ORIGINAL ARTICLE

THE EFFECT OF ATORVASTATINUM IN THE TREATMENT OF PATIENTS WITH RHEUMATOID ARTHRITIS

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ABSTRACT

The aim: Was to evaluate the effect of 6-month pathogenetic treatment in combination with atorvastatinum on the endothelium function, lipid and adipokine levels, paroxonase activity and activity of inflammatory process in RA patients.

Materials and methods: The study included 55 patients with RA, dividing into two groups depending on the intended therapy. The first group included 33 patients with "traditional" treatment by methotrexate, glucocorticoids, and non-steroid anti-inflammatory drugs. The second group included 22 patients with "traditional" treatment and additionally prescribed of atorvastatinum 20 mg/day. The lipid profile, leptin, adipokine, paroxonase activity. C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF-α) levels, FMDBA and IMT of carotid artery were determined in all participants of the study. Control parameters were recorded before the start, after 1 and 6 months of treatment.

Results: The FMDBA has increased by 32% in the second group, compared by only 10.9% in the first group. The dynamics of IMT in the first group was also twice lower than in group with the additional use of atorvastatinum. The leptin levels in the second group significantly decreased by 27% and adiponectin levels increased by 12.8%, than in the first group – by 12.8% and by 7% respectively. The appointment of statins over 6 months resulted in DAS28, TNF-α, ESR and CRP reduction by 15%, 31%, 25% and 21.5% respectively. In the first group the dynamics of indicate rates ranged from 7.8% to 22.5%, and was significantly lower than in the second group.

Conclusions: As a result of the study, it was found that the appointment of atorvastatinum 20 mg/day during 6 months not only reduces dyslipidemia, but also significantly reduces the inflammatory process and *adipokine dysregulation*, normalizes serum paraoxonase activity and improves the endothelium function.

KEY WORDS: metabolic desorders, inflammatory, endothelium dysfunction, statins

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INTRODUCTION

Cardiovascular events are known to be the main cause of mortality in patients with rheumatoid arthritis (RA) [1, 2, 3]. The main causes of the accelerated atherosclerotic process in RA patients are the result of the interaction between traditional risk factors of cardiovascular disease (dyslipidemia, arterial hypertension, limited physical activity, obesity) and chronic inflammation due to RA [4, 5, 6]. The prominent role of chronic inflammation in the pathogenesis of accelerated atherosclerosis in RA patients emphasizes the necessity of a modified approach in the management of patients, espacially to control not only traditional cardiovascular risk factors, but also the impact on a powerful autoimmune inflammatory process. There were studies which have justified the appropriateness of lipid metabolism disorders correction in RA patients with statins, which are known not only inhibit the synthesis of cholesterol, but also able to block the inflammatory process in the vascular wall and prevent the transformation of cellular elements in vessels [7, 8].

Data on the possible statin influence on adipokine level, serum paraoxonase activity was not detected, and the role of this group of drugs in reducing of the atherosclerotic progress in RA patients is discursive [9].

THE AIM

In view of this, the aim of the study was to evaluate the influence of 6-month pathogenetic treatment in combination with atorvastatinum on the endothelium function, lipid metabolism, adipokine levels, serum paroxonase activity, and inflammatory process in patients with RA.

MATERIALS AND METHODS

An "open"-controlled study was conducted, which included 55 patients with RA. The seropositive type of RA was diagnosed in 47 (85.5%) patients. All patients were divided into two groups depending on the intended therapy. The first group included 33 patients who received «traditional» treatment in accordance with the clinical protocol "Rheumatoid arthritis" (Order of the Ministry of Health of Ukraine dated April 11, 2014, No. 263), which included methotrexate 10-15 mg/week; glucocorticoids (GC) at a stable dose not exceed 10 mg/day by prednisolone; non-steroid anti-inflammatory drugs (NSAD) in a stable dose. The second group consisted of 22 patients, who with «traditional» treatment was additionally prescribed of atorvastatinum in dose 20 mg/day. The dose of GC, methotrexate and NSAD was stabile during the study

period. The duration of the controlled study was 6 months. The control rates were recorded before, after 1 and 6 months of treatment. The adiponectin level was determined in blood serum by immunoassay using AssayMax Human Adiponectin (ASSAYPRO, USA); leptin level was determined using standard sets of the "DRG", Germany. Serum C-reactive protein levels (CRP) and tumor necrosis factor-alpha (TNF-α) were detected by immunoassay using standard sets.

The total cholesterol level (TC), high density lipoprotein cholesterol (HDLP), and triglycerides (TG) in serum were determined according to the standard methodology. The value of low density lipoprotein (LDLP) was calculated according to the Friedwald formula: LDLP=TC-HDLP-0.45*TG. The activity of paraoxonase-arilesterase (CF 3.1.1.2) in serum was determined by spectrophotometric method [10].

High resolution ultrasound and Doppler ultrasonography of the brachial artery by D. Celermajer [11] were performed to study endothelium function. Flow-mediated vasodilation of the brachial artery (FMDBA) was assessed according to changes in its diameter and measured before and after temporary occlusion of the vessel with blood preasure cuff (reactive hyperemia). Location of the brachial artery was associated with visualization of its internal diameter and was measured in the middle third of the shoulder. Sonographic B-mode scanning and pulsed Doppler ultrasound of blood flow spectra were done on ultrasound scanner "Sonoline 6000 C" (Medisson, Southern Korea) on the 30th, 60th and 90th seconds after cuff decompression. Brachial artery dilation by more than 8% from baseline diameter in 30 seconds after decompression was considered to be the criteria of adequate endothelial response to ischemia. All measurements of endothelial relaxation were done from 8 to 10 a.m.

The thickness of intima-media complex (IMT) of the common carotid artery was determined at the time of B-mode ultrasonography of carotid artery in diastole 2sm from bifurcation at maximum magnification. The area of atherosclerotic plaques of carotid artery (cAP) was measured in all the patients, and the extent of vascular atherosclerotic damage was evaluated [12]. Echocardiography (EchoCG) was done for 63 patients with RA on ultrasound scanner "Sonoline 6000 C" (Medisson, Southern Korea) Statistical processing of the obtained results was carried out on a personal computer using the standard statistical programs. The results are presented as the mean ± standard error (m ± SE). All values were follow a normal distribution. The average value, standard errors, reliability of the differences were evaluated according to Student's t-criterion. Pearson's correlation coefficient test was used to measure the strength of a linear association between two variables. The statistical significance was determined if $P<0,05$

RESULTS

As can be seen from the data in Table I, the study groups were representative by age, gender, major severity, disease activity and laboratory data at the start of treatment. At the first stage of the study, we evaluated the influence of individual treatment on the dynamics of lipid metabolism. (Table II). Prior to the treatment, the levels of TC, LDLP, HDLP and TG were approximately the same in all study groups.

The «traditional» therapy had the slightest effect on the dynamics of lipid metabolism rates. After 6 months of treatment, the level of TC, LDLP and TG decreased by 4.2% -6.5% on average, while HDLP increased by 4.3%.

The inclusion of atorvastatinum in the complex of treatment after 1 month provided a significant decrease in the level of TC (by 5.6%), LDLP and TG (by 8.2%) and an increase in HDLP levels (by 10.9%), and after 6 months – by 16.8-21.6% respectively, which was significantly higher than in group with «traditional» treatment.

The influence of different treatment options on the dynamics of adipokin levels and serum paroxonase activity was also evaluated (Table III). It was established that «traditional» treatment had little effect on the dynamics of leptin levels, adiponectin levels and paraoxonase activity. After 6 months of pharmacotherapy, adiponectin levels increased by 7%, leptin levels decreased by 12.8%. The activity of serum paroxonase also increased by 7% after 6 months of treatment.

At the same time, the additional treatment with atorvastatinum significantly influenced the dynamics of adipocyne levels and paraoxonase activity. The leptin level significantly decreased by 27% and adiponectin leptin increased by 12.8% after 6 months of atorvastatinum use. Regarding the activity of paraoxonase, it has probably increased by 21% after 6 months of treatment.

The influence of different treatment options on the parameters of endothelial function (FDVBA, IMT of carotid artery) and the area of atherosclerotic plaques (AP) in the common carotid artery was evaluated (Table IV). The data from the tables 4 show that within 6 months, FMDBA has increased in both groups, regardless of pharmacotherapy. The largest, and significantly better, dynamics of the analyzed parameters was seen in the group of patients treated with atorvastatinum. In particular, the level of FMDBA in response to the test of reactive hyperemia has increased by 32%, while in the group of patients receiving «traditional» therapy only by 10.9%. The dynamics of IMT in the last group was also twice lower than in the group with the additional use of atorvastatinum. Less dynamic under the influence of treatment were in the area of AP. Traditional treatment was accompanied by the lower dynamics of the analyzed criterion, and the appointment of atorvastatinum for 6 months probably stabilized the size of AP.

Subsequently, the influence of different treatment options on the dynamics of the inflammatory process (ESR, CRP, TNF-α, DAS28) was evaluated (Table V). It was established that positive dynamics of clinical and laboratory parameters of inflammatory activity took place in both studied patients groups. It was lower in the group with traditional treatment and more prominent in the group of patients receiving atorvastatinum additionally. The appointment of statins over 6 months resulted in DAS28, TNF-α, ESR and CRP reduction by a 15%, 31%, 25% and 21.5% respectively.

In the group of patients receiving only traditional therapy, the dynamics of above indicated rates ranged from 7.8% to 22.5%, and was significantly lower than in the group with the additional appointment of atorvastatinum.

DISCUSSION

Thus, during the study, it was found that the effectiveness of the pharmacotherapy varied significantly depending on the treatment. Traditional therapy in patients with RA significantly reduced the intensity of the inflammatory response and to a lesser extent influenced the dynamics of the lipid spectrum, the levels of adipokines, the activity of serum paroxonase, and the functional capacity of the endothelium.

The inclusion of atorvastatinum in a complex treatment allows to achieve the target lipid levels in most patients with RA. We found that treatment with atorvastatinum over 6 months of treatment reduced the levels of TC (by 19.5%), LDLP (by 23.4%), TG (by 17.4%), and HDLP increased by 16.8%), which was in 3-4.1 times higher than in the group of patients receiving pathogenetic treatment without atorvastatinum. According to all indicators, the differences between the groups were reliable. In general, the data we have received coincide with the data of other researchers. In particular, the administration of statins reduced TC and LDLP levels by 27-38% in patients with RA [13, 14, 7]. The 6-week use of atorvastatinum in patients receiving *Janus kinase inhibitors* reduced LDLP by 35.2%, while in the group, with no additional use of atorvastatinum, it was only 5.8% [15]. According to Akiyama M., et al. (2015), the use of atorvastatinum with the traditional treatment, including immunobiologic agents also significantly influenced the dynamics of all lipid metabolism parameters in RA patients [7].

According to our data, the use of atorvastatinum significantly improved the functional capacity of the endothelium, with little effect on the IMT of carotid artery and the area of atherosclerotic plaques. After 6 months of treatment, FMVDBA increased by 32.4%. In our opinion, the relatively low dynamics of the IMT and the AP area is obviously related to the short period of statin using in our study. At the same time, according to the literary data, the appointment of hypolipidemic therapy in RA patients and ankylosing spondylitis during 18 months not only allowed to reach the target levels in most patients, but also provide regression of atherosclerotic plaques [16]. It is also reported that long-term administration of statins can prevent the development of endothelial dysfunction [13], as well as reduce cell adhesion-1 and fibrinogen molecules [17]. Although there are some studies that do not confirm the improvement of subclinical atherosclerotic vascular damage in response to the appointment of statins [9].

We have shown the ability of atorvastatinum to reduce the leptin concentration and increase adiponectin in blood serum of patients with RA. In particular, leptin levels in the second group significantly decreased by 27%, compared to 12.8% in the first group; adiponectin concentration increased by 12.8% in the second group, but it was only 7% in the first group. The positive role of statins in restoring adipokin status is also demonstrated in experimental studies [18]. Statins act directly on white adipocytes in humans, regulate adipokine secretion and reduce the expression of leptin [19], although there are such studies , which deny the relationship between statin administration and leptin secretion [20]. According to literature data the using of atorvastatinum has contributed to the leptin normalization in patients with RA [14].

One of the important pleiotropic statin effects that prevent the development of cardiovascular complications is increasing of serum paraoxonase activity [21]. According to Park and co-authored data, (2016) the using of rosuvastatin at a dose 10 mg / day for 8 weeks increased paraoxonase activity by 19.1% [22]. We also found the ability of atorvastatinum to increase the activity of paraoxonase in serum. In particular, after 6 months of treatment, the paraoxonase activity increased by 7% in the first group, whereas in the second group by 21%.

The hypolipidemic therapy significantly accelerated the dynamics of clinical manifestations of the disease (DAS28) and laboratory parameters of the inflammatory process. Thus, under the influence of atorvastatinum, the serum TNF-α concentration decreased by an average of 30%, CRP – by 21%, ESR – by 25%, while, the dynamics of disease activity laboratory parameters was less clear during the traditional therapy, and for the TNF -alpha, CRP and ESR it ranged from 15.8-22%. Other researchers point out the ability of statins to suppress the inflammatory marker synthesis in patients with RA [14]. In particular, according to McCarey et al. (2004) in the group of patients receiving atorvastatinum 40 mg/day the total inflammatory activity index DAS28 decreased by 31% and the CRP level decreased by 50% while in the group of patients without statins DAS28 decreased by only 10%, and CRP by 28% [23].

Thus, our data has shown that traditional therapy with the use of basic agents, GC and NSAIDs had a fairly moderate influence on the lipid spectrum, adipokine level, paraoxonase activity and endothelial dysfunction in patients with RA. Inclusion of atorvastatinum 20 mg/day during 6 months has resulted in decreasing of dislipoproteinemia, the severity of *adipokine dysregulation* and inflammation, normalizing serum paroxonase activity and reducing of atherosclerotic damage.

CONCLUSIONS

1. The pathogenetic therapy with methotrexate, GC, nonsteroidal anti-inflammatory drugs has significantly reduced the inflammatory response in RA patients (DAS28, ESR, CRP, TNF-α) but less influenced the dynamics of lipid and adipokine spectrum, serum paroxonase activity and functional endothelium status.
2. The administration of atorvastatinum in dose 20 mg/day during 6 months of treatment has not only reduced the TC (19.5%), LDLP (23.4%), TG (17.4%), and in-

creased the HDLP (by 16,8%), but also significantly reduced the inflammatory process (DAS28, ESR, CRP, TNF-α), removed *adipokine dysregulation*, normalized serum paroxonase activity, and improved endothelium functional status

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Conflict of interest:

The Authors declare no conflict of interest.

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