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THE EFFECTS OF COMBINED THERAPY OF RHEUMATOID ARTHRITIS ON THE ACUTE PHASE REACTANTS

UČINCI KOMBINIRANE TERAPIJE REUMATOIDNOG ARTRITISA NA REAKTANTE AKUTNE FAZE

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Summary

The paper presents the results of studies of acute phase reactants in the 60 treated patients with rheumatoid arthritis. Patients were divided into two groups, depending on the applied treatment: group I (n=30) was treated with methotrexate, sulfasalazine and hydroxychloroquine, and group II (n=30) with methotrexate. The results of our study shows that there is a statistically significant reduction in the value of acute phase reactants and clinical parameters after treatment in both investigated groups of patients, and also a significant statistical difference between the first and second group of treated patients.

Keywords

rheumatoid arthritis, combined therapy, acute phase reactants

Sažetak

U radu su prikazani rezultati ispitivanja reaktanata akutne faze u 60 liječenih bolesnika s reumatoidnim artritisom. Bolesnici su bili podijeljeni u dvije skupine, ovisno o primijenjenoj terapiji: I. skupina (n=30) je liječena metotreksatom, sulfasalazinom i hidroksiklorokinom, a II. skupina (n=30) metotreksatom. Rezultati našega istraživanja pokazuju da postoji statistički značajno smanjenje vrijednosti reaktanata akutne faze i kliničkih parametara nakon liječenja u obje ispitivane skupine bolesnika, a također i značajna statistička razlika između prve i druge skupine liječenih bolesnika.

Ključne riječi

reumatoidni arthritis, kombinirana terapija, reaktanti akutne faze

Introduction

In clinical practice, the most common laboratory testing is erythrocytes sedimentation rate (ESR) according to Westergreen. In rheumatic inflammatory diseases, ESR can be accelerated, which indicates the degree of inflammation. In these diseases, the measurement of ESR helps to monitor the activity of disease and therapeutic response. ESR can be accelerated in elderly, by anemia and hypercholesterolemia, in pregnancy and in kidney chronic failure. ESR can increase as a result of growing of fibrinogen and gamma-globulins. According to the current opinions, it the value for the first hour of measure is enough (1).

CRP increases 10-1000 times in the first 5-10 hours and it is presented as response in bacterial processes and in autoimmune diseases. Measurement of CRP concentration serves to monitor the activity of rheumatoid arthritis and other autoimmune diseases. Fibrinogen is a weaker reactant during the acute phase; 24-48 hours after the necrosis of tissue its levels raise 2-3 times.

In the acute phase of rheumatoid arthritis (RA), all inflammatory parameters are positive. In the assessment of disease activity and monitoring of the disease it is sufficient to measure ESR, the concentration of CRP and fibrinogen.

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Disease-modifying antirheumatic drug (DMARDs) belong to the category of anti-rheumatics used in early stage of disease, which slow the progress of the disease and prevent injuries and disabilities by achieving normalization of optimal function of joints. DMARDs, including injectibile and oral form of gold therapy, hydroxychlorochine sulphasalazine and methotrexate, have visible effects. Normalization of ESR and CRP in most of the patients is presented after 14 days, with disease remission after 1-2 months (44%), and complete improvement (in 45% of researched cases) (1). Treatment can start in the early phase and dosage should be individualized in accordance with the patient's tolerance and therapeutic response. Recently, methotrexate combined with sulphasalazine and hydroxychloroquine has shown to be more effective compared to the methotrexate therapy alone.

Mechanism of DMARDs is unknown. Various authors have attempted to explain the results obtained through the elimination of immunocompetence lymphocytes (1). Thus, immunosuppresion, as a result of the action of cytostatics, is clarified by inhibition of the responsible cell and humoral immunity. During the application of DMARDs, authors noticed the reduction of ESR, CRP, fibrinogen, as well as rheumatoid factor titer in serum, while the antiphlogystic action explains inhibition with the creation of inflammatory mediators (2). The best results are achieved if the usual dose is given. There are numerous side effects more frequent in the gastrointestinal system, alopecia, hemorrhagic cystitis, stomatitis, bacterial and mycosis infections, leucopenia, thrombocytopenia, while later side effects include hepatitis, azo- or oligospermia, fibrosis of the ovaries and malignant diseases (2).

Objective of study

The aim of the study was evaluation of the action of combined therapy in reactants in the acute phase and clinical symptoms in patients with rheumatoid arthritis. Hence, the purpose of study was the evaluation of drugs action that modifies disease (DMARDs) on reactants in the acute phase: ESR, CRP and fibrinogen, while clinical parameters were followed by the number of swollen joints and the number of sensitive joints in palpation.

Material and methods

In this study, in the Clinical Rheumatologic Department, in group I 30 patients were investigated (24 women and 6 men) with rheumatoid arthritis, with age of 23-72 (average age 46) treated with the onset therapy (MTX); in group II 30 patients (23 women and 7 men) with age 21 to 69 (average age 45) that were treated with triple therapy (MTX, SSZ, HCQ).

Patients involved in the study were part of the first and second functional phase according to Steinbrocker, revised by ACR - American College of Rheumatology's (1991) (3). Similarly, the majority of patients were in the first and second anatomic phase of radiological changes.

To all patients treated with DMARDs, conforming to the recommendations of the ACR (4), we conducted pre-therapeutic laboratory evaluation of the following parameters: rheumatoid factor, the number of erythrocytes, leukocytes, platelets, red blood cell formula, enzymes and urine analysis. From the data of patient's history, we have excluded the possibility of giving this medication to patients with any form of previous hepatitis. In the pre-therapeutic period, we did not have clinical indication for conducting of chest X-ray and lung functional tests.

We have done further monitoring through laboratory tests, performed every 14 days. At this stage, we incorporated the tests: hematological analysis (erythrocytes, leukocytes, platelets), biochemical analysis (liver analysis and enzymes), urine analysis and functional lung tests every month.

ESR, CRP and fibrinogen were tested at the beginning and at the end of treatment. For evaluation of the therapeutic effects subjective and objective parameters were used (average value of morning stiffness, grip of hands, and intensity of pain and average value of swelling). We used methodology of descriptive phase according to Likert for assessment of pain (5).

We have done statistical analysis of the results we obtained through the structure indicators and estimates of arithmetic averages. We have identified homogeneity set of statistics on the basis of these statistical parameters: the variation interval, standard deviation and coefficient variation. We tested with the T-test of arithmetic averages for small dependent samples to find the difference between arithmetic average, and we tested with the χ^2-test for no parametric data. All results obtained are presented in form of table.

Results

In table 1, we have presented gender structure of patients in group I and II of the research study. In the overall structure of the cases involved in the research, in the group I there were more females than males (80% vs. 20%), and in group II more males than females (77% vs. 23%), which is a statistically significant ($p<0.003$).

The average age of patients in the group I was 42.90 years old, while in group II 47.20 years old.

With the purpose of justifying the therapeutic effect of DMARDs, we followed subjective and objective parameters and laboratory analysis (SE, PCR, and fibrinogen) before and after the treatment, as presented in table 2.

Table 1. **Gender structure of patients in group I and II**
Tablica 1. **Podjela bolesnika po spolu unutar skupina I i II**

Gender	Group I		Group II	
	No.	%	No.	%
Male	6	20	7	23
Female	24	80	23	77
Total	30	100	30	100

p<0.003

groups before and after treatment (p<0.01). Therefore, therapy with DMARDs has good effects, and triple therapy has very good therapeutic effect on the reducing the length of morning stiffness.

The average value of grip of the hands to the patients of two groups before treatment was 67 to 64 mm, while after the treatment was 84 to 94 mm. In testing the average values of this parameter before and after treatment, we also found significant statistical difference (p<0.01). Triple therapy had much better therapeutic effect in terms of increasing the grip of hands after treatment, compared to the onset therapy.

Table 2. **Average values of objective and subjective parameters**
Tablica 2. **Prosječne vrijednosti objektivnih i subjektivnih parametara**

No.	Parameters	Before treatment		After treatment		T-test
		I	II	I	II	
1	Morning stiffness (min)	68	72	26	19	p<0.01
2	Grip of hands (mm)	67	64	84	94	p<0.01
3	Swollen in PIP joints (mm)	70	68	64	61	p<0.01
4	ERS	33	38	19	14	p<0.01
5	CRP	24	30	12	6	p<0.01
6	Fibrinogen	6.3	6.0	5.0	4.5	p<0.03

Table 3. **Structure of patients with rheumatoid arthritis according to pain intensity according to the descriptive phase of Likert**
Tablica 3. **Podjela bolesnika s reumatoidnim artritisom prema intenzitetu boli prema deskriptivnoj fazi Likerta**

Pain Modality	Code	Before treatment		After treatment	
		I	II	I	II
Without pain	0	0	0	8	12
Light pain	1	15	10	13	12
Medium pain	2	11	15	6	6
Sever pain	3	4	5	3	0
Extreme pain	4	0	0	0	0
Total		30	30	30	30

Average value of swollen proximal interphalangeal joints also has improved. At the beginning of treatment the average was 70 to 68 mm, and at the end of treatment, the average was 64 to 61 mm. By testing the average values swollen in proximal interphalangeal joints before and after treatment we found significant statistical difference (p<0.01) and with very good therapeutic effect of the triple therapy, in terms of reducing the swollen in PIF joints (table 2).

The average value of ESR before treatment was 33 versus 38, and after treatment was 19 versus 14. In testing average values, we found significant statistical difference regarding erythrocytes sedimentation rates values before and after treatment (p<0.01). Therapy with MTHX, CHQ and SSZ, in significant way, has improved ESR. The average value of PCR before treatment was 24 vs. 30, and after treatment was 12 versus 6. In testing average val-

Table 4. **Frequency of side effects in application of DMARDs** (MTX, SSZ, HCQ)
Tablica 4. **Učestalost nuspojava u primjeni DMARD-a** (MTX, SSZ, HCQ)

Side effects	Group I		Group II	
	No	%	No	%
Leucopenia	2	10	3	15
Thrombocytopenia	1	5	1	5
Proteinuria	1	5	1	5
Pruritus	1	5	1	5
GI disorders (nausea, eructation, epigastric pain)	2	10	2	10
With manifestations of side effects - subtotal	7	35	7	35
Without manifestation of side effects	13	65	11	55
Total	20	100	20	100

Average value of morning stiffness for all patients was 68 to 72 minutes at the beginning of treatment. The average value morning stiffness at the end of treatment was 26 to 19 minutes. In testing average values, we found difference with important statistical significance, respective to the duration of morning stiffness between the two

ues, we found significant statistical difference between PCR values before and after treatment ($p<0.001$). Treatment with combined therapy has significantly improved the PCR values in both groups, with a significant difference between group I and II ($p<0.001$).

The average value of fibrinogen before treatment was 6.3 to 5.0, and after treatment was 6.0 to 4.5. In testing average values, we found significant statistical difference in the values of fibrinogen before and after treatment ($p<0.03$), and also combined therapy has improved fibrinogen values in the two investigated groups.

The intensity of pain during treatment changed. Before treatment, all patients had light pain in the joints. (15 vs. 10), medium (11 vs. 15) and severe (4 vs. 5).

After treatment, dose of onset and triple therapy is reduced gradually. After therapeutic treatment, pain as a symptom was eliminated in 8 to 12 patients. Severe pain have persistent (3 vs. 0), while larger structure consisting patients with light pain (13 vs. 12 cases) and medium pain with the same number (with 6 cases) (table 3).

Side effects after taking DMARDs manifested only in 7 to 9 cases, of which leucopenia and gastrointestinal disorders, were more frequent (2 to 3 cases) than nausea, eructation and epigastric pain, while one in one case we observed thrombocytopenia, proteinuria and pruritus (table 4).

Discussion

Of the total number of 60 patients in both groups, in Group I were 24 females and 6 males, while in group II were 23 females and 7 males. This gender structure is consistent with other authors, who also found similar data, because as it is known, the disease attacks more women than men (6).

Improvement of subjective and objective parameters: the morning stiffness (before treatment 69.5 minutes to 69.5 minutes, while after treatment 26 minutes to 21); grip of the hands (67 to 62, while after treatment 85 to 92), and the intensity of pain, which after treatment was reduced gradually (only two patients had severe pain, pain was eliminated in five patients, while the pain was greatly reduced to others), and other data is consistent with the data of other authors, who also after treatment with DMARDs, not in large doses, have achieved high results in the treatment of patients with rheumatoid arthritis (7,8). Parameters that have shown greatest improvement to our patients were grip of hands and morning stiffness, while swollen PIF joints has shown less improvement.

Also, the average reduction in erythrocytes sedimentations rate, PCR and fibrinogen before and after treatment were statistically significant, and the results are consistent with the data of other authors. In our study, side effects were diverse from thrombocytopenia, leucopenia, pruritus, as well as gastrointestinal side effects. These results are consistent with findings of side effects even in the work of other authors (9,10,11).

Conclusions

Therapy combined with DMARDs (MTX, SSZ, and HCQ) is preferable to the patients with rheumatoid arthritis.

General doses of MTX of 15 mg/weekly, SSZ 2-3 grams and HCQ from 400 mg give high improvements in subjective and objective parameters. Early inflammatory reactants (ESR, CRP and fibrinogen) have improved after the application of DMARDs. Gastrointestinal side effects, leucopenia, thrombocytopenia had transitory character, disappearing after temporary termination of methotrexate. DMARDs (MTX, SSZ, HCQ) were not stopped to any patient due to toxic action.

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