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ASSESSMENT OF CARDIOVASCULAR RISK IN PATIENTS WITH RHEUMATOID ARTHRITIS AND THEIR CORRECTION WITH GENETICALLY ENGINEERED BIOLOGICAL PREPARATIONS

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Abstract

Rheumatoid arthritis (RA) is an immunoinflammatory rheumatic disease of unknown etiology, leading to early disability and a decrease in the life expectancy of patients [1]. The risk of atherosclerosis, as the leading cause of cardiovascular disease (CVD), increases in RA [2]. The purpose of our research is to study the effect of basic antirheumatic therapy and therapy of genetically engineered biological preparations on immunological markers of vascular atherosclerosis in rheumatoid arthritis. The study included 43 patients with RA and suspected coronary heart disease - CHD. The results of the study showed that after 12 months of therapy with infliximab, it was established a significant decrease in the level of pro-inflammatory cytokines: the concentration of TNF- α decreased by 3.9 times, IL-1β - by 2.8 times, IL-6 - by 7.6 times. Thus, a therapeutic approach that corrects the activity of immune inflammation seems promising for the prevention and treatment of cardiovascular events in RA.

Keywords: atherosclerosis, rheumatoid arthritis, inflammation, cytokines, genetically engineered biological preparations.

Introduction

Rheumatoid arthritis is a chronic immunoinflammatory (autoimmune) disease manifested by progressive joint destruction, systemic inflammation of internal organs and a wide range of comorbid diseases associated with chronic inflammation and/or undesirable drug reactions [1,2]. Being an inflammatory autoimmune disease, RA, along with joint damage, is characterized by extra-articular systemic pathology, a high burden of concomitant diseases, especially cardiovascular diseases, the risk of which is 1.5-2 times higher in RA than in the population[3,4,5]. Several studies have suggested that the risk of atherosclerosis, as the main cause of CVD, increases in RA [6].

Despite successes in the diagnosis and therapy of diseases and positive trends in reducing cardiovascular risk in patients with RA and in the population over the past

decades, the relative risk of developing cardiovascular complications in patients with RA remains high, and cardiovascular mortality is 48-54% higher than that in the general population [7,8].

Currently, there is insufficient data on the influence of cardiovascular risk factors, anti-rheumatic therapy and such indicators of immunoinflammatory activity as highly sensitive C-reactive protein (hsCRP), TNF- α, IL-1 and IL-6 on the progression of atherosclerosis of the carotid and coronary arteries in patients with RA, which has become the basis for this work[9,10].

Purpose of Scientific Research

Study of the effect of basic anti-rheumatic therapy with methotrexate (BART-MT) and therapy with genetically engineered biologic preparation- infliximab (GEBP - INF) on immunological markers (TNF- α, IL- 1β, IL-6, hsCRP) of vascular atherosclerosis in RA.

Material and Methods

The study included 43 patients with RA and suspected coronary heart disease - CHD. Inclusion criteria for RA patients: men and women aged 35 to 55 years with a disease duration of more than 5 years, with clinical suspicion of CHD (presence of pain in the chest or shortness of breath during exercise. The control group included 20 patients with CHD without RA, who are 42,5±5,3 years old. The median duration of follow-up was 6-12 months. The clinical and laboratory characteristics of the patients included in the study are presented in Table 1.

Table 1. Clinical characteristics of patients enrolled in the RA group and the comparison group

Indicator	Control Group, n=20	Patients with RA, n=43
Age, years	42,5±5,3	52±6,3
Men/Women	8/12	10/33
Hypertention	7	21
Dyslipidemia	5	22
Total CL, mmol/l	3,7± 5,6	4,4± 6,2
CL HDL, mmol/l	1,0± 1,6	1,1± 1,7
CL LDL, mmol/l	2,3± 3,8	2,4± 4,0
TG, mmol/l	0,95±1,86	0,96±1,89
Diabetes	6	4
DAS28 index	-	2,2± 5,0
Duration of RA, years	-	6± 14
RF positivity	-	21
ESR, mm/h	5,8± 4,7	7,3± 36
hs-SRP, mg/dl	1,6±0,6	0,2± 1,7

The data are presented as median and interquartile range - Me [25%; 75%] and absolute and relative frequencies - n (%). * - p<0,05

All patients with RA were evaluated for risk factors such as arterial hypertention, smoking, overweight, CVD-burdened heredity, diabetes mellitus, dyslipidemia. Concentrations of total cholesterol (TCL), cholesterol high-density lipoprotein (CL HDL), low-density lipoprotein (CL LDL) and triglyceride (TG) were determined prior to examination and at 6-12 months. RA activity was determined by the DAS28 index. The serum content of TNF- α, IL-1β, IL-6 in RA patients was determined by solid-phase enzyme-linked immunosorbent assay using the test of the "Protein Circuit LLC systems" in accordance with the attached instructions.

The determination of immunological markers of cardiovascular risk in patients with RA in serum was carried out before treatment and after 12 months of therapy with MT, the average dose of which was 13,72±0,06 mg/week, including GEBP-INF. The INF was administered intravenous drops of 200 mg/day according to the recommended regimen: 0-2-4-6 weeks, then every 8 weeks for 12 months. 95.6% of patients with INF in combination with MT.

Throughout the study, some patients were treated with cardiovascular drugs according to standard regimens. Statin therapy was prescribed to 25 patients with RA, who were classified as high and very high CVR (21 patients - again, 4 - continued statin administration, which began before the study). All patients in the control group took statins.

Statistical processing of the obtained data was carried out using Statistica 8.0 statistical program packages.

Results and Discussion

The study showed that in patients with RA, the serum content of TNF- α, IL-1β, IL-6 exceeded the level of these cytokines compared to the control group by 3.2 times (r<0,05); respectively (Table 2).

A significantly higher concentration of hsCRP in the serum of RA patients (9,9±1,7 mg/L) was established in comparison with the control (1,6±0,6 mg/L).

Table 2. Effect of infliximab therapy on cardiovascular risk immunologenous markers in RA patients (n = 43) (M±m)

Indicator	Control	Patients with RA before treatment	RA patients after 6 months of GEBP-INF therapy
TNF- α, pkg/ml	32,4±3,6	158,4±9,1*	49,8±5,7*
IL-1β, pkg/ml	35,4±4,1	134,7±12,3*	46,4±6,9*
IL6, pkg/ml	15,8±3,9	149,5±9,1*	19,6±4,4*
hs-SRP, mg/dl	1,6±0,6	9,9±1,7 *	2,8±0,3*

Note: * significant differences of arithmetic means ($p < 0.05$) were noted, the numbers next to the asterisk - in relation to the indicators of which group these differences are significant.

Multivariate correlation analysis showed direct associations between the DAS28 index reflecting the activity of systemic inflammation in RA and the level of pro-inflammatory cytokines: TNF- α, IL-1β and IL6 ($r = 0.59$, $p < 0.05$ $r = 0.48$, $p < 0.05$ $r = 0.66$, $p < 0.05$, respectively).

Direct correlations between hsCRP and TNF- α, IL-6 and IL-1β were determined ($r = 0.53$, $p < 0.05$; r=0,68, p<0,05; r=0,49,p<0,05; respectively). HsCRP is one of the main markers of inflammation, the main factors stimulating its production along with IL-6 may be IL-1β, TNF- α, which is confirmed by the presence of reliable correlation links between these mediators.

An association between blood lipid spectrum and RA activity was found. Initially, a negative correlation of levels of TCL, CL HDL, CL LDL and a positive correlation of AI with DAS28- ESR and DAS28-SRP, SRP was revealed (Table 3). After 12 months of treatment, Δ SRP was negatively correlated with ΔTCL, ΔCL HDL, ΔCL LDL,(r = -0.3; p<0,05). Thus, a more pronounced increase in lipid levels over time was observed with a more intense decrease in SRP concentration. The median change in SRP was -18.3 mg/l. If SRP decreased by 1 mg/l, the median change in TCL, CL HDL and CL LDL was + 0.014; + 0.012; + 0.008 mmol/l, respectively. After 6 months the start of treatment, a positive correlation of TG with DAS28- ESR and DAS28-SRP, CRP, ESR was revealed ($p < 0.01$).

Some RA patients were treated with statins during the study, and 25 patients received them in the first 6 months of follow-up.

After 6 months, the concentration of TCL, CL HDL, CL LDL and AI in patients taking statins ($n = 25$) increased significantly ($p < 0.05$). At the same time, in the absence of lipid-lowering therapy ($n = 18$), the level of these lipid parameters did not change significantly. Also, in the majority of patients in the control group taking statins, a positive correlation with baseline levels of TCL, CL LDL and AI was observed ($p < 0.05$).

Table 3. Baseline correlation between lipid parameters and RA activity parameters.

Lipid parameter	**Correlation coefficient (r)**		
	DAS28- ESR, mm/h	**DAS28- SRP**	**SRP, mg/l**
Total CL, mmol/l	-0,2*	-0,4**	-0,3**
CL LDL, mmol/l	–	-0,4**	-0,3*
CL HDL, mmol/l	-0,4**	-0,4**	-0,3**
AI	+0,3*	–	–

Note. * - $p < 0.01$.

Evaluation of clinical efficacy of INF therapy in examined patients showed that remission (DAS28<2,6) was diagnosed in 34 (79.6%) patients ($p < 0.05$); 10 (20.4%) patients ($p < 0.05$) had minimal disease activity (DAS28 < 3.2). The monitoring of laboratory parameters after 12 months of INF therapy established a significant decrease in the level of pro-inflammatory cytokines: the concentration of TNF- α decreased by 3.9 times, IL-1β - by 2.8 times, IL-6 - by 7.6 times. hsCRP decreased to 2,8±0,3 mg/L ($p < 0.05$), respectively.

Conclusions

Analysis of the obtained data established a high clinical efficacy of INF therapy in RA. In addition, studies have shown that a decrease in inflammation activity during antirheumatic therapy is accompanied by an increase in levels of CL HDL and a decrease in TCL, CL LDL, AI. Lipid levels rise more strongly with a more intense decrease in SRP concentration. With a decrease in RA activity, a correlation between the level of TCL, CL LDL and TG of CVD begins to be revealed. It is clear that a therapeutic approach that corrects the activity of immune inflammation seems promising for the prevention and treatment of cardiovascular events in this pathology.

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