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CONTENT

EARTH SCIENCES

ECONOMICS

HISTORICAL SCIENCES

JURISPRUDENCE

MEDICAL SCIENCES

PEDAGOGICAL SCIENCES

PHILOLOGY

MEDICAL SCIENCES

MODERN APPROACHES TO THE TREATMENT OF ARTERIAL HYPERTENSION, ABDOMINAL OBESITY AND TYPE 2 DIABETES IN PATIENTS WITH RHEUMATOID ARTHRITIS (LITERATURE REVIEW)

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Abstract

The development of modern approaches to the pharmacotherapy of rheumatoid arthritis (RA) in combination with arterial hypertension (AH), abdominal obesity (AB), and type 2 diabetes mellitus (T2DM) remains relevant today. In particular, due to inadequate control of systemic inflammation, simultaneous administration of a large number of potentially dangerous drugs: nonsteroidal anti-inflammatory drugs (NSAIDs), disease-modifying antirheumatic drugs (DMARDs), and glucocorticosteroids (GCs), a comorbid pathology occurs that complicates the course and treatment of RA.

In order to solve this problem, it is necessary to correct the risk factors of RA, choose an adequate disease-modifying antirheumatic therapy (DMRT) and treat concomitant pathology. This will improve the prognosis and improve the quality of life of RA patients.

Keywords: rheumatoid arthritis, arterial hypertension, abdominal obesity, type 2 diabetes, angiotensin II receptor blockers, statins.

The current concept of RA treatment consists in slowing the progression and achieving a long-term remission of the disease [1] by using methotrexate (MT), which is a first-line drug according to the recommendations of EULAR and ACR [2], and NSAIDs and GCS, which are able to reduce inflammation in the synovial membrane, relieve pain and joint stiffness [3]. However, high achievements in the search for effective means of treatment of RA, which allowed to achieve a significant reduction in the severity of the systemic immunoinflammatory process, often cause the emergence of comorbid pathology. Considering the frequent presence of high blood pressure, high blood pressure, and type 2 diabetes in patients with RA, it is advisable to use antihypertensive, hypolipidemic drugs, and metabolic therapy, including telmisartan, rosuvastatin, and L-arginine, in combination with basic therapy [4].

Despite the indisputable success of pharmacotherapy in recent years, the prognosis for RA patients with the indicated combined pathology remains disappointing. Therefore, improving the integrated approach to the treatment of RA with polymorbid pathology will improve the results of therapy, increase the duration of clinical remission, and improve the patient's quality of life.

In the treatment of hypertension in patients with RA, the choice of an antihypertensive drug consists not only in reducing blood pressure, but also in taking into account its effect on the course of the underlying disease.

A meta-analysis of INSIGHT, VHAS, ELSA studies proved that for the effective treatment of hypertension in patients with RA, it is necessary to use blockers of slow calcium channels, because they have an anti-inflammatory effect and suppress oxidative stress, which positively affects the prognosis and slows down the progression of atherosclerosis [5]. Currently, third-generation β-adrenoceptor blockers (nebivolol, carvedilol, bisoprolol, metoprolol) have been widely used, which show high cardioselectivity, improving the functional state of the endothelium, reducing lipid peroxidation (POL) [6].

But still, angiotensin-converting enzyme inhibitors (ACEI) and angiotensin II receptor blockers (ARBs) are preferred in the treatment of hypertension in patients with RA, which affect not only the blood pressure level, but also slow down the progression of atherosclerosis and exhibit an anti-inflammatory effect, reducing the level of inflammatory mediators, reactive forms of oxygen [7]. A new breakthrough in the treatment of hypertension with the achievement of optimal BP values within 24 hours was the use of ARBs [8]. ARBs, when compared with other groups of antihypertensive drugs, are characterized by very good tolerability, which contributes to high adherence of patients to treatment [9]. In addition, this group of drugs affects not only the blood pressure level, but also has positive metabolic properties: it increases the sensitivity of peripheral tissues to insulin, preventing the development of type 2 diabetes [10, 11, 12] and affects lipid metabolism, enhancing the utilization of fats to cover energy needs. needs of the body [13]. This was confirmed in the large-scale INNOVATION study, which demonstrated the prevention of progression of diabetic nephropathy with telmisartan and in the NAVIGATOR study with valsartan. At the same time, ARBs cause an anti-inflammatory effect, which is realized by reducing the level of pro-inflammatory cytokines [14].

Recently, the effectiveness of the use of ARBs, in particular telmisartan, in patients with RA in combination with hypertension has been studied. ARBs block the renin-angiotensin-aldosterone system (RAAS), which reduces the level of aldosterone without affecting the level of renin and the function of ion channels and does not lead to the accumulation of bradykinin, thus causing an increase in the level of eNOS, which improves the function of the endothelium [15, 16]

Another positive effect of telmisartan is the strengthening of mitochondrial activity, which prevents the development of obesity (OB), dyscirculatory encephalopathy (DE) and the occurrence of type 2 diabetes [17, 18].

A meta-analysis of the ONTARGET randomized study confirmed all the pleiotropic effects of ARBs, namely the reduction in the occurrence of cardiovascular diseases (infarction, stroke) at high cardiovascular risk with the use of telmisartan [19].

It is known that the T-786C polymorphism of the eNOS gene can predispose to the development of cardiovascular diseases (CVD) and influence the sensitivity to drugs, in particular, modulate the response to statin therapy - effects on the expression of eNOS and the formation of endogenous NO [20]. The study confirmed that the cardioprotective effect of statins is associated with an increase in NO production by the endothelium. In particular, low doses of statins activate eNOS phosphorylation and NO production, protecting endothelial cells from apoptosis and causing the formation of capillary-like structures in the matrix, which enhances angiogenesis in animals with models of autoimmune disease [21].

Statins are used in the presence of concomitant hypertension, high blood pressure, and type 2 diabetes. The main effect of statin treatment is to reduce the content of low-density lipoprotein cholesterol (LDL-C) and total cholesterol (CHD), with a slight increase in high-density lipoprotein cholesterol (HDL-C) [22] . In addition, in recent years, the anti-inflammatory effect of statins and the effectiveness of their use in the treatment of RA have been proven [23].

However, the choice of the safest, most effective statin, its dosage and duration of treatment is still debated.

For the first time, a study of the effectiveness of statins in patients with RA was conducted in the double-blind placebo-controlled study TARA, in which after 6 months of treatment with basic drugs in combination with atorvastatin at a dose of 40 mg, disease activity was significantly reduced by 0.5 according to DAS28; the level of C-reactive protein (CRP) - by 50%; erythrocyte sedimentation rate (ESR) - by 28% and the content of interleukin-6 (IL-6) compared to the placebo group [24].

I. Ikdahl et al. [25] in a placebo-controlled study, which included 20 RA patients with disease activity (DAS28>2.6), noted that the pronounced effect of simvastatin therapy at a dose of 40 mg per day was higher in patients with elevated CRP >10 mg/l. Therefore, it can be argued that patients with a high degree of RA activity respond better to statin treatment.

In the ANDROMEDA randomized double-blind clinical trial, the efficacy and safety of atorvastatin 10-20 mg and rosuvastatin 10-20 mg were compared in patients with type 2 diabetes. As a result of the data obtained, the levels of CHD and LDL-C were lower when using rosuvastatin compared to atorvastatin in equivalent doses. [26].

As part of the GALAXY program, which included more than 69 thousand patients, the hypolipidemic effectiveness of rosuvastatin was studied in comparison with other statins and its effect on inflammatory markers (STELLAR, MERCURY I, II; ORVITAL, DISSAVERIS, SOMETS, PLUTO, POЛARIS, SOЛAP, EXPЛOPEP and etc.), suppression of atherosclerosis (ORION, METEOR, ASTEROID, SATURN), as well as cardiovascular diseases and mortality (AURORA, SORONA, JUPITER, LUNAR) [27].

According to the results of the 6-week open randomized study STELLAR, it was established that when taking low doses of rosuvastatin (10-40 mg), the level of LDL-C decreased by 52-63%, TG - by 34%, and the level of HDL-C increased by 10%, which exceeded according to these indicators, all other statins in high doses. When using atorvastatin in a dose of 80 mg, the level of LDL cholesterol decreased by 50%, simvastatin in a dose of 40 mg - by 47%, pravastatin in a dose of 40 mg - by 29% [25].

In the 16-week MERCURI clinical trial, rosuvastatin 10-20 mg/day was superior to equivalent doses of atorvastatin, simvastatin, and pravastatin in achieving the LDL-C target according to the NCEP ATP III criteria and of the European Atherosclerosis Society (EAS) [28].

Therefore, according to the results of numerous studies (STELLAR, MERCURY I, SOLAR) it was established that rosuvastatin is the most effective statin, which allows blocking the activity of the key enzyme of cholesterol biosynthesis 3-hydroxy-3-methylglutaryl-coenzyme A-reductase (HMG-CoA) and activating the synthesis of the main protein of HDL - apolipoprotein in apo-AI, which increases from 5% to 15%, at low and medium doses of 10-20 mg, reaching the target levels of LDL cholesterol earlier. And the tolerability and safety of rosuvastatin is comparable to other statins [29].

There is an opinion that lowering the level of LDL cholesterol under the influence of statins contributes to the improvement of endothelial function, which is associated not only with the restoration of lipid metabolism indicators, but also with lipid-independent transcriptional activation of the eNOS gene [30].

The rational use of nitrogen monoxide (NO) (L-arginine) in the treatment program can improve the clinical course and prognosis of RA [31], since NO contributes to the immune defense of the body, acting as an immunoregulator, and in high concentrations exhibits a cytotoxic effect that complicates various manifestations of autoimmune character [32]. In a study by J. Y. Dong et al. [33], which included 387 patients, oral intake of L-arginine for an average of 4 weeks contributed to a statistically significant reduction in systolic blood pressure (SBP) and diastolic blood pressure

(DBP) and improved the functional state of the endothelium, which significantly reduced the risk of cardiovascular complications and events.

Therefore, taking into account the above, the correction of concomitant pathology will allow to increase the effectiveness of treatment of patients with RA, which served as arguments for conducting our study, and the study of genetic aspects of the development of polymorbidity in RA will allow to improve the prediction of the appearance of concomitant pathology and its early diagnosis.

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