OPORTUNIDADES MODERNAS DE FARMACOTERAPIA ATEROSCLEROSE: NOVAS DIREÇÕES

MODERN OPPORTUNITIES OF ATHEROSCLEROSIS PHARMACOTHERAPY: NEW DIRECTIONS

СОВРЕМЕННЫЕ ВОЗМОЖНОСТИ ФАРМАКОТЕРАПИИ АТЕРОСКЛЕРОЗА: НОВЫЕ НАПРАВЛЕНИЯ

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RESUMO

Apesar das realizações bem-sucedidas da medicina aplicada moderna e da aplicação de medicamentos hipolipidêmicos na prática clínica nos últimos 50 anos, a questão da prevenção e tratamento da doença vascular aterosclerótica (DVA) permanece sem solução. A implementação da teoria da imunopatogênese da aterosclerose, comprovada experimentalmente por estudos modernos, permite que os especialistas ampliem as possibilidades de farmacoterapia e farmacoprevenção para DVA. Assim, o objetivo do presente estudo foi analisar novas direções no desenvolvimento de medicamentos antiateroscleróticos (DAA) com atividade patogênica que suprimia a inflamação autoimune crônica nas áreas de lesão aterosclerótica dos vasos. No decorrer do estudo, foram realizadas a busca e análise das publicações nas bases de dados Web of Science, PubMed e RSCI (Russian Science Citation Index) para o período de 2016-2018. De acordo com a análise realizada, os alvos moleculares mais importantes para a DAA são citocinas pró-inflamatórias e anti-inflamatórias que desenvolvem um desequilíbrio em pacientes com DVA. Assim, os fármacos baseados em anticorpos monoclonais ao fator de necrose tumoral α (TNF α) e interleucinas pró-inflamatórias (1 β , 17A), utilizados no tratamento da artrite reumatóide e psoríase, podem ser utilizados para o tratamento da DVA. As interleucinas recombinantes 6, 13, 19 e substâncias que suprimem a expressão de fatores reguladores de interferon também exercerão um efeito antiaterogênico. Os estudos sobre a modelagem da patogênese da DVA em animais consanguíneos mostraram que outros alvos moleculares para DAA poderiam ser enzimas envolvidas no metabolismo lipídico e de células imunes. Eles incluem a enzima 1 requerente de inositol, a proproteína convertase subtilisina / Kexin tipo 9 e as enzimas da família paraoxonase. Além disso, a revisão inclui a discussão sobre a aplicação bem-sucedida de medicamentos baseados em anticorpos monoclonais ao TNF α (infliximabe), IL-17A (secukinumabe) e IL-1 β (canacinumabe), bem como os medicamentos com atividade anti-enzimática (evolocumabe e darapladib), na prática clínica para o tratamento da DVA. O conhecimento moderno sobre os mecanismos moleculares da imunopatogênese pode fundamentar o desenvolvimento de fármacos para farmacoterapia patogênica e a farmacoprevenção para as complicações da DVA. A solução mais eficaz seria a indicação de medicamentos que afetam o desequilíbrio de citocinas e processos metabólicos nas células imunológicas.

Palavras-chave: aterosclerose, farmacoterapia, medicamentos antiateroscleróticos, interleucinas, enzimas, placas ateroscleróticas.

ABSTRACT

Despite the successful achievements in modern applied medicine and the application of hypolipidemic drugs into clinical practice for the past 50 years, the issue of prevention and treatment of atherosclerotic vascular disease (AVD) remains unsolved. Implementation of the theory of immunopathogenesis of atherosclerosis that was experimentally proved by modern studies allows the specialists to expand the possibilities of pharmacotherapy and pharmacoprevention for AVD. Thus, the aim of the present study was to analyze new directions in the development of anti-atherosclerotic drugs (AAD) with a pathogenetic activity that suppressed chronic autoimmune inflammation in the areas of atherosclerotic damage of vessels. In the course

of the study, the search and analysis of the publications in the databases Web of Science, PubMed, and RSCI (Russian Science Citation Index) for the period of 2016-2018 were performed. According to the performed analysis, the most perspective molecular targets for AAD are pro-inflammatory and anti-inflammatory cytokines that develop a disbalance in patients with AVD. Thus, the drugs that are based on monoclonal antibodies to the tumor necrosis factor α (TNF α), and pro-inflammatory interleukins (1 β , 17A), used for the treatment of rheumatoid arthritis and psoriasis, can be used for the treatment of AVD. Recombinant interleukins 6, 13, 19, and substances that suppress the expression of interferon regulatory factors will also exert an antiatherogenic effect. The studies on the modeling of the pathogenesis of AVD in inbred animals showed that other molecular targets for AAD could be enzymes involved in the lipid and immune cells metabolism. They include inositol-requiring enzyme 1, proprotein convertase subtilisin/Kexin type 9, and the enzymes of paraoxonase family. Besides, the review includes the discussion of the successful application of drugs based on monoclonal antibodies to TNF α (infliximab), IL-17A (secukinumab) and IL-1 β (canakinumab), as well as the drugs with anti-enzymatic activity (evolocumab and darapladib), in clinical practice for the treatment of AVD. The modern knowledge on molecular mechanisms of immunopathogenesis can give grounds for the development of drugs for pathogenetic pharmacotherapy and pharmacoprevention for the complications of AVD. The most effective solution would be the indication of drugs that affect the disbalance of cytokines and metabolic processes in the immune cells.

Keywords: *atherosclerosis, pharmacotherapy, anti-atherosclerotic drugs, interleukins, enzymes, atherosclerotic plaques.*

АННОТАЦИЯ

Несмотря на успехи современной практической медицины и использование в клинической практике гипOLIпидемических лекарственных средств в течение почти 50 лет, проблема профилактики и лечения atherosclerotic vascular disease (AVD) остается нерешенной. Использование постулатов теории иммунопатогенеза атеросклероза, экспериментально подтвержденной современными исследованиями, позволяет расширить возможности фармакотерапии и фармакопрофилактики AVD. В связи с этим целью данного исследования явился анализ новых направлений в создании анти-атеросклеротических лекарственных средств (AAD) с патогенетическим действием, которые бы угнетали развитие хронического аутоиммунного воспаления в области атеросклеротического поражения сосудов. Для реализации цели был проведен поиск и анализ статей по базам данных Web of Science, PubMed и РИНЦ за период 2016-5-2018гг. Согласно проведенному анализу наиболее перспективными молекулярными мишенями для AAD являются провоспалительные и противовоспалительные цитокины, между которыми при AVD развивается дисбаланс. Поэтому лекарственные средства на основе моноклональных антител к фактору некроза опухолей альфа и провоспалительным интерлейкинам (1 β , 17A), используемые для лечения ревматоидного артрита и псориаза, могут быть использованы и при AVD. Противоатерогенным эффектом будут обладать и рекомбинантные интерлейкины 6, 13, 19 и вещества, угнетающие экспрессию interferon regulatory factor. По результатам изучения патогенеза AVD при моделировании этого патологического процесса у инбредных животных установлено, что другими молекулярными мишенями для AAD могут послужить ферменты, участвующие в обмене липидов и метаболизме иммунных клеток. Это inositol-requiring enzyme 1, proprotein convertase subtilisin/kexin type 9 и ферменты семейства paraoxonase. Кроме того, в обзоре обсуждаются результаты успешного применения в клинической практике для лечения AVD лекарственных средств на основе моноклональных антител к TNF α (инфликсимаба), IL-17A (секукинумаба) и IL-1 β (канакинумаба); а также препаратов с антиферментативной активностью (эволюкумаба и дарапладиба). Таким образом, на основе современных данных о молекулярных механизмах иммунопатогенеза вполне реальна разработка лекарственных средств для патогенетической фармакотерапии и фармакопрофилактики осложнений AVD. Для этой цели наиболее эффективно будет применение лекарственных средств, влияющих на дисбаланс цитокинов и обменные процессы в иммунных клетках

Keywords: *атеросклероз, фармакотерапия, анти-атеросклеротические лекарственные средства, интерлейкины, ферменты, атеросклеротическая бляшка.*

1. INTRODUCTION

Despite the successful achievements in modern applied medicine and the application of hypolipidemic drugs into clinical practice for the past 50 years, the issue of prevention and

treatment of atherosclerotic vascular disease (AVD) remains unsolved.

The analysis of the results of clinical observations after the patients with AVD and the studies on the modeled atherosclerosis (AS) in

animals revealed significant inconsistency with the lipid theory of AS pathogenesis (stereotype, focality, and localization of the process independent of the character of dyslipidemia; possibility of the development of AS in patients with normal lipid metabolism; simultaneous presence of atherosclerotic plaques (AP) of different maturity and they are under endothelial location; AVD relapse after the coronary artery bypass graft surgery) and brought proves in favor of the theory of immunopathogenesis (Kilessa, 2012).

The main role in the pathogenesis of AVD plays the process of autoimmune inflammation, which is confirmed by numerous facts on the protective properties of low-density lipoproteins (LDL) and cholesterol (Ch) in patients with bacterial and viral infections (Kovalenko, 2010). According to the concept of the immunopathogenesis of AS, the degree and reversibility of the vascular walls damage, and the stability of the formed AP are determined by the balance interleukins, interferons, TNFs, and colony-stimulating factors that regulate the interaction of the immune cells (Karagodin, 2014). As a rule, lipid disorders associated with AVD can be considered as one of the most important manifestations of the non-specific congenital immune response to the infectious agents (Kovalenko, 2010).

The abovementioned information can give grounds to the development of new approaches to the pharmacotherapy and pharmacoprevention of AVD. The aim of the present review was to describe modern tendencies in the pharmacotherapy of AS.

2. MATERIALS AND METHODS

In the course of the study, the search and analysis of the publications in the databases Web of Science and PubMed. The search query consisted of different combinations of keywords: «atherosclerosis + interleukins», «atherosclerotic plaques + interleukins», «atherosclerosis + pharmacotherapy», «anti-atherosclerotic drugs», «atherosclerosis + enzymes». Totally, 29 original articles were selected that contained the primary results of the studies and 9 review articles.

The search was also performed in the database RSCI (elibrary.ru – scientific electronic library) for the period of 2010-2018. The authors retrieved 10 review articles and 12 original articles that satisfied the search query

3. RESULTS AND DISCUSSION

3.1. Drugs that affect the synthesis and effects of cytokines

It is known that the disorders in the balance between the pro-inflammatory and anti-inflammatory cytokines lead to the induction of self-maintaining mechanisms of chronic inflammation in patients with AS. Hence, one of the main possible directions in the immunotherapy of AS can be the modification of the cytokine effects (Tedgui and Mallat, 2001; Beshpalova et al., 2013; Alexopoulos and Kaggi, 2014).

There is evidence of the prevalence of cytokines in the serum of patients with AS. These cytokines determine the polarization of the immune response to the activation of T-helper 1 (Th1) lymphocytes. These are anti-inflammatory cytokines (interleukin-1 (IL-1), interleukin-8 (IL-8), tumor necrosis factor-alpha (TNFα)) that enhance the migration of leukocytes to the focus of the immune inflammation, stimulate the migration and proliferation of smooth muscle cells as well as contribute to the apoptosis of immune-competent cells in the AP and enhance their destabilization (von Vietinghoff and Ley, 2010; Ershova et al., 2011; Ait-Oufella et al., 2011; Arabidze, 2013; Sineglazova, 2012; Shalenkova et al., 2013; Fatkhullina et al., 2016).

Besides, the hyperproduction of pro-inflammatory cytokines in patients with progressing AS is one of the main causes of acute disturbance of the regulation of the immune reactions and further progressing of a systemic inflammatory process in the arteries, which explains the relapse of AP in patients after endarterectomy (Curtiss and Tobias, 2009; Zaporozhec et al., 2012; Ramji and Davies, 2015).

The described facts are also confirmed by the results of the tests on the cytokines content in the samples of the arteries affected by AP. Thus, the results, obtained by the method of flow cytometry, revealed the increase in the expression of interleukin-2 (IL-2), interleukin-17 (IL-17) and interferon-gamma (INFγ) CD8 and CD4-T-lymphocytes found in the samples of AP in comparison with the blood cells (Grivel et al., 2012). In the samples of cultivated AP taken from the patients with AVD of carotid arteries, the content of TNFα positive cells was significantly higher than in the samples of the circulating lymphocytes. It should be mentioned that

unstable AP contained more CD4 T-lymphocytes, that express TNF α and IFN γ , than stable ones (Profumo *et al.*, 2013).

It was also established that the samples with unstable AP, taken from the areas of coronary arteries in men with coronary AS with a stable effort angina II-IV FC, had a significantly higher concentration of pro-inflammatory cytokines: interleukin-1 β (IL-1 β), interleukin-18 (IL-18), interleukin-6 (IL-6) and IL-8. It should be mentioned that the unstable AP of the dystrophic-necrotic type also had a significantly higher level of TNF α (Ragino *et al.*, 2011; Ragino *et al.*, 2012). Similar results were obtained during the study of the atherosclerotic areas of carotid arteries in humans (Shishkina *et al.*, 2014). Besides, the experiments on the modeled AS in animals with inhibited pro-inflammatory cytokines indicated the slowdown of the process of the development and progression of the disease (Tedgui and Mallat, 2001; Ershova *et al.*, 2011; Miossec, 2009).

Thus, one of the targets for anti-atherosclerotic drugs (AAD) can be pro-inflammatory cytokines.

It is known that one of the key roles in the pathogenesis of AS and ischemic heart disease plays a pro-inflammatory cytokine TNF α , which inhibits the synthesis of apolipoprotein A-1 (ApoA1) in hepatocytes leading to the decrease in the high-density lipoprotein (HDL) in blood, and induces the apoptosis of vascular smooth muscle cells (VSMC) by inhibiting the expression of connexins resulting in the destabilization of AP (Kovalenko *et al.*, 2010; Tang and Fang, 2017). Hence, the inhibition of this cytokine should have a favorable pathogenetic effect in patients with AS. As a result of a short-term indication of infliximab (drug based on monoclonal antibodies to TNF α) to 33 patients with rheumatoid arthritis, there was an increase in the HDL in plasma by 0.12 mmol/L in two weeks and a significant decrease in the index of atherogenicity (Popa *et al.*, 2007). Apart from infliximab, there are other drugs that reduce the effects of TNF α like etanercept, adalimumab, golimumab, and certolizumab (Geiler *et al.*, 2011; Tousoulis *et al.*, 2016). Presently, it is proved that the treatment of patients with autoimmune diseases (psoriasis, rheumatoid arthritis) with anti-TNF α agents improves the function of endothelium in arteries (Tousoulis *et al.*, 2016; Avgerinou *et al.*, 2011; Spinelli *et al.*, 2014).

IFN γ also plays an important role in the immunopathogenesis of AS stimulating the uptake of modified lipoproteins by the

macrophages and the development of foam cells. The experiment on the cross-breeding of IFN γ -deficient and LDLR-deficient mice (LDL receptor-deficient) on the cholesterol diet showed that there was a significant decrease in the level of IFN γ , which led to the reduction of AP size in several areas of the aorta and relative decrease in the macrophage and VSMC count in the AP that were formed earlier. The authors suggested that the inhibition of the effects of IFN γ -producing T-lymphocytes in the vascular walls was a potentially beneficial strategy for the control of AS (Buono *et al.*, 2003).

Further, in the experiment with inbred mice of IRF3-/-ApoE-/- line (apolipoprotein E knockout with impossibility to synthesize interferon regulatory factor 3, IRF3), the influence of IRF3 was established on the secretion of the molecules of adhesion by the endothelial cells and further infiltration of the vascular walls by macrophages in subjects with AS. IRF3 deficit led to the inhibition of the secretion of the molecules of adhesion in the vascular cells and expression of the molecules of intercellular adhesion, which resulted in the reduction of infiltration of the damaged arterial wall by macrophages. The authors of the study believed that IRF3 could be also used as a potential target for the development of AAD (Liu *et al.*, 2017).

It was also proved that interleukin-17 (IL-17) exerted pro-atherogenic effect due to its capacity to enhance the production of IL-1 β , IL-6, IL-12, and INF γ by macrophages (Ouyang *et al.*, 2008; Chen *et al.*, 2010; Kozlov, 2016). Inhibition of the effects of IL-17 reduces the manifestations of AVD in animal models, but there were no clinical trials performed (Erbel, *et al.*, 2016). Presently, a drug based on monoclonal antibody (MA) to IL-17A (secukinumab) was developed that can expand the therapeutic possibilities for patients with AS. The results of the performed clinical studies on subjects with ankylosing spondylitis showed that secukinumab had low immunogenicity, and its safety profile nearly similar to the one placebo (Jerdes, 2016). Brodalumab (antagonist of IL-17 receptors) and Ixekizumab (MA to IL-17A), used for the treatment of psoriasis, can be also potential AAD considering the pro-inflammatory character of IL-17 (Tousoulis *et al.*, 2016; Coimbra *et al.*, 2014).

In 2018, the results of the randomized controlled clinical study of canakinumab (human anti-IL-1 β MA) were published. The study included more than 10,000 patients with preceding myocardial infarction, an elevated level of C-reactive protein (CRP), and Ch LDL (despite

the therapy with statins). The results revealed the reduction of the primary endpoint of the death caused by the myocardial infarction or stroke by 15% (in the dose of 150 mg or 300 mg every 3rd month). There were no statistically significant changes in the cholesterol of low-density lipoproteins (Ch LDL) registered. Still, the level of CRP and IL-6 significantly decreased. The analysis of the secondary endpoint (a necessity in urgent revascularization) showed even more significant results with a relative reduction of the risk by 17% in comparison with the median. Besides, canakinumab demonstrated the importance of inflammation in patients with multiple systemic disorders. The inhibition of IL-1 β by canakinumab also reduced the mortality rate from lung cancer by more than a half, depending on the indicated dose (Lorenzatti and Servato, 2018).

There is less data on the application of drugs with anti-IL-6 effect. Tocilizumab (MA to the membrane and circulating IL-6), indicated to patients with rheumatoid arthritis in the course of a randomized study, increased total HDL, Ch LDL and triglycerides (Tousoulis *et al.*, 2016; Kawashiri *et al.*, 2011). But the application of tocilizumab also led to the improvement of endothelial function and reduction of aorta stiffness (Tousoulis *et al.*, 2016; Protogerou, 2011). There is an ongoing study on the possibility of an indication of tocilizumab to patients with rheumatoid arthritis and cardiovascular risk factors (Tousoulis *et al.*, 2016).

Another approach to the reduction of disbalance of cytokines in patients with AS can be based on the stimulation of the expression of anti-atherogenic (anti-inflammatory) cytokines. There are some published data that proves an anti-atherogenic role in the expression of interleukin-4 (IL-4), interleukin-13 (IL-13), and interleukin-1 (IL-19) in subjects with AS.

The positive effect of IL-4 and IL-13 lies in the enhancement of polarization of macrophages to a phenotype M2 (involved in the immune reactions of T-helper 2 (Th2), which stimulates the processes of proliferation and angiogenesis) that stimulates the tissue regeneration after the inhibition of inflammatory reaction (Bobryshev *et al.*, 2016; Zhao *et al.*, 2016; Chen *et al.*, 2017). The anti-atherogenic effect of IL-13 was proved by the results of the study on AS-prone mice that could not secrete IL-13, and that developed significantly bigger and more mature AP. A deficit of IL-13 also led to the accelerated development of AVD in LDLR-deficit mice without the influence on Ch in plasma. An indication of IL-

13 to animals limited the chemotaxis of macrophages to AVD foci and favorably modulated the morphology of the existing AP by increasing the content of collagen and decreasing the macrophage count. Besides, the experiments in vitro showed that the activated IL-13 macrophages (phenotype M2) had higher clearance to the oxidized LDL in comparison with M1 macrophages activated by IFN γ (Cardilo-Reis *et al.*, 2012).

The study on the IL-19 knockout mice showed that the deficit of this interleukin activated the proliferation of VSMC and synthesis of pro-inflammatory cytokines (including IL-1 β and TNF α). This fact allowed the authors to suggest the application of IL-19 as a potent suppressor of AS development (Fatkhullina, 2016). In 2016, a group of scientists from Medical Universities of Philadelphia and New-York conducted a study on the capability of exogenous IL-19 to reduce the progression of AVD. LDLR-knockout mice were given feed with increased content of Ch for 12 weeks and, further, given recombinant IL-19 for eight more weeks. The analyses of AVD in mice from the test group (receiving IL-19) revealed the key parameters of the AS regression: reduction of total macrophage count and increase in the M2 macrophage count. Additional studies showed that IL-19 played an important role in the regulation of lipid metabolism of macrophages by means of gamma-receptor regulation of Ch absorption that depended on peroxisome proliferates and increase in the outflow of Ch mediated by ATP-binding cassette transporter (ABCA1) (Gabunia *et al.*, 2016).

Besides, IL-19 plays an important role in the proliferation and transformation of VSMC, in particular, induces the expression of muscle-specific miRNA (miR133a) in these cells that can reduce the expression of low-density lipoprotein receptor adapter protein 1 (LDLRAP1) – an adaptor protein that is necessary for the internalization of LDLR. Thus, IL-19 reduced the accumulation of lipids in VSMC and the uptake of oxidized LDL in the miR133a-dependent mechanism (Gabunia *et al.*, 2016).

Herman *et al.* (2016) in their study, showed that the anti-inflammatory IL-19 reduces the function of mRNA-stability protein HuR in human VSMC, which could also reduce their capacity to proliferation (Herman *et al.*, 2016; Herman *et al.*, 2018). Thus, currently, the following mechanisms of anti-atherogenic activity of IL-19 were established:

- Th2-polarization of the immune response,

- regulation of the role of macrophages in the development of inflammation,
- regulation of macrophages lipid metabolism,
- the decrease in leukocyte adhesion,
- suppression of the expression of the genes of pro-inflammatory cytokines,
- reduction of neointimal hyperplasia by means of the reduction of activation of VSMC (Gabunia *et al.*, 2016; Gabunia *et al.*, 2017).

The interest of the researchers is also attracted by the possibility of target delivery of recombinant IL-19 to the foci of ADV by means of adenoviruses during the modeling of AS in animals. Presently, despite a positive effect of anti-inflammatory cytokines during the modeling of AS in animals, the anti-inflammatory cytokines drugs are not obtained yet (Tousoulis *et al.*, 2016; Tian *et al.*, 2008).

3.2. Drugs that affect enzymatic activity

The second important direction in the development of AAD can become the regulation of the activity of the enzymes that play an important role in the metabolism of immune cells involved in chronic autoimmune inflammation. In this aspect, kinase/endoribonuclease inositol-requiring enzyme 1 (IRE1) can be considered as a perspective target for the drugs. This enzyme is the most conservative regulator of the activity of the protein of a homeostatic regulatory net that reacts to a metabolic overload of endoplasmic reticulum in the conditions of the metabolically induced chronic inflammatory process (AS, diabetes mellitus, metabolic syndrome). IRE1 is also one of the most important regulators of the expression of pro-atherogenic genes that has cytoprotective and pro-apoptotic functions and is activated after the accumulation of lipids and proteins with a damaged quaternary structure in the endoplasmic reticulum. The method of the sequencing of ribonucleic acid (RNA) of macrophages was used to establish that IRE1 regulated the expression of numerous pro-atherogenic genes. Hence, AAD inhibitors of IRE1 could be used for the prevention of activation of the inflammatory process by macrophages in the vascular endothelium under the effect of lipid-induced stress (Pavlova *et al.*, 2014; Tufanli *et al.*, 2017). During the modeling of AS in inbred ApoE-knockout mice, it was established that the introduction of IRE1 inhibitors significantly reduced the production of IL-1 β and IL-18, the activity of Th1 immune response, and

size of AP without the changes in lipid profile of plasma. The authors believed that the pharmacologic modulation of the activity of IRE1 could contribute to the slowdown of the progression of AS (Tufanli *et al.*, 2017). Presently, several substances with the activity of IRE1 inhibitors based on the aromatic or heteroaromatic hydroxy aldehydes are obtained (Pavlova *et al.*, 2014).

Another target for AAD can be the enzymes of the paraoxonase (PON) family. These enzymes prevent the oxidation of lipids to LDL by means of their hydrolysis, inhibit the differentiation of monocytes in macrophages, and uptake of the oxidized LDL by the macrophages and their conversion to foam cells. Besides, the enzymes of the PON family regulate some functions of macrophages: stabilize their mitochondria, contribute to their differentiation to M2 phenotype, and prevent the induction of their apoptosis. The increase in the expression and/or activity of PON can contribute to the metabolism of Ch in macrophages and weaken the inflammatory process in the vascular endothelium (Watson *et al.*, 1995; Whit and Anantharamaiah, 2017).

When the new facts were obtained on the regulation of the expression of LDLR on the hepatocytes surface, that provide the clearance of LDL from the bloodstream, a new target for ADD was identified that took part in the destruction of the receptors to LDLR – proprotein convertase subtilisin/Kexin type 9 (PCSK9) (Kuharchuk and Bazhan, 2013). A recent clinical study on the application of evolocumab (PCSK9 inhibitor) showed a decrease in the Ch LDL level in patients by 70% and more.

In comparison with the apheresis of LDL, two-week injection therapy with this drug proved to be more effective, less expensive, and less invasive without serious side effects (Kawashiri *et al.*, 2017). The analysis of the results obtained in other clinical studies on the evaluation of the effects of PCSK9 inhibitors in patients with a high risk of cardio-vascular disorders showed that there was a positive effect of this pharmacological group on the levels of Ch, LDL in blood, AP volume, decrease in CD rate, and total mortality rate (Kawashiri *et al.*, 2017; Karpov and Talickij, 2015; Schmidt *et al.*, 2017; Karpov, 2017).

Another enzyme was described that could be used as a target for AAD - lipoprotein-associated phospholipase A2 (Lp-PLA2) – that was secreted primarily by macrophages. This

enzyme hydrolyzes phosphatidylcholine on the surface of LDL in plasma. The increase in the activity of Lp-PLA2 leads to the intensive expression of the products of peroxidation and, as a result, to the enhancement of the inflammatory process in the altered vascular walls (Kuharchuk and Tararak, 2010). An inhibitor of Lp-PLA2 (darapladib (GlaxoSmithKline, UK)) was developed. According to the results of the study, published by the manufacturer, the indication of darapladib led to a relative decrease (6%) in the development of myocardial infarction or stroke in patients. The study on drug effectiveness is ongoing (White *et al.*, 2014).

Presently, the results of some clinical studies on potential AAD drugs are published (Table 1).

It was established that anti-cytokine drugs used for the treatment of systemic autoimmune diseases (rheumatoid arthritis, ankylosing spondylitis, psoriasis, acute gouty arthritis, ulcerative colitis) significantly influenced on the mortality rate from CD and the parameters that characterized the presence of AVD.

Thus, the application of AAD – MA to pro-inflammatory cytokines (infliximab, etanercept, adalimumab, golimumab, canakinumab) and their receptors (anakinra, tocilizumab) led to the increase in the HDL level, decrease in the CRP and IL-6 levels, decrease in the atherogenic index, and improvement of the endothelial function (Popa *et al.*, 2007; Geiler *et al.*, 2011; Tousoulis *et al.*, 2016; Avgerinou *et al.*, 2011; Spinelli *et al.*, 2014; Jerdes, 2016; Lorenzatti and Servato, 2018; Kawashiri *et al.*, 2011; Protogerou *et al.*, 2011). Indication of tocilizumab to patients with rheumatoid arthritis in the course of pharmacotherapy resulted in a decrease in LDL, CH LDL levels, and reduction of aortic stiffness (Geiler *et al.*, 2011; Kawashiri *et al.*, 2011; Protogerou *et al.*, 2011). The authors did not reveal any data on the drugs that decreased the expression of IFN γ .

Despite the proven anti-atherogenic activity on AS models, the drugs based on anti-inflammatory cytokines are still not developed and clinically not tested.

When it comes to AAD (enzymes inhibitors), presently, there are only three drugs (evolocumab, alirocumab, darapladib) that are clinically tested in patients with lipid metabolic disorders and CD. The application of evolocumab and alirocumab led to a statistically significant decrease in the level of Ch LDL and the risk of CD development (Kawashiri *et al.*, 2017; Karpov

and Talickij, 2015; Schmidt *et al.*, 2017; Karpov, 2017). The introduction of darapladib to the treatment plan did not show any significant progress in patients with CD (White *et al.*, 2014).

There are some data on the substances with anti-enzymatic activity towards IRE1 (Pavlova *et al.*, 2014), but there are no drugs developed.

Thus, there are some potential targets for the development of innovative AAD drugs that would exert the pathogenetic effect on the process of the development of AVD, and they, certainly, need further investigation.

4. CONCLUSION

Further development of pharmacotherapy for AS can be directed to the influence on the realization of adaptive (shift of cytokine profile to Th2 immune response) and congenital (enhancement of macrophages differentiation to M2 phenotype, regulation of lipid metabolism of macrophages) immune reactions, as well as on the activity of enzymes that play an important role in the metabolism of the immune cells and regulation of the lipid metabolism.

The analysis of the retrieved publications showed that new approaches to the pharmacotherapy of AS were based on different aspects of the theory of immunopathogenesis. According to the performed analysis, the most perspective new directions in the development of AS pharmacotherapy were the following:

- influence on the synthesis and effects of cytokines,
- inhibition, and induction of the activity of the enzymes that take part in the lipid metabolism of immune cells.

The results of the ongoing upscale studies give hope that the application of new AAD drugs in pathogenetic therapy for AS could reduce the risk of complications in patients with AVD.

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Table 1. Characteristics of new targets for the treatment of as and aad

Nº	Target	Drug	Used for therapy	The results of clinical studies in patients with AVD
1	TNF α	Infliximab Etanercept Adalimumab Golimumab	Rheumatoid arthritis, ulcerative colitis, ankylosing spondylitis, psoriasis	increased HDL level decreased atherogenic index, decreased endothelial dysfunction
2	IFN γ	—*	—	—
3	IRF3	—	—	—
4	IL-17A	Secukinumab Ixekizumab	Psoriasis, active ankylosing spondylitis	—
5	IL-17R	Brodalumab	Psoriasis	—
6	IL-1 β	Canakinumab	Acute podagric arthritis, juvenile idiopathic arthritis	decreased CRP and IL-6 levels decreased mortality rate from CD
7	IL-1Ra	Anakinra	Rheumatoid arthritis	decreased CRP and IL-6 levels decreased CD recurrence and mortality rate
8	IL-6	Tocilizumab	Rheumatoid arthritis	decreased LDL, and Ch LDL levels decreased improved endothelial function and decreased aortic stiffness
9	IL-13	—	—	—
10	IL-19	—	—	—
11	IRE1	—	—	—
12	PON	—	—	—
13	PCSK9	Evolocumab Alirocumab	Primary hyperlipidemia, hypercholesterinemia, mixed dyslipidemia	decreased Ch LDL level decreased risk of developing CD
14	Lp-PLA2	Darapladib	CD	decreased LDL level, decreased AP volume, decreased risk of developing CD, the general mortality rate

* – No information.

List of abbreviations:

AAD – anti-atherosclerotic drugs
ApoA-I – apolipoprotein A-I
ApoE – apolipoprotein E
AP – atherosclerotic plaques
AS – atherosclerosis
AVD – atherosclerotic vascular disease
CD – cardiovascular diseases
CRP – C-reactive protein
Ch – cholesterol
IL – interleukin
INF γ – interferon-gamma
IRE 1 – inositol-requiring enzyme 1
IRF3 – interferon regulatory factor
HDL – high-density lipoprotein
LDL – low-density lipoprotein
LDLR – low-density lipoprotein receptor
Lp-PLA2 – lipoprotein-associated phospholipase A2
MA – monoclonal antibody
PCSK9 – proprotein convertase subtilisin/Kexin type 9
PON – paraoxonase
Th – T-helper cells
TNF α – Tumor necrosis factor
VSMC – Vascular smooth muscle cell