades, a lot of numerical methods – radiographic indexes have been proposed for detection of the radiographic abnormalities of the hand, wrist and feet joints (which refer to the counting of erosions, tight joint spaces in some joints or evaluation of joint damage with graduation). Radiographic indexes are mainly semiquantitative methods that enable displaying of joint damages expressed in numerical values – scores, which directly assess two anatomic characteristics of joints in RA – cartilage damage and joint destruction. Series of radiographic scores express the rate of joint damage progression and are predictors of disease outcome. Evaluation of the rate progression of joint damage enables selection of high-risk groups for aggressive course of disease and points the need of early and suitable treatment [4].

Standard indexes for evaluation of the disease damage are Sharp and Larsen radiographic indexes [5]. Both methods have been modified several times [6-7]. Biochemical variables such as ESR and CRP (reactants of the acute phase) indirectly reflect synovitis, but at the same time they are sensitive tools for objectivization and measurement of the immuno-co-mediated inflammatory response in RA. Simultaneous tests are recommended especially for ESR, CRP and RF (which represent reversible inflammatory variables), with clinical and radiographic variables (reversible) of the inflammatory synovitis. They are used to evaluate which of these three parameters better correlate with the other articular and radiographic indexes of disease activity. Taking into consideration the changeable course of disease activity, the most appropriate are serial measurements of ESR and CRP (time integrated) for credible evaluation of RA [8-10].

Reports from the studies are paradoxical in terms of joint damage and inflammatory synovitis expressed in the acute phase reactants. Although there is a correlation between radiographic progression and the reactants of the acute phase, certain studies show that erosion progresses despite suppression of the joint inflammation.

ACPA autoantibodies react with linear synthetic peptides that comprise unusual amino-acid citrulline. They are present in 76% in RA, with specificity of 96%. Antibodies in patients with RA are predominantly from IgG class and have relatively high affinity. The ELISA test, based upon these cyclic citrullinated peptides (CCP), haa superior characteristics in detection of RA, with different sensitivity and specificity. Sensitivity of the anti-CCP test in different population varies between 64% and 74%, while specificity varies between 90% and 99%.

Aim

The aim of this study was to evaluate the RA activity with radiographic evaluation of the hand joints, reactants of the acute phase (ESR and CRP), ACPA autoantibodies and to analyze them as prognostic markers of disease outcome in patients with RA, treated with Methotrexate.

Material and methods:

The disease diagnosis in patients included in the study was made upon the classification criteria from the European Leaque against Rheumatism (EULAR), and diagnostic criteria for classification of RA by 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.

In this study we examined 35 pts (25 women, 10 men) suffering from RA, as well as 35 pts (20 women, 15 men) as a healthy control group. Their mean 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. The mean disease duration from the beginning was 43.97 (± 45.23) months, in the interval 6-48 of months.

The examinations were made in 4 time points: 0-time, after 6, 9 and 12 months. For the first time in these patients immunomodulatory therapy with Methotrexate was indicated (average dose 10 mg once weekly), in addition to the treatment with non-steroidal anti-rheumatics. At the same time the preventing effect of Methotrexate therapy was evaluated, measuring the free interval from the moment of entrance in the study to the occurrence of the first erosion.

None of the patients included in the study has previous or actual hystory of disease.

For radiographic assessment of disease progression in the specified time intervals in every patient was analyzed the radiographic index which evaluates 29 joint surfaces for bone erosions and destructions and 27 joints for tight joint spaces on every hand and wrist joint.

The sum of the score for erosions and score for tight joint spaces represents the total (TS) score of joint destruction from 0-5. Joints evaluated for erosions on every hand and wrist are: 14 joints on the fingers, 5 metacarpal, 8 carpal, radio-carpal and radio-ulnar. Each and every joint is evaluated for erosions, scoring from 0-5. The sum of the individually evaluated joints for erosions and destruction gives the cumulative score for joint damage of hands and wrists.

The score for tight joint spaces was evaluated on 27 joints on every hand and wrist (14 joints on the fingers, 5 carpometacarpal, carpal, radio-carpal and radio-ulnar joints). Scoring is from 0-4 depending on the distance of the joint space. The sum of the individual scores gives the cumulative score for tight joint spaces.

Clinical evaluation of the 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, auto-immune 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. This test is complementary tool in diagnosing patients with RA.

Principles of work

The microtiter walls are wrapped with high protein synthetic cyclic peptide that contains modified arginine residues. In the period of the first incubation specific autoantibodies from deluted

serum or plasma are binding for the antigen wrapped surface. After that the probe is washed to get rid of the unbound components.

During the second incubation the conjugate, which is an enzyme for monoclonal autoantibody for human IgG is bound to the surface as autoantibody. After the second wash, the specific autoantibodies are incubated with the substrate.

By adding the stop solution, the reaction is interrupted, which results in colored end-product. The amount of the absorbed conjugate is expressed with absorption units. In the qualitative protocol, the amount of the absorbed conjugate that is bound to the sample is compared to that from the reference control. In the semiquantitative protocol, the anti-CCP concentration of autoantibodies could be expressed in percentage with interpolation of the curve based upon the standard.

Calculation and interpretation of the results for the qualitative protocol was done from the absorption value (optical density), from the positive and negative control for every sample.

$$\text{Absorbent value} = \frac{\text{Sample or control absorbent value}}{\text{Mean referent control absorbent value}}$$

Absorbent value	**Interpretation of results**
<0.95	negative
≥0.95≤1.0	borderline
>1.0	positive

Statistical analysis

Data analysis was made with the statistical package Statistica 7.0.

For data processing we used statistical methods for measuring central tendency. 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 made. P-value between 0.05 and 0.1 was considered to be statistically significant.

Results

RA was evaluated following the dynamics of the changes of the mean values of the RI score, mean values of sedimentation, 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	Erosive score	Tight joint space	Total score
0 time	0 - 2	0 - 16	0 - 18
6 months	0 - 3	0 - 20	0 - 23
9 months	0 - 5	0 - 20	0 - 25
12 months	0 - 6	0 - 20	0 - 26

1. The analysis made with Wilcoxon test showed that differences in the average number of tight joint spaces were statistically significant between 0 time and 9 months for p = 0.0288, as well as between 0

time and 12 months for p = 0.0205. Differences in the average number of tight joint spaces were not statistically significant (p > 0.05).
2. Differences in the average number of erosive changes were statistically significant between 0 time and after 9 months for p = 0.0169, as well as between 0 time and after 9 months for p = 0.0034. The differences considering the average number of erosive changes between other measurements were not statistically significant (p > 0.05).
3. Differences in the average number of total score were statistically significant between 0 time and 12 months for p = 0.0167, as well between 0 time and 18 months for p = 0.0089. Differences in the average number of the total score between other measurements were not statistically significant (p > 0.05).
Analysis with Wilcoxon test showed that the differences in the average number of tight joint spaces were not statistically significant among all measurements (p > 0.05).
4. Differences in the average number of erosive changes were not statistically significant among all measurements (p > 0.05).
5. Differences in the average number of total score were not statistically significant among all measurements (p > 0.05).
6. Friedman's analysis of variance showed that there were no statistically significant differences between mean values of ACPA, mean time intervals - Fr $\chi^2 = 1.017$ p = 0.3875 (standard deviations showed great variations). $\chi 2$ test showed that the number of patients in whom values of ACPA were negative increased over time, but differences were not statistically significant ($\chi 2 = 1.99$ df = 3 p = 0.573) (Fig.1).

Table 2. Mean values of sedimentation, CRP and RF in patients with RA

Time intervals	0 time	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
Se 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

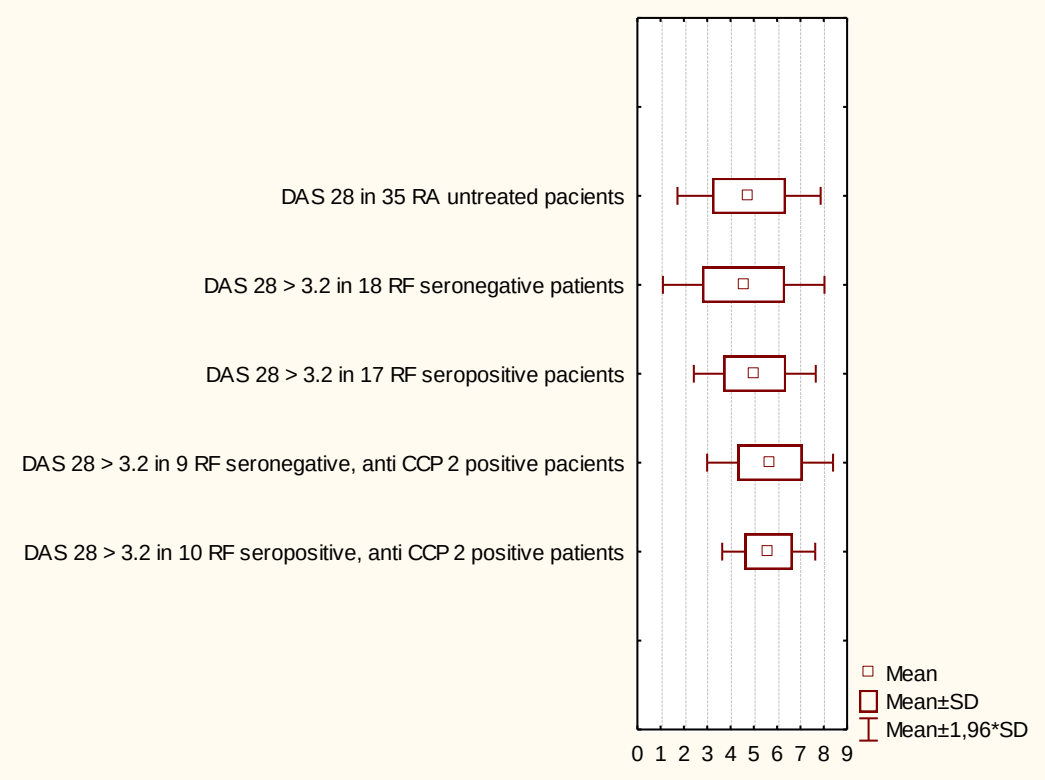

Fig. 1. Mean values of DAS 28 in patients with RA

In 0 time, changes in RI were registered in 10% of pts; in 2 of them changes in the score of tight joint spaces and in 1 changes in the erosive score. Two of them were with elevated values of RF and CRP, while in 1 negative values for RF and CRP were registered.

After 6 months from the beginning of treatment with Methotrexate, we registered progression of the score for tight joint spaces in 12 pts, and in 13 (44%) pts progression of the total score (TS). Four pts had negative values of RF and CRP. In the remaining pts elevated values of RF and CRP were registered.

After 9 months from the beginning of the treatment with Methotrexate, progression of the score for tight joint spaces was registered in 14 pts, and in 15 (50%) pts progression of the TS. In 9 pts elevated values of RF were registered, and in 6 pts elevated values of CRP.

After 12 months from the beginning of treatment with Methotrexate, the number of patients regarding the score for tight joint spaces and erosive score was equal as in the previous control (after 9 months), i.e., in 15 (50%) pts progression of the score of the Sharp's index was registered. In 9 of them, elevated values of RF were registered, and in 11 pts negative values for CRP.

In terms of ESR, we registered consecutive decrease of the values in each successive control and in specified time intervals in most patients progression of the RI score.

Discussion

The disease activity and the therapeutic effect of Methotrexate were evaluated by following the dynamics of the radiographic progression, acute phase reactants and ACPA antibodies. With reference to the progression of joint damage, the statistical analysis showed that the differences in the average number of erosive changes were statistically significant between 0 time and after 9 months, as well as between 0 time and 12 months (similar to the reports from the literature for slower radiographic progression in the course of 12 months and for faster progression after that) [11].

Statistically significant differences were found in the number of tight joint spaces between 0 time and after 9 months, as well as between 0 time and after 12 months. The total score consisting of the cumulative sum of cores for sedimentation and joint space showed also statistically significant differences in equal time intervals.

Reports from several clinical studies regarding the rate of radiographic progression of the joint damage are heterogeneous. Two studies found neither radiographic progression, nor radiographic improvement (absence of periarticular soft tissue swelling and juxtaarticular osteoporosis) after one year therapy in most of the patients [12-13].

Other three studies reported radiographic progression (without radiographic improvement), despite of clinical improvement in most patients [14], which was similar to the results obtained in our group of patients with RA, as well as with the results from another study were more expressed radiographic progression of the erosions after 6 and 9 months from the treatment in comparison with the first 6 months in early RA were found, with linear progression of the erosions [15].

Statistical analysis showed that there were no statistically significant differences of ACPA in the four time intervals (standard deviations showed great variations). Some patients had very elevated values of ACPA.

The number of patients in whom the values of ACPA were negative increased within the course of time, but the differences were not statistically significant. Just in patients with elevated values of ACPA increased progression of disease damage was noticed in the probe time intervals of RA activity.

The knowledge from several studies has shown that the radiographic progression of the hand joint damage continues despite the decrease of the mediators of inflammation, although there is mutual dependence among inflammatory variables and acute phase reactants from one side and radiographic joint damage from the other side [16-17].

The significant difference in regards to inflammatory variables and joint destruction has been recently proved in experimental modes of arthritis [18-24].

It seems that it is present only in the very early phase of the disease when the inflammation is active, but cartilage and bone structures are not entirely affected. Data suggest that, although the inflammation could stop similarly in very early RA, the joint damage process once started somehow is partly "autonomous" later. Follow-up of the patients in the four time intervals showed a higher progression of the joint damage in patients with elevated values of RF and CRP.

The chronic active course of RA reflects the elevated values of the reactants of the acute phase, sedimentation, CRP and rapid radiographic progression [25].

CRP is more superior in comparison with sedimentation, as a predictor for radiographic progression and indicates a higher correlation of CRP with radiographic progression than with the number of sensitive joints, Ritchie's articular index or number of swollen joints.

The same study showed that in regards to radiographic progression, it correlates more with serial measurements of CRP than with sedimentation and/or articular indexes.

Radiographic progression was noticed also in normal values of CRP with tendency of greater progression in the already damaged joints, with smaller number of newly involved joints.. CRP more precisely and in a shorter period reflects the changes in disease activity in comparison with sedimentation which registers changes in RA activity after few weeks.

Conclusion

ACPA antibodies are useful in everyday clinical practice in diagnosis of early untreated RA. ACCP antibodies are excellent serologic markers in diagnosis and differential diagnosis of RA and are a clear predictor of aggressive course of the disease. Reactants of the acute phase enable selection of the high risk groups for aggressive disease course and indicate the need for early and aggressive treatment in selected patients.

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