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Original article

Targeting Inflammation: Cohort Study of the Influence of Methotrexate Therapy on Sideropenic Anemia and Reduction of Inflammatory Markers in Rheumatoid Arthritis Patients

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SUMMARY

Background/Aim. Rheumatoid arthritis (RA) is a systemic autoimmune disease that can cause destructive joint disease and progressive disability. The diagnosis of RA is based on laboratory and clinical evidence, which includes the analysis of inflammatory markers, hematological, and biochemical parameters.
Methods. Fifty patients diagnosed with RA without methotrexate (MTX) therapy and 50 patients with therapy (MTX, 7.5 mg/week; after three months prednisolone 10 mg/day) were included in this study. After six months of therapy, inflammatory biomarkers, hematological, and biochemical parameters were analyzed.
Results. Inflammatory biomarkers: sedimentation rate (SE), C-reactive protein (CRP), and anti-cyclic citrullinated peptide (anti-CCP) are significantly lower in the group of patients on therapy compared to patients without MTX therapy. Significant differences were not found for the rheumatoid factor (RF). Significant differences were not found for hematological parameters between the compared groups. Analysis of serum biochemical parameters showed significant differences for aspartate aminotransferase (AST) and iron values. In patients without MTX therapy, the incidence of anemia was recorded in 68%, which is significantly higher than the incidence of 32% in patients with therapy.
Conclusion. Prescribed therapy has shown effectiveness in the treatment of RA and reduction of the inflammatory process. The success of the treatment depends on the timely diagnosis of RA. Postponement of therapy and late-detected disease prolongs therapy treatment and often requires a combination of several drugs.

Keywords: **rheumatoid arthritis, anti-cyclic citrullinated peptide, C-reactive protein, methotrexate**

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic and progressive autoimmune disease, which causes joint impairment, arthralgia, joint swelling, disability, and shortened life expectancy (1). It is characterized by erosive synovitis associated with many inflammatory conditions (2). Patients diagnosed with RA have an increased risk of coronary heart attack, arterial sclerosis, and stroke (3). The diagnosis of RA is based on laboratory and clinical evidence that includes determination of inflammatory markers: rheumatoid factor (RF) test, erythrocyte sedimentation rate (SE), C-reactive protein (CRP), and cyclic citrullated peptide antibody test **(**anti-CCP test) and a blood count. The origin of RA is not fully understood, but current research suggests a combination of several possible factors, such as an abnormal autoimmune response, genetic predisposition and viral and/or bacterial infection.

Common symptoms of RA include morning stiffness, fatigue, fever, weight loss, tenders, swollen and warm tenders, and rheumatoid nodules under the skin. The onset of this disease is usually from the age of 35 to 60 years, with remission and exacerbation (4, 5). The aim of treating rheumatoid arthritis is clinical remission of the disease. If the treatment of RA is prolonged, progressive bone impairment occurs, along with the appearance of joint deformities with a complete loss of their function (6, 7). Treatment for RA is used to reduce joint inflammation and pain, maximize joint function, and prevent joint destruction and deformity. Treatment regimens consist of combinations of pharmaceuticals, weight-bearing exercise, educating patients about the disease and rest. Treatments are generally customized to a patient's needs and depend on their overall health. This includes factors such as disease progression, age, overall health, occupation, compliance and education about the disease.

Treatment of RA includes the use of glucocorticosteroids (GCs), most often in combination with other antirheumatic drugs–disease modifying antirheumatic drugs (DMARD) (8-10). A large number of GCs are available whose main role is to reduce inflammatory processes and pain, and their use depends on the degree of tissue involvement and the duration of the disease. Well-known drugs from the group of GCs are: budenofalk, dexamethasone, prednisolone, and berlicort. DMARDs are recommended in the first three months after the onset of rheumatoid arthritis symptoms with the aim of reducing inflammatory processes, improving joint function, achieving remission, and preventing permanent damage (11-13).

Well-known drugs from this group are: methotrexate (MTX), leflunomide, antimalarial, penicillamine, hydroxychloroquine, and sulfasalazine (14). Treatment of RA begins with MTX, which has been declared the essential drug by the World Health Organization (WHO). MTX is a structural analogue of folic acid that competitively inhibits the binding of dihydrofolic acid (FH2) to the enzyme that is responsible for converting FH2 to folinic acid (FH4). Without FH4, the metabolism of purine and pyrimidine is impaired, and the synthesis of amino acids and polyamine is inhibited (15). MTX prevents further permanent damage that occurs if rheumatoid arthritis is left untreated (3). The dosage of MTX depends on the activity, duration of the disease, age and comorbidities; standard doses are from 7.5 to 25 mg per week. Side effects caused by MTX can be symptomatic (nausea, headache, fatigue, mucositis) and potentially life-threatening (cytopenia, hepatotoxicity, pulmonary damage, sudden vision loss, and nephrotoxicity) (16).

The goal of our research was to analyze the effectiveness of RA patient therapy at the hematological, biochemical, and inflammatory levels.

PATIENTS AND METHODS

Participants and inclusion criteria

This study included 100 patients diagnosed with rheumatoid arthritis (RA). Clinical parameters for patients in these studies were taken from the database of the University Clinical Hospital in Mostar (Bosnia and Herzegovina). Access and use of data was approved by the Ethics Committee of the University Clinical Hospital Mostar, number: 834/21. Diagnosed RA and informed consent of all participants were the criteria for inclusion in the study. The diagnosis of RA was made based on the patient's history, physical examination, laboratory and radiological findings. The subjects were divided into two groups of 50 patients each, patients on therapy (Th), and patients without MTX therapy (NTh). Therapy included methotrexate (MTX) in the initial stage of the disease, 7.5 mg per week, according Lopez-Olivo MA et al. (17) weekly doses that ranged between 5 mg and 25 mg, and after three months prednisolone

10 mg (1 x 1). After six months on therapy, blood was sampled for analysis. The study included patients who were not on therapy, and based on the anamnesis, it was determined that the disease had been present for an average of six months. Patients without MTX therapy were under medical supervision and used non-steroidal anti-inflammatory drugs (NSAIDs), and according to ACR/EULAR criteria and DAS28-ESR score, did not require treatment with the use of DMARDs (18).

Inflammatory markers

The analysis of inflammatory markers included the titer of rheumatoid factor (RF), the value of anti-citrulline antibodies (anti-CCP), erythrocyte sedimentation rate (SE), and the value of C-reactive protein (CRP). The immunoturbidimetric method was used to analyze RF and CRP; the parameters were analyzed using a Beckman Coulter DxC 700 AU analyzer. SE value was determined by photometric principle using iSED®, fully-automated ESR analyzer, while anti-CCP was analyzed by ELISA method.

Biochemical parameters

Analysis of biochemical parameters included values of urea, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyltransferase (GGT), glucose, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), total cholesterol, triglycerides, and iron (Fe). All biochemical parameters were analyzed on a Beckman Coulter DxC 700 analyzer. Glucose was determined by the hexokinase method. HDL, LDL and triglycerides were determined by an enzymatic staining test. The photometric UV method was used to analyze enzyme activity (AST, ALT, and GGT). Iron was determined by a photometric staining test.

Hematological parameters

The analysis of hematological parameters included the number of platelets, erythrocytes and leukocytes, hemoglobin concentration, hematocrit values, values of the hematological indices: mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC). The mentioned hematological parameters were analyzed using an automated hematological analyzer Sysmex XN 1000 (Sysmex Corporation, Kobe, Japan).

Statistical analysis

Statistical analysis data was performed by variance analysis (ANOVA) using the IBM SPSS (Version 20.0, SPSS, Inc., Chicago, IL, USA). Differences between the groups were determined by a range test ($p < 0.05$ and $p < 0.001$). The Pearson's correlation coefficient was used as a measure of the strength of the linear association between the two variables.

RESULTS

Figure 1 presents the analysis of inflammatory markers. By comparing the results, significant values for CRP (Th = 12.15 mg/L; NTh = 23.12 mg/L), SE (Th = 20.98 mm/h; NTh = 40.60 mm/h) and anti-CCP (Th = 215.35 IU/mL; NTh = 355.07 IU/mL) were determined. Rheumatic factor values (Th = 89.26 IU/mL; NTh = 107.06 IU/mL) did not differ between the compared groups. The greatest variations of inflammatory markers were recorded for SE values. High individual variations were recorded in both examined groups.

Analysis of hematological parameters (Table 1) did not reveal statistically significant differences between the compared groups. Higher values of PLT and MCHC were recorded in the group of patients without therapy, while other observed parameters had similar average values.

The values of biochemical parameters are shown in Table 2. Statistically significantly higher values were recorded for the concentration of Fe and AST in Th group.

Table 3 shows the assessment of genetic predisposition for the development of RA. In 18% of respondents from the Th group, there is a genetic predisposition to the rheumatoid arthritis occurrence. In the NTh group, genetic predisposition was found in 28% patients. Although a genetic predisposition was confirmed, it was not significant.

The presence of anemia was recorded in 32% of subjects from the Th group and in 68% of patients from the NTh group (Table 4). Anemia of chronic disease was present in 15% of patients in the Th group, in 85% in the NTh group; 55% of subjects have sideropenic anemia in the Th group, and 45%

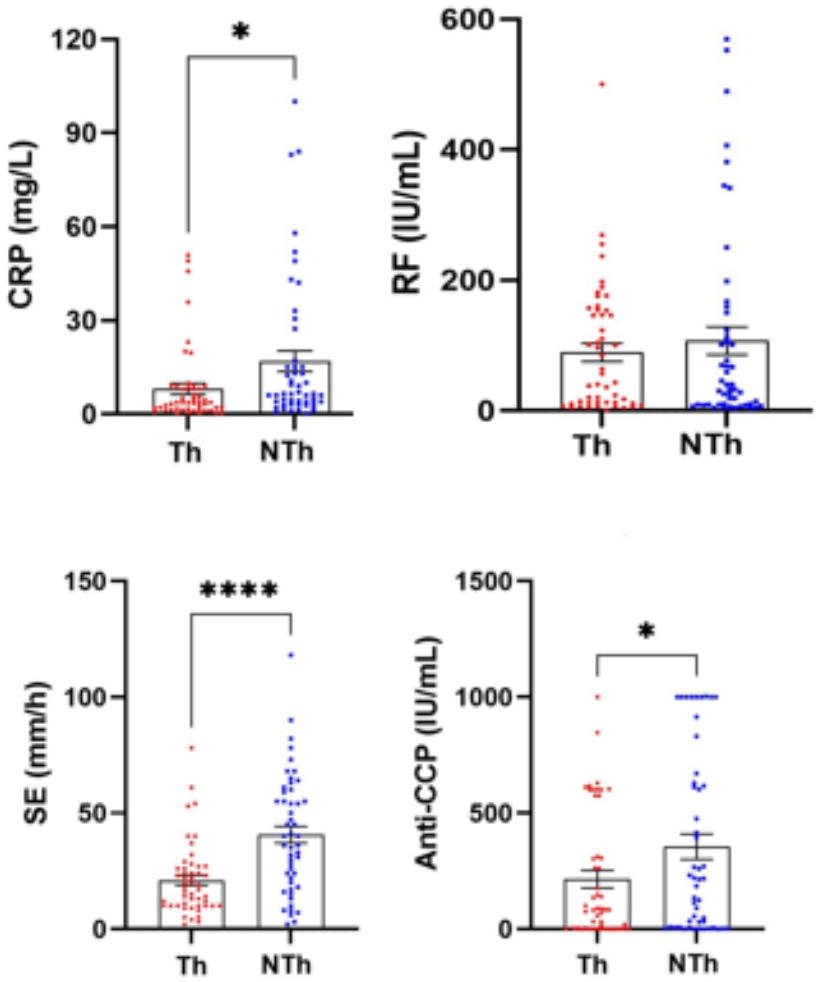

Figure 1. *Inflammatory biomarker values between groups (CRP—C reactive protein, SE— sedimentation rate; anti-CCP antibody; RF—rheumatoid factor). Th—patients with MTX therapy; NTh—patients without MTX therapy. *Significant at 0.05; ****Significant at 0.001. Data are presented as average and median*

Table 1. *Overview of hematological parameters*

Parameters	Reference range	Th	NTh	Sig.
RBC (x10^{12}/L)	4.20–5.90	4.56 ± 0.32	4.49 ± 0.48	0.371
WBC (x10^{9}/L)	4–10	8.01 ± 2.20	8.05 ± 2.37	0.920
PLT (x10^{9}/L)	150–400	252.32 ± 65.62	291.08 ± 78.31	0.270
Hb (g/L)	120–170	132± 12.95	131.10 ± 15.05	0.525
HCT (L/L)	0.356–0.510	0.40 ± 0.03	0.39 ± 0.04	0.203
MCV (fl)	83.0–97.2	88.03 ± 5.66	86.97 ± 4.78	0.313
MCH (pg)	27.4–33.9	29.07 ± 2.55	29.06 ± 2.31	0.977
MCHC (g/L)	320–345	331.24 ± 12.43	335.50 ± 14.07	0.111

Table 2. *Overview of biochemical parameters*

Parameters	Reference range	Th	NTh	Sig.
Fe (μmol/L)	8–30	15.30 ± 5.47	11.52 ± 4.28	0.000**
Urea (mmol/L)	3.0–9.2	5.71 ± 1.57	5.53 ± 1.97	0.620
Creatinine (μmol /L)	63.6–110.5	68.29 ± 15.52	73.94 ± 14.37	0.062
AST (U/L)	8–38	21.84 ± 6.09	18.75 ± 4.90	0.006*
ALT (U/L)	10–48	24.05 ± 11.27	20.31 ± 9.07	0.071
GGT (U/L)	10–50	20.91 ± 13.41	21.11 ± 12.87	0.939
GUK (mmol/L)	4.4–6.4	5.54 ± 1.34	6.24 ± 2.58	0.088
HDL (mmol/L)	1.03–1.55	1.78 ± 0.49	1.77 ± 0.57	0.872
LDL (mmol/L)	1.55–4.53	3.32 ± 0.77	3.45 ± 0.96	0.457
HOL (mmol/L)	3.1–5.5	5.74 ± 0.95	5.67 ± 1.09	0.756
TRIG (mmol/L)	0.46–2.28	1.49 ± 0.57	1.52 ± 0.62	0.770

*Significantly different at 0.05 and ** at 0.001

Table 3. *Genetic predisposition to the rheumatoid arthritis occurrence*

			Th	NTh	Total
Genetic predisposition	NO	N	41	36	77
		%	82	72	
	YES	N	9	14	23
		%	18	28	
Total		N	50	50	100
		%	100	100	
Pearson Chi-Square		F = 1.412 (p = 0.235)			

Table 4. *Types of anemia within the examined groups*

		Anemia presence		Anemia type	
		YES	NO	Anemia of chronic disease	Sideropenic anemia
Th	N	7	43	2	5
	%	32	55	15%	55%
NTh	N	15	35	11	4
	%	68	45	85%	45%
Pearson Chi-Square				F = 3.730 (p = 0.053)	

Table 5. *Correlation relationship of SE. RF and anti-CCP within the examined groups*

		SE-RF	SE-Anti-CCP	RF-Anti CCP
T-test	Th	0.323	0.000**	0.019
	NTh	0.649	0.007*	0.931

*Significantly different at 0.05 (P<0.05) and **at 0.00 (p < 0.001)

in the NTh group. Confirmed anemia was not significant when comparing both groups.

By comparing the values of inflammatory markers within the Th group (Table 5), a statistically significant correlation was found between the values of SE and anti-CCP, as well as RF and anti-CCP, while statistically significant correlation was not observed between the values of SE and RF. A statistically significant correlation in the NTh group was observed only between SE and anti-CCP values.

DISCUSSION

Rheumatoid arthritis (RA) is a chronic, inflammatory, systemic autoimmune disease affecting the joints with varying severity among patients. The risk factors include age, gender, genetics, and environmental exposure (8). As there is no cure for RA, the treatment goals are to reduce the pain and stop/slow further damage (19). Inflammatory markers (SE, RF, anti-CCP, and CRP) have great diagnostic significance in patients with RA. In our study, the six-month treatment of patients diagnosed with RA showed a statistically significant decrease in inflammatory markers (SE, CRP, and anti-CCP) in the Th group compared to the NTh group; significant differences were not found for the rheumatism factor RF. The research conducted by Shrivastava et al. (20) on 110 RA patients showed statistically significantly higher values of inflammatory markers compared to the control group. Patients with RA have high levels of inflammatory markers, and that it is very important to start treatment in a timely manner. Ruof et al. (21) conducted research on 200 RA patients and found a significant correlation between the inflammatory markers SE and CRP. The obtained results support the point of view on the simultaneous use of SE and CRP and their significance in the clinical practice of rheumatologists. In the research of Alessandri et al. (22), the effect of infliximab treatment on inflammatory markers anti-CCP and RF in patients with rheumatoid arthritis was investigated. At baseline, 38 of 43 patients (88%) were positive for anti-CCP antibodies and 41 (95%) were positive for RF. The values of inflammatory markers anti-CCP and RF significantly decreased after six months of treatment, which suggests that these measurements may have diagnostic significance in evaluating the effectiveness of RA treatment. The conclusions of this study are in correlation with current results because statistically significantly lower values of the inflammatory markers RF and anti-CCP were found in the Th group compared to the values of the inflammatory markers of patients from the NTh group.

Most rheumatologists believe that MTX has a major role in the treatment of RA, alone or in combination with other DMARDs. Because MTX had a dominant therapeutic role, the new drugs were also studied in combination with it. Cohen et al. (23) investigated the effectiveness of combined therapy in 419 RA patients for six months. The combination of MTX with another drug (anakinra) was safe and well tolerated and provided significantly greater clinical benefits than MTX alone. Maini et al. (24) demonstrated in a two-year study that infliximab and MTX provided significant, clinically relevant improvement in physical function and quality of life, accompanied by inhibition of progressive joint impairment and sustained improvement in the signs and symptoms of RA among patients who had previously incomplete response to MTX alone. Visser and der Heijde (25) concluded that any new antirheumatic drug must be combined with MTX. RA treatment is continuous and lasts as long as the drug is effective or until side effects appear. The most common hematological side effect in the treatment of RA with high doses of MTX is myelosuppression. Changes in hematological parameters caused by treatment with MTX can lead to macrocytosis, however, pancytopenia is not excluded either (26). MTX is excluded in patients whose MCV value is higher than 110 fL, i.e. if there is significant macrocytosis (27). Thrombocytopenia, leukopenia, and anemia are successfully regulated by lowering the dose and stopping taking the medication, depending on the intensity of the disorder. During treatment with MTX, monthly controls of liver and kidney function and complete blood counts are required (28). The values of hematological parameters are not statistically significant when comparing the two examined groups in the present study. A study of Dechanuwong and Phuan-Udom (29), including 365 patients with RA, proved that there are changes in the hematological profile of patients that are related to the activity of the disease. The findings of this study show that the level of hemoglobin (Hb), neutrophil/lymphocyte ratio (NLR), and mean platelet volume (MPV) are independent factors for disease activity in RA. Numerous studies indicate that hematological parameters such as leukocytes (WBC), hemoglobin (Hb), and platelets are associated with inflammatory pro-

cesses in patients with RA (30-32). Some authors found lower values of Hb and mean platelet volume (MPV) (33-35), but higher neutrophil/lymphocyte ratios (NLR) and platelet count (36) in patients with RA.

Statistically significantly higher values of the examined biochemical parameters were recorded for iron concentration and AST in patients on therapy (Th) in the current study. Kremer et al. (37) investigated the effectiveness of MTX therapy on AST and ALT values in patients suffering from RA. The research results showed a statistically significant decrease in AST and ALT values after a period of six months. Biochemical markers of bone and cartilage turnover are also receiving increasing attention in other conditions characterized by joint and/or skeletal inflammation and damage. They may provide an additional and potentially more sensitive method of detection of active bone and cartilage degradation that is likely to lead to structural damage in RA (38).

Pallinti et al. (39) found that ferritin levels are not significant in RA patients. Smith et al. (40) analyzed 35 anemic patients with rheumatoid arthritis to determine the relationship between serum iron levels and its body status by assessing bone marrow iron stores. The study shows that reduced bone marrow iron stores are common in patients with rheumatoid arthritis, and that serum ferritin levels may be a useful indicator of reduced body iron stores in these patients. In the present study, the incidence of anemia in patients from the NTh group was recorded in 68%, which is significantly higher than the incidence of 32% in patients from the Th group. Anemia of chronic disease and sideropenic anemia are the two most common types of anemia in RA patients. Anemia of chronic disease in Th group was found in 15% of patients, and in NTh group was recorded in 85% of the total number of 13. Sideropenic anemia in group Th was found in 55% of patients, and in the NTh group in 45% of patients. Research of Peeters et al. (41) included 225 patients with RA for two years; anemia was recorded in 64% of patients, of which 77% had anemia of chronic disease, and 23% of patients had anemia due to iron deficiency. Our research was in correlation with the previeous study, considering that among NTh group patients, anemia of chronic disease was the most prevalent (85%), and more than half of NTh group patients were anemic (68%).

CONCLUSION

MTX in combination with prednisolone is an effective therapy for the treatment of RA, however, therapy did not reduce the high values of the RF. Significant variations were not found for hematological parameters, but biochemical parameters showed a significant decrease in AST activity and iron. It seems that the analysis of inflammatory markers with serum iron could be very important for monitoring the therapy of RA patients due to the high incidence of anemia of chronic disease and sideropenic anemia associated with inflammatory changes in rheumatoid arthritis. Further studies are needed to allow efficacious and cost-effective drugs to be used to prevent the long-term complications of uncontrolled RA.

Authors' contribution

Study conception and design: DS, EM, MF. Data collection: MMB. EM. Data analysis: DS. Data interpretation: EM, DS. Drafting the manuscript: MMB, DS. Revising the manuscript critically for important intellectual content: MM, DS, MF. All authors approved the final version of the manuscript.

Declarations

Conflict of interest

The authors declare no competing interests.

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Fokus na inflamaciju: kohortna studija o uticaju terapije metotreksatom na sideropenijsku anemiju i smanjenje inflamatornih markera kod bolesnika sa reumatoidnim artritisom

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SAŽETAK

Uvod/Cilj. Reumatoidni artritis (RA) jeste sistemska autoimuna bolest koja može uzrokovati degenerativno oboljenje zglobova i progresivni invaliditet. Dijagnostika RA zasniva se na laboratorijskim i kliničkim dokazima koji obuhvataju analizu upalnih markera, hematoloških i biohemijskih parametara.
Metode. U studiju je uključeno 50 bolesnika sa dijagnozom RA koji nisu lečeni metotreksatom (engl. *methotrexate* – MTX) i 50 bolesnika koji jesu lečeni metotreksatom (7,5 mg/nedeljno), a nakon tri meseca prednizolonom (10 mg dnevno). Nakon šestomesečne terapije, analizirani su inflamatorni biomarkeri, hematološki i biohemijski parametri.
Rezultati. Inflamatorni biomarkeri (sedimentacija eritrocita – SE; C-reaktivni protein – CRP i antitela na ciklični citrulinski peptid (engl. *anti-cyclic citrullinated peptide* – anti-CCP)) signifikantno su niži u grupi bolesnika koji su primali terapiju nego u grupi bolesnika koji nisu bili na terapiji MTX-om. Nisu utvrđene značajne razlike za reumatoidni faktor (RF). Između poređenih grupa nisu utvrđene signifikantne razlike za hematološke parametre. Analiza serumskih biohemijskih parametara pokazala je signifikantne razlike za aspartat aminotransferaze (AST) i gvožđe. Kod bolesnika koji nisu primali terapiju MTX-om incidencija anemije zabeležena je kod 68%, što je značajno više u odnosu na incidenciju od 32% kod bolesnika koji jesu primali terapiju.
Zaključak. Ordinirana terapija pokazala je efikasnost u lečenju RA i u redukciji inflamatornog procesa. Uspešnost lečenja zavisi od pravovremene dijagnoze RA; odlaganje terapije i kasno detektovana bolest produžavaju terapiju koja često zahteva kombinaciju više lekova.

Ključne reči: **reumatoidni artritis, antitela na ciklični citrulinski peptid, C-reaktivni protein, metotreksat**