EXPERIENCE IN THE USE OF ATORVASTATIN IN PATIENTS WITH RHEUMATOID ARTHRITIS AND HYPERCHOLESTEROLEMIA

N.S. Komendantova, Post Graduate Student
Y.V. Kulakov, Prof.
P.A. Lukyanov, Prof.
A.A. Sinenko, Associate Prof.
Pacific State Medical University, G.B. Elyakov Pacific Institute of Bioorganic Chemistry of the Far-Eastern Branch of the Russian Academy of Sciences, Russian Federation

Abstract

In recent years there has been increased interest in the problem of reducing cardiovascular risk in patients with rheumatoid arthritis (RA). To this end it is proposed to use statins, the effects of which are now being actively studied. The purpose of this work is to determine the possibility of use of atorvastatin in patients with RA and hypercholesterolemia. The study included 42 patients with RA and moderate hypercholesterolemia and 26 practically healthy women (control). We studied lipid spectrum, DAS28, levels of erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-alpha), interleukin 1β, 10 (IL-1β, IL-10), matrix metalloproteinase-9 (MMP-9) and its complex with tissue inhibitor-2 (MMP-9/TIMP-2). Patients with RA and moderate hypercholesterolemia in the complex therapy atorvastatin were administered at a dose of 20mg per day. We analyzed the stated figures in these patients before and after 6 weeks of treatment. In all patients with RA and moderate hypercholesterolemia on therapy with atorvastatin decreased total cholesterol (TC), low-density lipoprotein (LDL) and triglycerides (TG), indicators DAS28, ESR, CRP, concentrations of TNF-alpha, IL-1β, IL-10, MMP-9, MMP-9/TIMP-2. These data prove lipid-reducing and anti-inflammatory effects of atorvastatin, that allows to consider the application of this drug in patients with RA hypercholesterolemia in the complex therapy to reduce cardiovascular risk.

Keywords: Rheumatoid arthritis, hypercholesterolemia, atorvastatin, cytokines, matrix metalloproteinases

Introduction

Cardiovascular pathology acts as the most common comorbid conditions in patients with RA and occurs in approximately one third of people suffering from this disease (C. Meune, E. Touzé, L. Trinquart, Y. Allanore, 2009; M.J. Peters, D.P. Symmons, D.W. McCarey et al., 2010). In numerous studies have shown that the RA development of atherosclerosis and related cardiovascular complications due not only to the traditional risk factors (NCEP) (M.J. Peters, D.P. Symmons, D.W. McCarey et al., 2010; T.V. Popkova, D.S. Novikova, E.L. Nasonov, 2012), and inflammatory mechanisms underlying pathogenesis of these diseases (P.Libby, 2008; F. Montecucco, F. Mach, 2009).

Deficiencies in the system of transport of TC play an important role in the development of atherosclerosis and RA. As is known, high levels of LDL, the prevalence in the spectrum of small, dense LDL particles and low value high density lipoprotein (HDL), hypertriglyceridemia are the principal determinants of high risk of development of atherosclerosis (M.J. Peters, D.P. Symmons, D.W. McCarey et al., 2010; T.V. Popkova, D.S. Novikova, E.L. Nasonov, 2012).

An important role in the development of cardiovascular complications in RA plays the severity of the disease, characterized by high joint account, the presence of extra-articular manifestations, expressed functional failure of joints, positivity in respect of rheumatoid factor and antibodies to cyclic caroliniana peptide and high levels of markers of inflammation (ESR, CRP, IL-1, TNF-alpha, etc.) (F. Montecucco, F. Mach, 2009; T.V. Popkova, D.S. Novikova, E.L. Nasonov, 2012).

The cause of chronic inflammation in RA is the imbalance between the production of proinflammatory (TNF-alpha, IL-1, -6, -8, -12, -15 and others) and anti-inflammatory (IL-4, -10, receptor antagonist of IL-1 and others) cytokines with a predominance of products over the first synthesis of the second (I.B. McInnes, G. Schett, 2007; A.A. Novikov, E.N. Aleksandrova, M.A. Diatroptova, E.L. Nasonov, 2010; V.S. Sviridova, E.N. Kologrivova, N.A. Pronina et al., 2011).

Recently, great attention of the authors aimed to investigate the role of matrix metalloproteinases (MMP) and tissue inhibitors (TIMP) in the pathogenesis of atherosclerosis and coronary heart disease, including patients with RA (N.P. Mitkovskaya, T.A. Kurak, L.L. Avdej et al., 2011; A.A. Turna, R.T. Toguzov, 2009). Works related to the definition of activity of MMP in clinical practice, a little bit, and mostly they are presented experimental research.

Systemic inflammation in patients with RA promotes greater severity of processes and endothelial metalloproteinases activation with increased content in the blood MMP-9 (N.P. Mitkovskaya, T.A. Kurak, L.L. Avdej et

al., 2011). High serum activity of MMP-9 is an indicator of unstable atherosclerotic plaques in acute coronary syndrome and help to identify patients with an increased risk of adverse cardiovascular events (N.M. Lupach, E.A. Khludeeva, V.N. Potapov, P.A. Lukyanov, 2010].

TIMPs play an important role in keeping MMPs in latent form and preventing their excessive activation. Among them TIMP-1, TIMP-2 regulate the enzymatic activity of MMP in vivo. For normal processes of reorganization of the extracellular matrix is a need to balance the activity of MMP and their inhibitors (A.A. Turna, R.T. Toguzov, 2009).

Now to slow the progression of atherosclerotic vascular lesions and reduce the risk of cardiovascular accidents in RA was suggested to use statins (A.A. Novikov, E.N. Aleksandrova, M.A. Diatroptova, E.L. Nasonov, 2010; D.S. Novikova, T.V. Popkova, E.L. Nasonov, 2010; V.S. Tutunov, M.Y. Zubareva, P.P. Malyshev, V.V. Kukharchuk, 2011). In addition to improving lipid metabolism, are studied pleiotropic, namely anti-inflammatory effects of statins, which allows to discuss the prospects of their application in the treatment of RA (S. Van Doornum, G. McColl, I.P. Wicks, 2004; A.A. Novikov, E.N. Aleksandrova, M.A. Diatroptova, E.L. Nasonov, 2010; V.V. Yarosh, O.V. Radchenko, 2010).

There are few studies on the use of statins in RA. Mainly work in this area is devoted to the study of the effect of simvastatin and atorvastatin, and today the main focus of attention is paid to the application of the drug in patients with RA (classic study TARA (Trial of Atorvastatin in Rheumatoid Arthritis), completed in 2004 (D.W. McCarey, I.B. McInnes, R. Madhok et al., 2004), from 2011 launched 5-year-old largest clinical study TRACE RA (TRial of Atorvastatin for the Primary Prevention of Cardiovascular Events in Rheumatoid Arthritis) (V.S. Tutunov, M.Y. Zubareva, P.P. Malyshev, V.V. Kukharchuk, 2011).

Thus, the study of the application of atorvastatin in patients with RA and hypercholesterolemia is important for timely correction of cardiovascular risk, which in the future could reduce mortality from cardiovascular complications of RA.

The aim of the present work is to study of the dynamics of lipid spectrum, of activity indicators of RA (ESR, DAS 28), cytokine profile (TNF-alpha, IL-1-beta, IL-10), concentrations of MMP-9 and complex MMP-9/TIMP-2 in using of atorvastatin in patients with RA and hypercholesterolemia.

Material and methods

He studied the possibility of application of atorvastatin in 42 women aged 38 to 59 years with reliable diagnosis seropositive RA and moderate hypercholesterolemia IIA and IIb types on Fredriksen without clinical

manifestations of cardiovascular disease. Control was 26 practically healthy women at the age from 33 to 59 years, not having hypercholesterolemia and diseases of musculoskeletal apparatus. The research was carried out on the basis of Primorsky rheumatology center of Primorsky regional clinical hospital №1 (Vladivostok, Russian Federation).

The diagnosis of RA verified on the basis of the criteria proposed by American College of Rheumatology (ACR, 1987) and revised by American College of Rheumatology and European League Against Rheumatism (EULAR, 2010) (D. Aletaha, T. Neogi, A.J. Silman et al., 2010). Duration of RA in the monitoring group ranged from 4 months to 18 years of age. Prevailed patients with moderate disease activity (average index DAS28 4,84±0,12). As a basic treatment of the patient was receiving a stable dose of methotrexate 10-20 mg per week in combination with folic acid, and also as a pathogenetic and symptomatic therapy, nonsteroidal anti-inflammatory drugs, the majority of patients took prednisone in the dose of 10-15 mg per day. Patients in the study group atorvastatin was administered at a dose of 20 mg per day for 6 weeks.

Exclusion criteria patients were: cardiovascular disease, including detection during instrumental examination (X-ray of the chest, according to electrocardiogram, ultrasound of the heart) subclinical lesions of the cardiovascular system; liver disease; diabetes mellitus, renal insufficiency, contraindications for purpose of basic and lipid-lowering therapy; in history for the last 5 years any malignant tumors; alcohol and drug dependence; pregnancy and lactation.

The thorough clinical examination was conducted all patients. TC, TG, HDL was determined in blood serum enzymatic method. Level of LDL was calculated by the formula W.T. Friedewald:

LDL = TC - HDL - TG/2,2,

where LDL - cholesterol of low density lipoprotein, TC - total cholesterol, HDL - lipoproteins of high density, TG – triglycerides.

The activity of rheumatoid arthritis was assessed by indicators DAS28, levels ESR, CRP. Concentrations of TNF-alpha and IL-1β, IL-10, MMP-9 and complex MMP-9/TIMP-2 in the blood serum of the examined patients was determined highly sensitive immunoassay methods with the help of test-systems of the company "R&D Systems" (USA).

After 6 weeks was re-assessed the above clinical and laboratory parameters.

Statistical processing of the material was carried out by methods of parametric statistics using the built package of the statistical analysis with Microsoft Excel and Statuistica 6.0. Data are presented as the arithmetic mean (M) and its error (m). The statistical significance of differences was estimated by t-student test. Differences between groups were considered

statistically significant when p<0,05 (the probability of erroneous judgments less than 5%).

Results

The study involved RA patients with moderate hypercholesterolemia. The initial concentration of TC, LDL, TG in these patients was higher in comparison with the control group - TC 7,21±0.08 and 4,53±0.11 mmol/l, LDL 3,91±0.12 and 2,17±of 0.07 mmol/l, TG 1,47±0.03 and 0,91±0.03 mmol/l, respectively (p<0.001). HDL in patients in both groups the original had no significant differences (p>0.05).

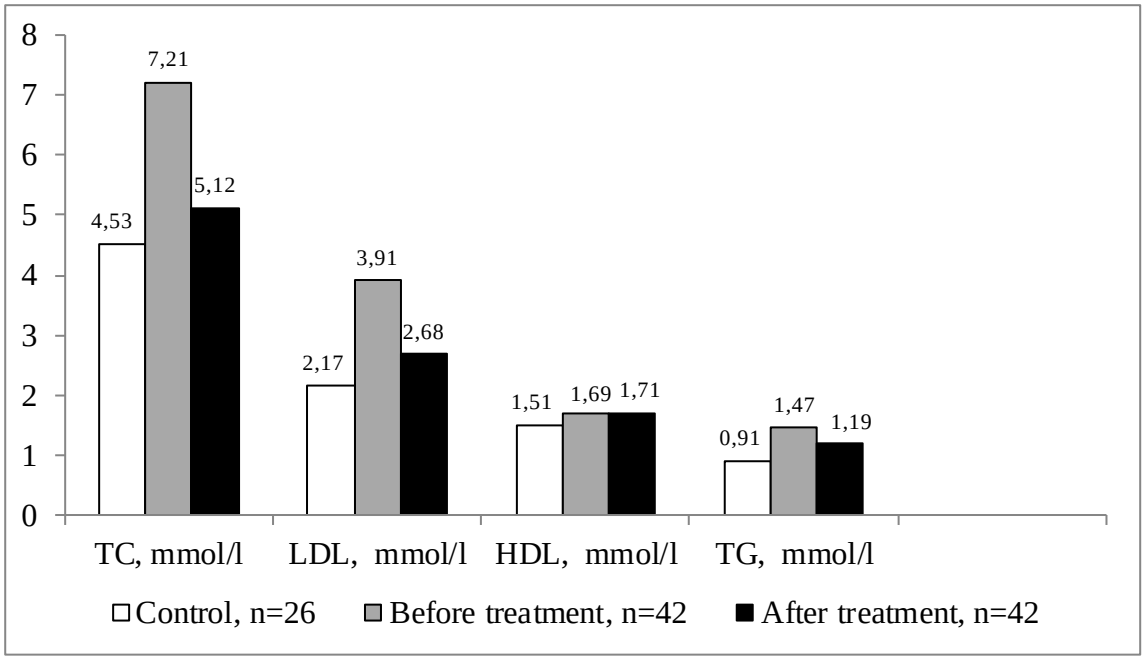

Figure 1. Dynamics of average lipid spectrum in patients with RA moderate hypercholesterolemia before and after treatment with atorvastatin, M±m (mmol/l).

After 6 weeks of starting treatment with atorvastatin was showed a significant decrease of the levels of TC by 29%, LDL by 31%, TG - 19% (p>0.05). The concentration of HDL in patients with RA and moderate hypercholesterolemia before and after 6-week lipid-lowering therapy has not changed. According to the data presented in figure 1, levels of TC and its fractions almost began to correspond to the norm.

Table 1. Dynamics of immune markers of inflammation and cytokines in patients with RA and moderate hypercholesterolemia before and after treatment with atorvastatin, M±m

Parameter	Control n=26	Before treatment n=42	After treatment n=42
ESR, mm/h	6,18±0,57	28,46±4,11	20,12±3,34
CRP, mkmol/ml	4,12±0,18	42,96±6,68	12,41±2,26
DAS28	-	4,84±0,27	2,88±0,11
IL-1β, pkg/ml	0,39±0,08	4,02±0,29	2,43±0,19
TNF-α, pkg/ml	2,49±0,31	13,89±1,55	8,37±1,02
IL-10, pkg/ml	2,41±0,52	11,42±1,61	7,81±0,92

The difference with the control and group "Before treatment" statistically significant.

After 6 weeks of starting treatment with atorvastatin is decreased activity of the RA to the minimum extent (table 1). In the dynamics of indicators ESR and CRP decreased almost to normal, but did not reach the levels in the control group. The analysis of changes from the side markers of immune inflammation in RA patients with moderate hypercholesterolemia was found to increase in all indicators - ESR, CRP, IL-1β, TNF-alpha, IL-10 in comparison with the control group ($p<0.001$). The source patients were registered moderate level of activity of the RA. The highest level of increase among all the studied cytokines in comparison with indexes in the control group reached IL-1β. The concentrations of all cytokines were decreased in 1,5-2 times on a background of treatment with atorvastatin, but remained higher than in the control group.

Table 2. Indicators of changes in MMP-9 and complex MMP-9/TIMP-2 in patients with RA and moderate hypercholesterolemia before and after treatment with atorvastatin, M±m

Parameter	Control n=26	Before treatment n=42	After treatment n=42
MMP-9, ng/ml	234,83 ± 11,38	337,14 ± 14,68	268,21 ± 13,24
MMP-9/TIMP-2, ng/ml	7,83 ± 1,69	19,96 ± 2,04	12,42 ± 1,87

The difference with the control and group "Before the treatment" statistically significant.

The original levels of MMP-9 and complex MMP-9/TIMP-2 in the blood serum of patients with RA and moderate hypercholesterolemia were higher than in the control group ($p<0.001$) - 1.5 and 2.5 times respectively (table 2). In the dynamics of the treatment is marked decline in these indices. However, the content of MMP-9 and complex MMP-9/TIMP-2 in patients with RA and moderate hypercholesterolemia after treatment with atorvastatin do not reach those in the control group.

Discussion

The original everyone who participated in the study RA patients with moderate hypercholesterolemia was identified atherogenic lipids spectrum - elevated levels of LDL cholesterol, triglycerides, combined with the normal concentration of HDL cholesterol. As a result of atorvastatin after 6 weeks

showed a significant decrease in total cholesterol and atherogenic fractions (LDL, TG) on 19-31% from baseline almost to normal values. The concentration of HDL for the whole period of the study was not significantly changed and varied within limits.

The original everyone who participated in the study RA patients with moderate hypercholesterolemia noted moderate inflammatory activity. For the period of treatment with atorvastatin dose of 20 mg per day on obligatory condition of reception of the basic anti-inflammatory drugs all indicators of systemic inflammation were decreased and became characteristic of the minimal activity of the RA.

The data we obtained coincides with literature data of ukrainian authors (V.V. Yarosh, O.V. Radchenko, 2011), russian reseachers (N.M. Nikitina, A.P. Rebrov, 2010). In these studies, in appointing patients RA without cardiovascular disease, but with the presence of dyslipidemia atorvastatin in dose 10 and 20 mg/day is also marked by a significant reduction of the levels of total cholesterol, LDL cholesterol, triglycerides and activity of the RA.

Our results partially correlates with the data of Van Doornum S. et al. (2004), in which atorvastatin dose of 20 mg was significantly reduced total cholesterol, LDL cholesterol, especially in patients with high activity, however, the levels of CRP, ESR not changed.

Patients included in our study noted the good tolerability of all drugs. Side effects during the observation period were not registered.

Conclusion

Thus, when using atorvastatin in combination therapy RA are achieved lipid-reducing and anti-inflammatory effects. The use of atorvastatin in patients with RA and hypercholesterolemia is expedient to reduce the risk of cardiovascular complications and augmentation of anti-inflammatory action the basic drugs.

References:

Aletaha D, Neogi T, Silman AJ et al. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Ann Rheum Dis 2010, 69, 1580-1588.

Van Doornum S, McColl G, Wicks IP. Atorvastatin reduces arterial stiffness in patients with rheumatoid arthritis. Ann Rheum Dis 2004, 63, 1571—1575.

Libby P. Role of inflammation in associated with rheumatoid arthritis. Am J Med 2008, 121 (Suppl 1), 21-31.

Lupach NM, Khludeeva EA, Potapov VN, Lukyanov PA. Matrix metalloproteinases, oxidative status and endothelial dysfunction in

individuals with hypercholesterinaemia and in patients with different forms of ischemic heart disease. Pacific Medical Journal 2010, 4, 71-74.
McCarey DW, McInnes IB, Madhok R et al. Trial of Atorvastatin in Rheumatoid Arthritis (TARA): doubleblind, randomized placebo-controlled trial. Lancet 2004, 363, 2015—2021.
McInnes IB, Schett G. Cytokines in the pathogenesis of rheumatoid arthritis. Nat Rev Immunol 2007, 7, 429-442.
Meune C, Touzé E, Trinquart L, Allanore Y. Trends in cardiovascular mortality in patients with rheumatoid arthritis over 50 years: a systematic review and meta-analysis of cohort studies. Rheumatology (Oxford) 2009, 48, 1309-1313.
Mitkovskaya NP, Kurak TA, Avdej LL et al. Activity of metalloproteinases in patients with rheumatoid arthritis: the role of systemic inflammation and traditional risk factors of cardiovascular diseases. Cardiology in Belarus 2011, 3, 34-44.
Montecucco F, Mach F. Common inflammatory mediators orchestrate pathophysiological processes in rheumatoid arthritis and atherosclerosis. Rheumatology (Oxford) 2009, 48:11-22.
Nikitina NM, Rebrov AP. The application of atorvastatin in patients with rheumatoid arthritis and hyperlipidemia. Cardiology 2009, 9, 21-26.
Novikov AA, Aleksandrova EN, Diatroptova MA, Nasonov EL. The role of cytokines in the pathogenesis of rheumatoid arthritis. Scientific-Practical Rheumatology 2010, 2, 71-82.
Novikova DS, Popkova TV, Nasonov EL. Statins as a basis of prevention of cardiovascular complications in rheumatoid arthritis. Clinical pharmacology and therapy 2010, 2, 71-82.
Peters MJ, Symmons DP, McCarey DW et al. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other types of inflammatory arthritis — task force «Cardiovascular risk management in RA». Ann Rheum Dis 2010, 69 (2), 325-331.
Popkova TV, Novikova DS, Nasonov EL. Cardiovascular risk factors in rheumatic diseases: links with inflammation. Heart disease and blood vessels 2012, 4, 30-39.
Sviridova VS, Kologrivova EN, Pronina NA et al. Cytokine regulation of immune responses in rheumatoid arthritis. Cytokines and inflammation 2011, 2, 28-32.
Solomon DH, Kremer J, Curtis JR, Hochberg MC, Reed G et al. Explaining the cardiovascular risk associated with rheumatoid arthritis: traditional risk factors versus markers of rheumatoid arthritis severity. Ann Rheum Dis 2010, 69, 1920-1925.

Turna AA, Toguzov RT. Matrix metalloproteinases and cardiovascular disease. Arterial hypertension 2009, 15(5), 532-538.
Tutunov VS, Zubareva MY, Malyshev PP, Kukharchuk VV. Statins in rheumatology. Atherosclerosis and dyslipidemia 2011, 2. URL: http://cyberleninka.ru/article/n/statiny-v-revmatologii (reference date: 22.12.2013).
Yarosh VV, Radchenko OV. The comparative analysis of influence of various doses of simvastatin and atorvastatin on immunological indices in patients with rheumatoid arthritis a high degree of activity. Taurida medical-biological vestnik 2010, 13, 1 (49), 193-197.