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Original Research

I. M. Fushtey, S. L. Podsevahina, A. I. Palamarchuck, O. V. Tkachenko
State Institute "Zaporizhzhia Medical Academy of Postgraduate Education of Ministry of Health of Ukraine"

INFLUENCE OF THE COMBINED LIPID-LOWERING THERAPY ON IMMUNINFLAMMATORY REACTIONS AND ENDOTHELIAL FUNCTION IN PATIENTS WITH RHEUMATOID ARTHRITIS AND ISCHEMIC HEART DISEASE

Optimization of lipid-lowering therapy can be achieved in three ways: statins dosage increasing; application of new drugs of this group (increases the economic costs of patients treatment), and finally, the use of combination therapy with drugs with different mechanisms of action. For now is of interest to evaluate its impact on such aspects as pathogenesis immuno-inflammatory reactions and endothelial dysfunction in ischemic heart disease combined with systemic inflammatory diseases, in particular – RA.

The aim of the work – to study the safety and efficacy (lipid-lowering and anti-inflammatory efficiency level, influence on endothelial function) of low-dose combined lipid-lowering therapy compared with aggressive statin therapy in patients with rheumatoid arthritis in combination with ischemic heart disease.

Materials and methods. We examined 42 patients (14 men and 28 women) aged (53,4±3,8) years with seropositive RA (average disease duration (10,2±1,5) years) in combination with ischemic heart disease – stable angina of II-III functional class. As basic therapy patients took methotrexate at a dose of (10,5±2,5) mg/week in combination with folic acid. The control group consisted of 30 healthy individuals.

Patients were randomly divided into two groups. Group 1 included 21 subjects who received as lipid-lowering therapy a low-dose combination of atorvastatin (Atoris, KRKA, Slovenia, 10 mg daily) and ω-3 PUFAs (Tecom, "Kiïvsky vitaminny Factory", 2,0 gr/day twice a day (A10/T2). Group 2 – included 21 patients who received atorvastatin 40 mg (A40).

Results. Combined low-dose lipid-lowering therapy by its efficacy is comparable to aggressive monotherapy with atorvastatin. At the same time, both tested treatment regimens made it possible to achieve the recommended reduction in LDL cholesterol: <2,5 mmol/l – only at approximately ⅔ of patients and <1,8 mmol/l – in ⅓ of patients. A10/T2 combination was comparable with A40 one by anti-inflammatory effect and had an advantage effect over atorvastatin monotherapy on endothelial function, manifested in a significant increase of vasodilation function and significant decrease of vasoconstrictive function.

Conclusions. Taking to account a more favorable profile of safety and tolerability of low-dose lipid-lowering therapy it can be used as an alternative to statin monotherapy in patients with high and/or very high risk.

Keywords: rheumatoid arthritis, ischemic heart disease, cytokines, endothelium, lipid-lowering therapy.

According to the modern conceptions, the importance of cardiovascular pathology as the main cause of death in patients with rheumatoid arthritis (RA) [8] is determined by its ability to accelerate the development of atherosclerosis and give the essential features of its pathogenesis [12]. This is manifested asymptomatic, in a significant number of cases, the nature of the clinical course, atheromatous plaques severe instability, as well as the acute onset of clinical events. A distinctive feature of cardiovascular pathology in RA is a high risk of its development in young people and women, as well as increased mortality of subjects with low body mass index (less than 20 kg/m2) [7].

Causes of atherosclerosis rapid development and progression, particularly of the ischemic heart disease (IHD) in patients with RA has not been fully determined. It is shown that the pathogenesis of these processes in RA is determined not only by the traditional risk factors such as dyslipidemia, diabetes, hypertension, increased body mass index, decreased physical activity [2, 14], but bythe presence of specific factors, primarily – chronic systemic inflammation of high graduation [4]. It was proved in several studies that systemic inflammation and immune system dysfunction are among the leading risk factors of cardiovascular disease in patients with RA, and the endothelium is the primary target of the action of inflammatory mediators [1, 11].

According to the ESC/EAS clinical guidelines (Guidelines for the management of dyslipidaemias

2011) for treatment of dyslipidemia and recommendations of the Association of Cardiologists of Ukraine (2012), the intensity of medical intervention depends on the initial value of calculated cardiovascular risk (CVR). It is recommended to start from the maximum aggressive tactics of lipid-lowering therapy in patients with high and very high CVR [3]. But, in spite of widespread use of lipid-lowering therapy, physicians often fail to achieve target levels in their routine clinical practice. More than half (52%) patients did not reach target values of LDL after statin therapy in the initial dose, and 86% of these patients do not achieve therapeutic goals after months [6].

There are three ways to achieve optimization of lipid-lowering therapy: statins doses increasing, which can potentiate risks of their toxicity; the use of new drugs of this group (this increases the economic costs of patients treatment), and finally, the use of combined therapy with drugs of different mechanisms of action [3]. One of the most perspective groups of drugs that are effective for both prevention and treatment of patients with ischemic heart disease, are drugs of ω-3 polyunsaturated fatty acids (ω-3 PUFA). The positive effect of omega-3 PUFA was proved in many multicenter clinical trials, during which a strong correlation between the level of income of these acids in the human body and decreased morbidity and mortality from cardiovascular disease, especially myocardial infarction and stroke was revealed [5, 10]. For now is of interest to evaluate its impact on such aspects as pathogenesis immuno-inflammatory reactions and endothelial dysfunction in ischemic heart disease combined with systemic inflammatory diseases, in particular – RA.

The **aim** of the work – to study the safety and efficacy (lipid-lowering and anti-inflammatory efficiency level, influence on endothelial function) of low-dose combined lipid-lowering therapy compared with aggressive statin therapy in patients with rheumatoid arthritis in combination with ischemic heart disease.

Materials and methods

We examined 42 patients (14 men and 28 women) aged (53,4±3,8) years with seropositive RA (average disease duration was (10,2±1,5) years) in combination with ischemic heart disease – stable angina of II-III functional class, Canadian Cardiovascular Society classification; average disease duration was (5,2±3,2) years. The diagnosis of RA was set according to the classification criteria of the American College of Rheumatology and the order of MH of Ukraine № 676 from 12.10.2006. As basic therapy patients took methotrexate at a dose of (10,5±2,5) mg/week in combination with folic acid. The study excluded patients who received previously treatment with biologically active drugs. In all patients along with standard clinical and laboratory diagnostic procedures we performed clinical evaluation of joints damage, an overall assessment of disease activity and functional abilities of the patient, followed by a quantitative assessment of RA activity using composite index DAS 28. IHD diagnosis was verified on the basis of clinical, biochemical and instrumental data. Clinical course, the typicality of anginal syndrome, and historical data, the specificity of ECG changes – data at rest and during exercise stress during veloergometry were assessed. Individual assessment of the fatal risk was carried out according to the SCORE table (Systemic Coronary Risk Evaluation), according to which the patients had high (56,4%) and very high (44,6%) CVR. The control group consisted of 30 healthy individuals. All subjects signed informed consent form for study participation.

Laboratory methods included the determination of total cholesterol (TC), low density lipoproteins (LDL), high density lipoproteins (HDL) and triglycerides (TG). These parameters were determined by ELISA using «HUMAN» (Germany) reagent kits. Concentration of C-reactive protein (CRP) was determined by means of immunoturbidimetric method; the diagnostic kit «BioSystems» and multifunction biochemical analyzer «Cobas Fara» were used. Serum proinflammatory cytokines – interleukin (IL)-1ß, IL-6 and tumor necrosis factor (TNF)-α were performed using ELISA method and commercial test kits "Protein contour" (St.Petersburg). Endothelin (ET)-1 plasma levels were analyzed by ELISA using test systems "Biomedica" (Austria).

Endothelial function was investigated by means of D.S. Celermajer method before and after of brachial artery occlusion, after nitroglycerin sublingual intake in the dose of 500 mg. Endothelial dysfunction was diagnosed at BA EDVD values decreasing less than 10%.

All patients underwent ischemic heart disease therapy according to generally accepted standards, including aspirin (97,3%), ß-blockers (95,6%); if it was necessary, calcium antagonists (45,4%), short-acting nitrates (56,8%) were added. Patients were randomly divided into two groups. Group 1 included 21 subjects who received as lipid-lowering therapy a low-dose combination of two drugs: atorvastatin 10 mg daily (Atoris, KRKA, Slovenia) and ω-3 PUFAs (Tecom, "Kiev Vitamin Factory") at a dose of 2,0 gr/day twice a day (A10/T2). Subjects of group 2 (n=21) were treated with atorvastatin 40 mg (A40). Safety control of treatment included alanine aminotransferase (ALT), aspartate aminotransferase (AST) and creatinephosphokinase (CPK) serum levels monitoring. Elevation of these enzymes ≥3 times upper limit of their normal range was the criterion for dose reduction/cancellation of lipid-lowering drugs.

The obtained data were processed by means of «Microsoft Excel XP» and Statistika 6.0 («Stat-

Soft», USA) programs. To describe the normal distribution of the data sample we used the average value of the characteristic (M) and standard error (m). Obtained data considered as significant at p-value <0D,05. Relationship between parameters was assessed by means of Spearman rank correlation method.

Results and discussion

Both lipid-lowering therapy regimens were well tolerated. However, the level of ALT in 30 days in group 2 (A40) was significantly higher than in those one in the 1-st group (A10/T2). During the study in 2 patients of group 2 atorvastatin dose was reduced to 20 mg 1 time per day due to increased ALT and/or AST levels (>3 times the upper limit of their normal range). To stabilize the level of liver enzymes in one of these patients there was a need of further reducing of atorvastatin dose up to 10 mg once daily. There were no increasing of liver enzymes above the safety levels in group 2.

At baseline, dyslipidemia type IIa was diagnosed in 41,90% of patients, dyslipidemia type IIb was determined in 28,57% and dyslipidemia type IV – in 29,53% of examined subjects. Mono- and combined lipid-lowering therapy in patients with RA in combination with ischemic heart disease demonstrated marked hypolipidemic effect (Table 1). After 12 weeks of treatment both lipid-lowering therapy regimens allowed to achieve recommended levels of the LDL-cholesterol (Cl) (<2,5 mmol/l) in 78,4% and 73,6% of patients of the 1-st and 2-nd groups, respectively. Initially and at the end of the study there were no differences in both groups by TC, LDL cholesterol, HDL cholesterol and VLDL levels. After 12 weeks of treatment we revealed a significant decrease of serum TG levels in patients treated with combined lipid-lowering therapy and a significant increase of HDL in 34,3% of patients of the first group and in 26,7% of patients of the second one.

Several studies have found that increased risk of cardiovascular disease in patients with RA is associated with the presence of dyslipidemia. Dyslipidemia in RA has a special character, typical for acute-phase inflammatory response. At the same time, changes in the lipid profile in patients with RA do not have natural character. Levels of TC and LDL cholesterol can both increase and decrease, and the content of HDL cholesterol naturally decreases in such patients [9]. In most studies, lipid profile (TC, TG, LDL and HDL levels) in patients with RA was not significantly disrupted even on the background of the marked atherosclerosis. At the same time, there were significant increasing of small LDL particles concentration and reducing of small HDL particles levels which has significant direct strong correlation with disease severity, activity and CRP levels [8].

Table 1

Changes of the blood lipids levels in patients with RA in combination with ischemic heart disease on mono- and combined lipid-lowering therapy (M±m)

Parameter, mmol/l	Group 1 (A10/T2) (n=21)		Group 2 (A40) (n=21)	
	Initial	12 week	Initial	12 week
TC	6,81±0,25	4,17±0,19*	6,73±0,22	4,06±0,36*
LDDL-cholesterol	3,08±0,23	2,35±0,17*	3,36±0,24	2,38±0,32*
VLDL-cholesterol	0,98±0,14	0,61±0,11*	0,89±0,14	0,52±0,09*
HDL-cholesterol	1,18±0,04	1,43±0,03*	1,20±0,05	1,32±0,03*
TG	1,63±0,17	1,06±0,07*	1,59±0,17	1,35±0,05*

Note: * – *significant changes of parameters in groups before and after treatment with p<0,05–0,001*

Table 2

Influence of mono-and combined lipid-lowering therapy on markers of systemic inflammation and endothelial function in patients with effort angina (M±m)

Parameter	Control (n=20)	Group 1 (A10/T2) (n=21)		Group 2 (A40) (n=21)	
		Initial	12 week	Initial	12 week
CRP, mg/l	4,2±0,27	10,17±1,52	6,18±0,25*	9,98±1,52	7,53±0,25*
IL-1ß, pg/ml	34,3±3,61	48,6±2,91	34,8±2,36*	47,28±2,91	38,1±1,43*
IL-6, pg/ml	40,7±2,91	57,8±3,56	40,2±3,18*	58,2±3,61	46,3±2,81*
TNF-α, pg/ml	22,4±3,18	35,7±2,67	23,6±1,52*	36,8±2,72	28,5±1,24*
EDVD, %	12,7±0,78	8,2±0,56	11,6±0,62*	8,9±0,68	10,8±0,72*
ET-1, ng/ml	4,6±0,41	7,4±0,42	4,9±0,36*	6,7±0,39	5,2±0,27*

Note: * – *significant changes of parameters in groups before and after treatment with p<0,05–0,001*

Comparative evaluation of anti-inflammatory effects of mono- and combined lipid-lowering therapy presented in Table 2. Under the influence of the treatment a significant decrease of CRP level and pro-inflammatory cytokines in both groups were revealed. However, it is important to note, that the degree of systemic inflammation suppression was most significant in the group of patients receiving low-dose combination therapy. Thus, in patients of group 1 the content of IL-1ß decreased on 29,2% ($p<0,001$) versus 19,3% ($p<0,05$) in subjects of the second group. There was also significant ($p<0,05$) decreasing of IL-6 level in group 1 on 18,6% and more expressed significant ($p<0,01$) it's decreasing in group 2 (on 25,8%). The most significant changes of anti-inflammatory factors in group 2 were found in the expression of TNF-α. It's values for this mode of treatment decreased on 32,8% ($p<0,001$) and were significantly lower than those, obtained in monotherapy group (17,5%, $p<0,05$).

It is important to note, that the use of combination therapy was enough effective as after 12 weeks of treatment cytokines levels become close to the control values ($p<0,05$).

Thus, combined low-dose lipid-lowering therapy in patients with RA in combination with ischemic heart disease provided significant anti-inflammatory effects, which, probably, in many ways are due to the positive effects of ω-3 PUFAs, that have the ability to inhibit the migration of monocytes into inflammation site, to suppress neutrophils pro-inflammatory action and the synthesis by hepatocytes of inflammation acute phase proteins [13].

Increasing of the brachial artery diameter growth at reactive hyperemia test during treatment was observed in both treatment groups, but it was significantly higher in patients with combined one. Similar trends were also observed in the dynamics of BA EDVD and ENDVD. Influence of Atorvastatin on ET-1 level was significant (20,2%, $p<0,01$), but application of a low-dose combined therapy with the addition of ω-3 PUFA levels led to at an even greater rate of significant ET-1 decreasing (on 30,5%, $p<0,001$). Literature data suggested, that ω-3 polyunsaturated fatty acids are involved in to eicosanoids metabolism and effectively compete with the ω-6 PUFA for cyclooxygenase. At the same time synthesized ω-3 prostacyclin is the active vasodilator and ω-3 thromboxane practically does not activates platelet aggregation, that reduces gene expression of adhesive molecules [15].

Conclusions

1. Combined low-dose lipid-lowering therapy by its efficacy is comparable to aggressive monotherapy with atorvastatin. At the same time, both tested treatment regimens made it possible to achieve the recommended reduction in LDL cholesterol: <2,5 mmol/l – only at approximately ⅔ of patients and <1,8 mmol/l – in ⅓ of patients.

2. A10/T2 combination was comparable with A40 one by anti-inflammatory effect and had an advantage effect over atorvastatin monotherapy on endothelial function, manifested in a significant increase of vasodilation function and significant decrease of vasoconstrictive function.

3. Taking to account a more favorable profile of safety and tolerability of low-dose lipid-lowering therapy it can be used as an alternative to statin monotherapy in patients with high and/or very high risk.

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І. М. Фуштей, С. Л. Подсевахіна, О. І. Паламарчук, О. В. Ткаченко
ДЗ «Запорізька медична академія післядипломної освіти МОЗ України»

ВПЛИВ КОМБІНОВАНОЇ ГІПОЛІПІДЕМІЧНОЇ ТЕРАПІЇ НА ІМУНОЗАПАЛЬНІ РЕАКЦІЇ І ФУНКЦІЮ ЕНДОТЕЛІЮ У ХВОРИХ НА РЕВМАТОЇДНИЙ АРТРИТ У ПОЄДНАННІ З ІШЕМІЧНОЮ ХВОРОБОЮ СЕРЦЯ

Мета роботи – вивчити безпечність та ефективність (вираженість гиполіпідемічного, протизапального ефектів, вплив на функцію ендотелію) низькодозової комбінованої гіполіпідемічної терапії у порівнянні з агресивною терапією статинами у хворих з ревматоїдним артритом у сполученні з ішемічною хворобою серця. Обстежено 42 пацієнта (14 чоловіків і 28 жінок) віком (53,4±3,8) року з серопозитивним ревматоїдним артритом (тривалість процесу в середньому склала (10,2±1,5 року) у поєднанні з ішемічною хворобою серця стабільною стенокардією напруги II–III функціонального класу з тривалістю захворювання в середньому (5,2±3,2) року. Залежно від проведеної терапії пацієнтів розподілили на дві групи: 1-а група (n=21) в якості гіполіпідемічної терапії отримували низькодозову комбінацію аторвастатину 10 мг (аторис, KRKA, Словенія) на добу та ω-3 поліненасичені жирні кислоти (теком, ЗАТ « Київський вітамінний завод») у дозі 2,0 г / добу в два прийоми та 2-а (n=21) – аторвастатин у дозі 40 мг. У 3 пацієнтів 2-ї групи відзначалося підвищення печінкових трансамінаназ >3 рази від верхньої межі норми, що вимагало зниження дози. У групі комбінованої терапії підвищення рівня печінкових ферментів вище допустимих значень не спостерігали. Тестовані режими гіполіпідемічної терапії дозволили через 12 тижнів лікування досягти рекомендованого рівня ліпопротеїдів низької щільності у 78,4% і 73,6% хворих 1 та 2 груп відповідно. Відзначено більш істотне зниження вмісту тригліцеридів у сироватці крові пацієнтів, що приймали комбіновану гіполіпідемічної терапії і значуще підвищення ЛПВЩ у (34,3%) пацієнтів 1-ї і у (28,6%) – 2-ї груп. Низькодозова комбінована гіполіпідемічна терапія володіла порівнянним з монотерапією протизапальним ефектом і мала переваги перед агресивною терапією аторвастатину з впливу на функцію ендотелію, що проявилося в достовірному підвищенні вазоділятірующої і зниженні вазоконстрикторной функцій.

Ключові слова: ревматоїдний артрит, ішемічна хвороба серця, цитокіни, ендотелій, гіполіпідемічна терапія.

И. М. Фуштей, С. Л. Подсевахина, А. И. Паламарчук, О. В. Ткаченко
ГЗ «Запорожская медицинская академия последипломного образования МЗ Украины»

ВЛИЯНИЕ КОМБИНИРОВАННОЙ ГИПОЛИПИДЕМИЧЕСКОЙ ТЕРАПИИ НА ИММУНОВОСПАЛИТЕЛЬНЫЕ РЕАКЦИИ И ФУНКЦИЮ ЭНДОТЕЛИЯ У БОЛЬНЫХ С РЕВМАТОИДНЫМ АРТРИТОМ В СОЧЕТАНИИ С ИШЕМИЧЕСКОЙ БОЛЕЗНЬЮ СЕРДЦА

Цель работы – изучить безопасность и эффективность (выраженность гиполипидемического, противовоспалительного эффектов, влияние на функцию эндотелия) низкодозовой комбинированной гиполипидемической терапии по сравнению с агрессивной терапией статинами у больных с ревмато-

идным артритом в сочетании с ишемической болезнью сердца. Обследовано 42 пациента (14 мужчин и 28 женщин) в возрасте (53,4±3,8) года с серопозитивным ревматоидным артритом (длительность процесса в среднем составила 10,2±1,5 года) в сочетании с ишемической болезнью сердца стабильной стенокардией напряжения II–III функционального класса с длительностью заболевания в среднем (5,2±3,2) года. В зависимости от проводимой терапии пациентов распределили на две группы: 1-я группа (n=21) в качестве гиполипидемической терапии получали низкодозовую комбинацию аторвастатина 10 мг (аторис, KRKA, Словения) в сутки и ω-3 полиненасыщенные жирные кислоты (теком, ЗАО «Киевский витаминный завод») в дозе 2,0 г/сут в два приема и 2-я (n=21) – аторвастатин в дозе 40 мг. У 3 пациентов 2-й группы отмечалось повышение печеночных трансаминаз >3 раза от верхней границы нормы, что требовало снижение дозы. В группе комбинированной терапии повышение уровня печеночных ферментов выше допустимых значений не наблюдали. Тестируемые режимы гиполипидемической терапии позволили через 12 недель лечения достичь рекомендуемого уровня липопротеидов низкой плотности у 78,4% и 73,6% больных 1-й и 2-й групп соответственно. Отмечено более существенное снижение содержания триглицеридов в сыворотке крови пациентов, принимавших комбинированную гиполипидемическую терапию и значимое повышение ЛПВП у (34,3%) пациентов 1-й и у (28,6%) – 2-й групп. Низкодозовая комбинированная гиполипидемическая терапия обладала сравнимым с монотерапией противовоспалительным эффектом и имела преимущества перед агрессивной терапией аторвастатина по влиянию на функцию эндотелия, проявившееся в достоверном повышении вазодилятирующей и снижении вазоконстрикторной функций.

Ключевые слова: ревматоидный артрит, ишемическая болезнь сердца, цитокины, эндотелий, гиполипидемическая терапия