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EFFECT OF DISEASE-MODIFYING ANTIRHEUMATIC DRUGS ON THE VALUES OF APOLIPOPROTEIN A-1 AND ACUTE PHASE REACTANTS IN PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS

UČINAK ANTIREUMATIKA KOJI MIJENJAJU TIJEK BOLESTI NA VRIJEDNOSTI APOLIPOPROTEINA A-1 I REAKTANATA AKUTNE FAZE U BOLESNIKA S AKTIVNIM REUMATOIDNIM ARTRITISOM

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Abstract

In this observational study we examined the impact of disease-modifying antirheumatic drugs (DMARDS) on the disease activity as well as the values of acute phase reactants and the apolipoprotein A1 (Apo A1) in patients with active rheumatoid arthritis (RA). Eighty patients with active RA and newly discovered RA patients who meet the American Rheumatology Association (ARA) 1987 revised criteria were treated with disease modifying anti-rheumatic drugs – DMARDs according to the standard protocol of everyday clinical practice. At 6 and 12 months of treatment the patients achieved a significant decrease in the disease activity score 28 (DAS28), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) values. On the other hand, the levels of Apo A-1, which were low at baseline, were significantly higher. In conclusion, the use of DMARDs in patients with RA reduced disease activity and inflammation, but also had a beneficial effect in increasing the levels of atheroprotective Apo A-1 lipoprotein, which can reduce CV risks in these patients.

Keywords: Arthritis, rheumatoid – drug therapy; Antirheumatic agents – pharmacology, therapeutic use; Apolipoprotein A-1 – blood; Blood sedimentation; C-reactive protein – analysis; Severity of illness index; Atherosclerosis – metabolism, prevention and control

Sažetak

U ovom opservacijskom radu istražili smo utjecaj antireumatskih lijekova koji mijenjaju tijek bolesti (BMARL) na: aktivnost bolesti, vrijednosti reaktanata akutne faze i apolipoproteina A-1 (Apo A-1) u bolesnika s aktivnim reumatoidnim artritisom (RA). Osamdeset pacijenata s aktivnim i novootkrivenim RA, u skladu s revidiranim klasifikacijskim kriterijima Američkoga reumatološkog udruženja (ARA) iz 1987. godine, liječeno je lijekovima koji mijenjaju tijek upalne reumatske bolesti – BMARL-ima, u skladu sa standardnim protokolom liječenja u svakodnevnoj praksi. Nakon 6 i 12 mjeseci liječenja pacijenti su postigli značajno smanjenje vrijednosti DAS28 *(disease activity score)*, CRP-a (C-reaktivni protein) i SE (sedimentacija eritrocita). S druge strane, razine Apo A-1, koje su na početku bile niske, značajno su se

povisile. Zaključno, primjena BMARL-a u bolesnika s RA smanjila je aktivnost bolesti i upalu, ali je imala pozitivne učinke u smislu povišenja razine ateroprotektivnog Apo A-1, što može sniziti kardiovaskularne rizike.

Ključne riječi: Reumatoidni artritis – farmakoterapija; Antireumatici – farmakologija, terapijska primjena; Apolipoprotein A-1 – u krvi; Sedimentacija krvi; C-reaktivni protein – analiza; Indeks težine bolesti; Ateroskleroza – metabolizam, prevencija

Introduction

Rheumatoid arthritis (RA) is the most common inflammatory chronic arthritis. It is a symmetric polyarthritis associated with significant structural damage and functional impairment. The main goals of treatment in RA are: controlling the signs and symptoms of the disease, preventing further damage of joints, and improving functional ability. Studies conducted many years back have shown that patients with RA die at a younger age compared to the general population (1–3). In general, the most common cause of death is cardiovascular disease (CVD), and patients with RA are at a 2–5 times higher risk to develop a CVD, which in turn leads to a 5–10 years shorter lifespan than that of the general population (4, 5).

Various studies have confirmed that endothelial dysfunction and dyslipidemia are present in patients with RA. Immune deregulations with systemic inflammation are integral parts of the development of atherogenesis, and the majority of cardiovascular (CV) deaths in patients with RA result from accelerated atherosclerosis (3, 6–8). There is a significant association between the immunological and pathological processes occurring in the synovium and atheromatic lesions of blood vessel walls. Higher levels of rheumatoid factor (RF), anti-cyclic citrullinated peptide antibodies (anti-CCP), markers of systemic inflammation like erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), or some pro-inflammatory cytokines (tumor necrosis factor a – TNF-a; interleukin-6, IL-6), as well as a higher number of inflamed joints, considerable dysfunction at disease onset, and the presence of extra-articular changes are closely related to CV changes that occur in patients with RA (6–10).

In general, the lipid profile of patients with active and newly discovered RA is characterized by a decrease in serum levels of high density lipoproteins (HDL), total cholesterol (TC), and low-density lipoproteins (LDL); thus, according to some authors, low TC and LDL levels are associated with an increased CV risk (11–14). It is important to note that the reduction of HDL levels results in increasing the ratio of TC/HDL, an atherogenic index, which in turn is a very important prognostic marker for CVD. The levels of TC and HDL cholesterol (HDL-C) in RA are inversely correlated with disease activity, which confirms the role of inflammation in the atherogenic profile of these patients (11, 13).

Another group of researchers focused on the function of HDL-C. Normal HDL-C shows its antiatherogenic role by protecting LDL-C from oxidation and inhibiting the expression of adhesion molecules and their role in the reverse transport of cholesterol. These antioxidant effects are largely dependent on the HDL-C content of apolipoprotein A-1 (Apo A-1) and the enzyme paraoxonase (PON1) (15). During acute-phase responses, HDL loses this antioxidant capacity and can even promote an increased oxidation of LDL, thus becoming pro-inflammatory. According to some authors, pro inflammatory HDL-C was detected more often in patients with RA than in controls. Therefore, pro inflammatory HDL-C can be a novel biomarker for the increased atherosclerotic risk in RA (16–20). Apo A-1-containing particles mediate the reverse cholesterol transport, returning excess cholesterol from peripheral tissues to the liver, the only organ capable of excreting it in significant quantities (in bile). Also, Apo A-1 is a major protein of HDL-C, and its main function is to act as a structural protein, to mediate the transfer of cholesterol from cell surfaces to lipoprotein particles, and to activate the enzyme responsible for cholesterol esterification in the circulation (21).

The aim of this study was to examine Apo A-1 levels in newly diagnosed patients with active RA and conventional synthetic disease-modifying drug (csDMARD)-naïve RA patients, as well as the impact of treatment with csDMARDs on acute phase reactants and Apo A-1 lipoproteins at 6 and 12 months of treatment.

Material and methods

A group of 80 patients with active RA and DMARD-naïve RA patients were enrolled in this study. These patients were treated with csDMARDs and followed up for 12 months. The study was conducted at the Rheumatology Clinic of the Clinical Center Skopje and the Clinical Center in Tetovo, Republic of Macedonia. All the patients with RA met the ARA 1987 revised classification criteria. Exclusion criteria were conditions that may directly or indirectly affect the status of lipids, such as: Cushing syndrome, diabetes mellitus, acute infections, advanced diseases of liver, kidney, thyroid, CVD and associated conditions (stroke, myocardial infarction), cancer, treatment with beta blockers, vitamin E, hypolipidemic drugs, oral contraceptives, pregnancy, BMI over 30 kg/m^2, and vegetarian/vegan diet (22, 23).

The distribution of treatment with DMARDs according to drugs was as follows: 46 patients were treated with methotrexate (average dose 15 mg OW), 23 patients with hydroxychloroquine (300 mg OD), 9 patients with sulfasalazine (2–3 g/day), 1 patient with gold salts (25–50 mg OW), and 1 patient with azathioprine (150 mg TD). The patients who did not respond to the therapy according to the American College of Rheumatology (ACR) 20 criteria (n=7) were excluded from the follow up.

The laboratory tests were performed at the Institute of Biochemistry in Skopje at baseline as well as at 6 and 12 months during the treatment with DMARDs. The serum levels of Apo A-1 were determined using the radial immunodiffusion method. The ESR was determined by the Westergren method and CRP by immunofluorometric methods. Blood samples were taken in the morning, after at least 12 hours of fasting, as well as after consumption of greasy food the day before drawing blood samples. The rheumatoid factor test was performed using the latex method.

Immediately before the treatment, as well as at 6 and 12 months, several parameters of disease activity and functional ability were obtained, too: Tender Joint Count (TJC), Swollen Joint Count (SJC), Global patient's assessment (on horizontal VAS), and Global physician's assessment (on horizontal VAS). The physical examination was done by experienced rheumatologists (HI, NK). A structured questionnaire was used to obtain the data.

The main characteristics of the patients are presented in Table 1.

Table 1. Patient characteristics (n=80)
Tablica 1. Obilježja ispitivane grupe bolesnika (n = 80)

Variable	Value
Age (years)	45.7±9.8
BMI (kg/m2)	22.3±2.6
Tender Joint Count (28)	7.8±7.1
Swollen Joint Count (28)	5.2±3.7
Global patient's assessment of the disease (on VAS)	7.0±2.1
Global physician's assessment of the disease (on VAS)	4.5±2.3
ESR (mm/h)	45.4±30.3
CRP (mg/L)	41.4. ±29.4
RF positive/negative	67/13

Legend: BMI: body mass index, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein

Statistical analysis was performed using Statistica software, ver 7.1. Due to the distribution which was not normal (according to Kolmogorov-Smirnov test), the variable differences were tested using non-parametric tests (Wilcoxon Matched Pair Test or Friedman ANOVA test – Chi Square). The correlation between the parameters was analyzed using Pearson's correlation coefficient. Significance was set up at $p < 0.05$.

Results

DAS28 scores after 6 months of treatment were significantly lower that at baseline ($p<0.01$), and the difference was even more pronounced at 12 months in comparison to baseline, as well as in comparison to the results obtained at 6 months ($p<0.001$ for both) (Figure 1).

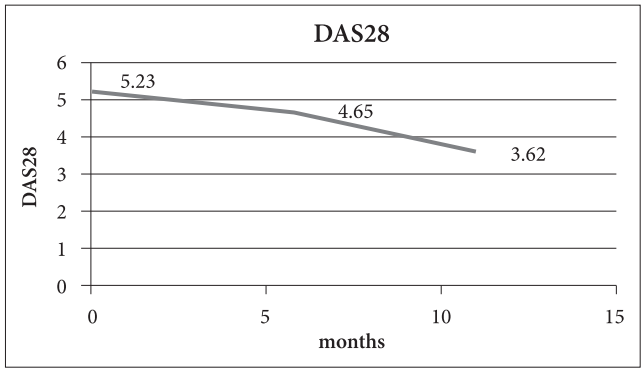

Figure 1. Disease activity score 28 (DAS28) at baseline, at 6, and at 12 months during the treatment
Slika 1. Indeks aktivnosti bolesti (DAS28) na početku te nakon 6 i 12 mjeseci liječenja

As for ESR and CRP, there was a significant consecutive decrease from baseline, both at 6 and at 12 months (for both variables, between each of time-points; Friedman ANOVA; $p < 0.001$) (Table 2).

Table 2. ESR and CRP levels at baseline, at 6 months, and at 12 months
Tablica 2. Razina SE i CRP-a na početku te nakon 6 i 12 mjeseci liječenja

	Average Rank	Sum of Ranks	Mean	Std. Dev
ESR at baseline	2.53	182.50	40.78	28.07
ESR at 6 months	1.99	143.50	29.06	22.29
ESR at 12 months	1.47	106.00	24.89	22.15
CRP at baseline	2.44	175.50	21.69	15.98
CRP at 6 months	2.08	150.50	20.51	36.19
CRP at 12 months	1.48	106.50	12.31	11.95

Table 3. Levels of Apolipoprotein A-1 (Apo A-1) at baseline, at 6 months, and at 12 months
Tablica 3. Razina apolipoproteina A-1 (Apo A-1) na početku te nakon 6 i 12 mjeseci liječenja

	Average Rank	Sum of Rank	Mean	St. Dev.
Apo A-1 at baseline	1.63	117.00	1.91	0.35
Apo A-1 at 6 months	1.83	132.00	1.96	0.43
Apo A-1 at 12 months	2.54	183.00	2.08	0.37

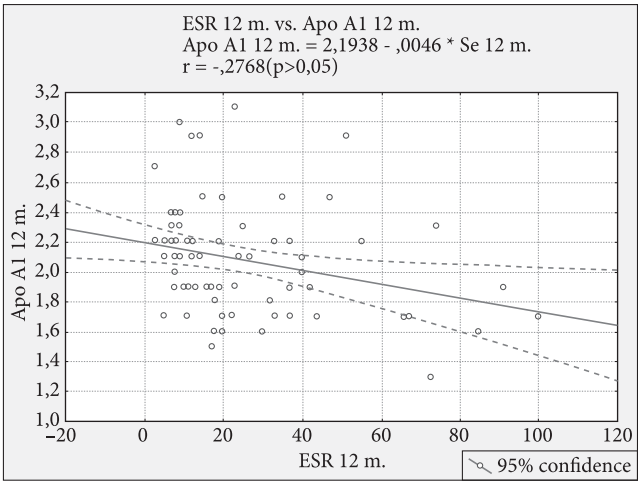

Figure 2. Correlation of ESR and Apo A-1 levels at 12 months
Slika 2. Korelacija vrijednosti SE i Apo A-1 nakon 12 mjeseci liječenja

Table 3 shows the results of testing for Apo A-1 at baseline, at 6 months, and at 12 months. There was a significant difference between Apo A-1 levels in the specified period: the levels decreased during the therapy (Friedman ANOVA; $p < 0.001$).

Comparing the results of ESR, CRP, and Apo A-1 at baseline, at 6 months, and at 12 months, we found a moderately weak significant negative correlation only in relation to the values of ESR and Apo A1 at 12 months ($r = -0.28$; $p<0.05$). In other words, the elevation of ESR by 1mm/hour was accompanied by a decrease of Apo A1 values by 0.005 g/l (Figure 2). As for the relationship of the other variables, we found a moderately poor and weak insignificant correlation ($p>0.05$) (data not shown).

Discussion

Data support the view that chronic inflammation affects the endothelium, and that, in association with dyslipidemia, it may be the mechanism that at least partly explains the increased mortality and morbidity occurring in patients with RA. Our goal was to determine the values of Apo A-1 lipoproteins in patients with active RA and DMARD-naïve RA patients before treatment and after 6 and 12 months of treatment with csDMARDs. The patients with active RA had low levels of Apo A-1 before the treatment, while after 6 and 12 months of treatment with csDMARDs the Ap A-1 levels significantly increased. On the other hand, the values of acute phase reactants (ESR and CRP) were lower after 6 months and one year of treatment. This suggests that increasing levels of Apo A-1 lipoproteins were accompanied by a decrease of inflammation at the end of the study. In other words, the results tell us that the inflammation in RA in some way induces the proatherogenic lipid profile. Conventional therapy with DMARDs has a positive effect on Apo A-1 values and atherogenic index Apo B/Apo A1. This is in accordance with other findings supporting the thesis that treatment with DMARDs has an impact on the mechanisms that affect cardiovascular morbidity and mortality in these patients (7, 8, 11, 21, 23).

A broad body of evidence indicates that inflammation contributes to the pathogenesis of atherosclerosis and CVD in the general population. Epidemiological studies suggest that a number of pro-inflammatory factors, such as CRP, ESR, fibrinogen, and some cytokines are involved in the mediation of this process. They not only promote endothelial dysfunction and structural vessel abnormalities, but also induce other cardiovascular risk factors, such as changes in lipid levels, insulin resistance, and oxidative stress. They are increased in RA patients and some studies have demonstrated a significant association between their levels, ESR in particular, and the risk of CVD (11, 18, 24).

The underlying cause of atherosclerosis are autoimmune inflammatory disorders, in which lipoprotein metabolism alterations are associated with the activation of the immune system, with consequent proliferation of smooth muscle cells, narrowing of the arteries, and formation of atheroma (25). Therefore it is plausible to infer that atherosclerosis and RA share common pathogenetic mechanisms. For instance, CRP, which is increased in active RA, may contribute to atherosclerosis because it stimulates macrophages to produce tissue factor, a procoagulant found in atherosclerotic plaques. On the other hand, the presence of CRP in atheromatous lesions suggests the cause-and-effect relationship between this acute phase reactant and coronary artery events (11, 13, 24, 26, 28).

When lipid profiles were investigated in patients with RA, some of them showed lower values of HDL-C and TC, and increased values of lipoprotein-A (Lp-A), with increased proportions of TC/HDL, LDL/HDL, and Apo B/Apo A-1 in patients with active RA and DMARD-naïve RA patients, compared to the general population (16, 20, 31). Lipids may have paradoxical associations with the risk of CVD in RA, where lower TC and LDL levels are associated with an increased CV risk, called the "lipid paradox". Also, there are studies that show a decline across the lipid fraction in the acute phase of the illness. Such differences that arise in different diseases can be explained by insufficient sample size, type of study (prospective, cross-sectional, or observational), as well as differences in the disease type (early or established) or disease activity (14, 16, 24, 25).

One of the first controlled studies reporting on apolipoprotein levels in RA was performed in 42 untreated patients (mean disease duration 27 months) and 42 age- and sex-matched controls. The authors presented the 12-month changes and found that CRP levels correlated significantly with the change in HDL-C levels

(r=–0.38, p<0.001) and Apo A-1 levels (r=–0.29, p<0.01). The mean HDL-C levels increased by 21% (p<0.001), and the mean Apo A-1 levels increased by 23% (p<0.001) after treatment with DMARDs. Studies also mention that the change of protective Apo A-1 showed a strong negative correlation with the changes in CRP levels (26).

In their study, Taysi et al. presented significantly higher values of Lp-A in the sera of RA patients compared to those of the control group (p <0.01), while Apo A-1 levels were significantly lower in patients with RA (p < 0.01). ESR and CRP were positively correlated with the levels of Lp-A in RA patients, and negatively correlated with HDL-C and Apo A-1. The authors also emphasized that RA patients with such lipid levels were at higher risk for developing CVD and atherosclerosis compared to controls (27).

Van Halm et al. support the observations that patients with RA have an atherogenic lipid profile even 10 years before the clinical onset of RA, which itself may explain the increase of cardiovascular risk in patients with RA. The study was conducted on 79 patients, blood donors who later developed RA. These patients had low levels of HDL-C and high levels of TC, triglyceride (TG), and apolipoproteins B (Apo B) compared with controls, even 10 years before the disease appeared. This suggests that lipid changes are associated with, and in some way may be a promotive factor for, a higher susceptibility to RA; perhaps these patients are genetically predisposed for dyslipidemia, or the transcriptions of these genes are altered by the presence of inflammation (28).

A recent research has shown that systemic inflammation plays a pivotal role in the development of atherosclerosis, and thus may explain the increased CV risk in RA patients. Also, this study confirmed that inflammation leads to pro-atherogenic changes of the lipoprotein metabolism, and an increased disease activity is associated with lower TC levels, as well as even more depressed HDL-C levels and lowered Apo A1 levels (25).

Treatment with csDMARDs has beneficial effects on the lipid profile in RA, and it is tempting to assume that the favorable effect of these drugs on the CV morbidity and mortality in RA might be partially mediated by this mechanism (30).

Management of dyslipidemia should be considered as part of the cardiovascular risk management in patients with RA. It is clear that good control of the disease has a positive effect on the lipid profile, especially in increasing the anti-inflammatory and atheroprotective Apo A-1 and HDL-C levels. An adequate treatment of traditional, but also nontraditional, CV risk factors is absolutely necessary in these patients; this is supported by epidemiological studies in the field, with more precise and comprehensive guidelines addressing this issue (29, 30–32).

The strength of our study is the coherent cohort of newly diagnosed patients with RA and the fact that the evaluation was done at the designated times, as well as the fact that the laboratory measurements were performed using reliable methods. The obvious limitation is the design of the study with no control group, and the differences in treatment regimens during the study.

In conclusion, the results of our observational study indicate that patients with active RA and DMARD-naïve RA patients have high levels of acute phase reactants (ESR and CRP) and low levels of atheroprotective Apo A-1. Treatment of these patients with csDMARDs resulted in lower levels of disease activity paremeters and the increase of Apo A-1. Therefore, apart from their beneficial effects on disease activity, these drugs have positive effects in reducing the CV risk.

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