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Anti-cytokine therapy for prevention of atherosclerosis

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ABSTRACT

Background: Currently a chronic inflammation is considered to be the one of the most important reasons of the atherosclerosis progression. A huge amount of researches over the past few decades are devoted to study the various mechanisms of inflammation in the development of atherosclerotic lesions.
Purpose: To review current capabilities of anti-inflammatory therapy for the prevention and treatment of atherosclerosis and its clinical manifestations.
Methods: Appropriate articles on inflammatory cytokines in atherosclerosis and anti-inflammatory prevention of atherosclerosis were searched in PubMed Database from their respective inceptions until October 2015.
Sections: "The role of inflammatory cytokines in the development of atherosclerotic lesions" describes available data on the possible inflammatory mechanisms of the atherogenesis with a special attention to the role of cytokines. "Modern experience of anti-inflammatory therapy for the treatment of atherosclerosis" describes modern anti-inflammatory preparations with anti-atherosclerotic effect including natural preparations. In "the development of anti-inflammatory herbal preparation for atherosclerosis prevention" an algorithm is demonstrated that includes screening of anti-cytokine activity of different natural products, the development of the most effective combination and estimation of its effect in cell culture model, in animal model of the acute aseptic inflammation and in a pilot clinical trial. A natural preparation "Inflaminat" based on black elder berries (*Sambucus nigra* L.), violet tricolor herb (*Viola tricolor* L.) and calendula flowers (*Calendula officinalis* L.) possessing anti-cytokine activity was developed using the designed algorithm. The results of the following 2-year double blind placebo-controlled clinical study show that "Inflaminat" reduces carotid IMT progression, *i.e.* has anti-atherosclerotic effect.
Conclusion: Anti-cytokine therapy may be a promising direction in moderation of atherogenesis, especially when it begins on the early stages of subclinical atherosclerosis. The use of herbal preparations with anti-cytokine mechanism of action is the most perspective for timely prevention of atherosclerosis, as they have no significant side effects and can be prescribed for long-term administration.

Introduction

Atherosclerosis is a multifactorial disease, and it is the basis for stroke, coronary heart disease and myocardial infarction, which remain the leading cause of mortality in Western countries.

A large number of studies on the role of inflammation in atherogenesis have been held since eighties of last century (Ammirati et al. 2015; Falk 2006; Hansson 2009; Tousoulis et al. 2015; Wolf et al. 2014). Currently there is a strong perception that local aseptic inflammation plays an important role in the progression of atherosclerosis (Aidinian et al. 2006; Libby 2006). It is known that the primary act of atherogenesis at the arterial wall is an accumulation of intracellular lipids, which is accompanied by other manifestations of atherosclerosis at the cellular level, such as stimulation of proliferation and increased synthesis and secretion

Abbreviations: BMI, body mass index; CRP, C-reactive protein; ICAM-1, intercellular adhesion molecule; IL-1, interleukin 1; IL-6, interleukin 6; cIMT, carotid intima-media thickness; LDL, low-density lipoproteins; M-CSF, macrophage colony-stimulating factor; MCP-1, monocyte chemoattractant protein 1; NSAID, nonsteroidal anti-inflammatory drug; TNF-α, tumor necrosis factor α; VSMCs, vascular smooth muscle cells.

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of extracellular matrix and induction of synthesis and secretion of inflammatory cytokines (Orekhov et al. 1990). Under unfavorable circumstances the formation of foci of chronic inflammation leads to development of morphologically unstable plaques prone to rupture, which cause the clinical manifestations of atherosclerosis. It is necessary to conduct timely prevention in people with subclinical atherosclerosis to prevent the development of serious complications such as stroke, acute coronary syndrome and other life-threatening atherosclerotic diseases. Since atherosclerosis develops over many years, the atherosclerosis prevention should be lifelong. Taking into account the need for long-term antiatherosclerotic therapy our research team considers effective and safe natural products as promising candidates for the antiatherosclerotic agents that do not cause side effects and phenomena.

About 30 years ago, it was discovered the phenomenon of serum atherogenicity—its ability to induce lipid accumulation in cultured cells of the arterial intima (Chazov et al. 1986). It has been found that the atherogenic blood components are modified low-density lipoproteins (LDL) that are present in large amounts in the blood of patients with atherosclerosis (Tertov et al. 1989). Previously it has been established in a clinical trial using the ultrasound monitoring of the carotid atherosclerosis progression that a steady decrease of patients' serum atherogenicity leads to regression of atherosclerosis in the carotid arteries (Orekhov et al. 1995). Thus, the pathogenetic approach to the prevention of arteriosclerosis in its early stages was developed, which includes the suppression of the cholesterol accumulation in arterial wall cells. Currently, local inflammatory process is considered to be the most likely cause of the progressive development of atherosclerotic lesions in the arterial wall. The important role of inflammatory cytokines at all stages of the formation of atherosclerotic lesions and clinical manifestations of atherosclerosis is described in numerous studies (Daugherty et al. 2005; Gopal et al 2014; Hansson GK et al. 2006; Ikonomidis et al. 2012; Ramji and Davies 2015; Von der Thusen et al. 2003; Young et al. 2002).

This review describes the symptoms of inflammation in atherosclerosis, that allow to consider atherosclerosis as a chronic inflammatory process. Modern experience of anti-inflammatory therapy in atherosclerosis treatment is presented. We have designed an algorithm of the development of anti-cytokine therapy for prevention and treatment of atherosclerosis that include screening of anti-cytokine activity of different natural substances, the development of the most effective combination and estimation of its effect in *in vitro, ex vivo* and *in vivo* models and clinical trial of the anti-atherosclerotic action.

Methods

Appropriate articles on inflammation in atherosclerosis and anti-inflammatory prevention of atherosclerosis were searched in PubMed Database from their respective inceptions until October 2015. More 50 publications describing the inflammatory mechanisms of atherogenesis, in particular, the role of inflammatory cytokines in the development of atherosclerotic lesions were examined in this review. About 20 publications describing the contemporary experience of anti-inflammatory therapy in the prevention and treatment of atherosclerosis, including natural preparations, were considered.

The role of inflammatory cytokines in the development of atherosclerotic lesions

Basic researches in the field of atherosclerosis reveal a lot of data about the role of inflammation in the cellular and molecular mechanisms of atherogenesis in all its stages from the initial signs of the process until the destabilization of atherosclerotic plaques and thrombotic events, with special attention paid to the participation of inflammatory cytokines in the development of atherosclerotic lesions (Daugherty et al. 2005; Gopal et al 2014; Hansson GK et al. 2006; Ikonomidis et al. 2012; Ramji and Davies 2015; Von der Thusen et al. 2003; Young et al. 2002).

Several types of immune cells, primarily monocytes, T- and B-lymphocytes and perhaps mast cells are involved in the inflammatory process in atherosclerosis. In the process of atherosclerotic inflammation the key role belongs to monocytes/macrophages (Chavez-Sanchez et al. 2014; Legein et al. 2013; Tuttolomondo et al. 2012). Apparently, the overexpression of inflammatory cytokines by dysfunctional endothelial and blood cells due to influence of modified LDL should be considered as the first step of inflammation in atherosclerosis (Nikoforov et al. 2013). Inflammatory cytokines, basically tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1) promote adhesion of monocytes to activated endothelial cells due to excessive expression of vascular cell adhesion molecules, intercellular adhesion molecules (ICAM-1), endothelial adhesion molecules for leukocytes and E-selectin are expressed by endothelial cells, vascular smooth muscle cells (VSMCs), tissue macrophages (Blake and Ridker 2001). Adhesion molecules cause rolling of blood cells, monocytes and lymphocytes, their binding and transendothelial migration. Endothelial adhesion molecules specifically and strongly bind to monocytes and lymphocytes of the blood, that is the basis for subsequent differential migration of these cells in the subendothelial space of the vessel, induced by specific factors (TNF-α, monocyte chemoattractant protein (MCP-1)). Soluble forms of the adhesion molecules can be determined in plasma and are an indicator of adhesion molecules expression on the cell membrane (Lind 2003). The next stage is the differentiation of monocytes into macrophages. A part of monocytes influenced by macrophage colony-stimulating (M-CSF), granulocyte-macrophage colony-stimulating and other factors secreted by endothelial cells penetrate in the intima and are exposed differentiation and proliferation, express scavenger receptors than transforming into macrophages (Rosenfeld et al. 1992). With the assistance of M-CSF the macrophage phenotype occurs that is not transformed into foam cells but subsequently secrete inflammatory cytokines (IL-1, TNF-α). Chemoattractants secreted by these macrophages, such as osteoptin, mitogens and platelet derived growth factor activate VSMCs, causing their migration from media into intima of the arterial wall. Macrophages of the other phenotype uptake excess of modified LDL, are transformed into foam cells. Macrophages and mast cells secrete a growth factor which causes proliferation of VSMCs and regulates the production of the extracellular matrix, as well as metalloproteinases that cause the degradation of the extracellular matrix. Inflammatory cytokines may also have procoagulant effects, directly or via endothelial dysfunction. Thus, macrophages and mast cells regulate the growth of atherosclerotic plaque and contributing to its further destabilization with thrombosis (Biasucci et al. 1998; Galis et al. 1995).

IL-1 and interleukin-6 (IL-6) also have a great importance in the development of atherosclerosis as mediators of interactions between the leukocytes. IL-1 can induce a large part of local and systemic manifestations of the inflammatory response in atherosclerosis. This is achieved by improving the adhesion of the blood cells to the vascular endothelial cells and increasing blood procoagulant activity. IL-1 is a chemoattractant for a variety of cells, it increases the mobility of neutrophils, promotes cell activation in the locus of inflammation, enhances the production of other cytokines and prostaglandin as well as synthesis of collagen and fibronectin, stimulates phagocytosis, and production of superoxide radicals, cause degranulation of mast cells. IL-1 binds to a receptor on the endothelial surface and stimulates a whole cascade of