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ARTYKUŁ SPECJALNY / *STATE-OF-THE-ART REVIEW*

Anti-inflammatory therapy in the treatment of cardiovascular diseases

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INTRODUCTION

Inflammatory response underlies each step of atherosclerosis progression, from endothelial dysfunction to plaque rupture or erosion [1]. Large prospective cohort studies confirmed the importance of nonspecific systemic inflammation markers such as increased leukocyte count, and the levels of C-reactive protein (CRP), serum amyloid A, interleukin 6 (IL-6), and fibrinogen in cardiovascular risk stratification (Fig. 1) [2]. We still do not know, however, whether reduction of inflammation per se may result in a reduced rate of adverse cardiovascular events. The central pathway of inflammatory process that includes interleukin 1 (IL-1), tumour necrosis factor alpha (TNF-α), and IL-6 [3] is considered a particularly attractive pathway for anti-inflammatory therapy to prevent cardiovascular events.

The present paper summarises available data on inhibition of the inflammatory response in the treatment of cardiovascular disease (CVD), including compounds with an established anti-inflammatory effect, new drugs studied in the population of CVD patients, and drug classes used therapeutically for years, the inflammatory effect of which has been discovered only recently (Fig. 2).

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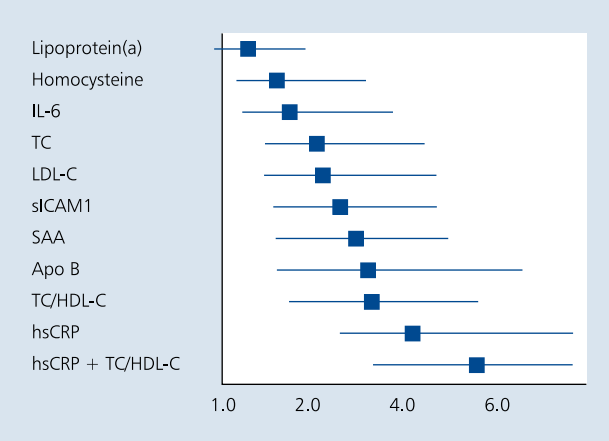

Figure 1. Relative risk of future cardiovascular events in healthy women in relation to baseline lipid levels and inflammation markers; Apo B — apolipoprotein B; HDL-C — high-density lipoprotein cholesterol; hs-CRP — high-sensitivity C-reactive protein; IL-6 — interleukin 6; LDL-C — low-density lipoprotein cholesterol; SAA — serum amyloid A; sICAM1 — soluble intercellular adhesion molecule type 1; TC — total cholesterol. Modified based on: Ridker PM et al. Prospective study of C-reactive protein and the risk of future cardiovascular events among apparently healthy women. Circulation, 1999; 98: 731–733

CONVENTIONAL ANTI-INFLAMMATORY DRUGS AND THE CARDIOVASCULAR RISK

Acetylsalicylic acid

Acetylsalicylic acid (ASA), which is currently the most commonly used drug for the prevention in high-risk patients and the treatment of CVD, has anti-inflammatory and antiplatelet properties. Due to the presence of the acetyl moiety, it irreversibly inhibits the active site of cyclooxygenase 1 (COX-1), and in higher doses also of cyclooxygenase 2 (COX-2), thus irreversibly blocking its function and reducing synthesis of thromboxane A2 and prostaglandins involved in the regulation of haemostasis and platelet and macrophage function [4]. Results of the recent studies indicate, however, that the anti-inflammatory effect of ASA results not only from COX inhibition, as in the case of other non-steroidal anti-inflammatory drugs (NSAIDs), but also from involvement in the formation of a lipid mediator, 15-epi-lipoxin A4, which is characterised by an even stronger inhibition of leukocyte chemotaxis and activation, and possibly has cytostatic properties. This compound acts on cytoplasmic kinase complexes, affecting the activity of a transcription factor, nuclear factor kappa B (NF-κB), which plays an important role in the regulation of various steps of the inflammatory response and has been found to show an increased activity in atherosclerotic plaques [5].

In 1997, Ridker et al. [3] were first to show that the highest reduction of cardiovascular risk is achieved in ASA-treated patients with high baseline CRP levels, regardless of the degree of platelet inhibition. This was the first study to show that anti-inflammatory treatment may potentially be effective in CVD prevention.

Non-steroidal anti-inflammatory drugs and salicylates

One of the most commonly used anti-inflammatory drugs, NSAIDs, inhibit prostaglandin synthesis by blocking COX-1 and COX-2 enzymes and thus contribute to a reduction of inflammation and decreased pain sensation.

Multiple clinical studies and metaanalyses show that both selective COX-2 inhibitors and conventional NSAIDs (non-selective COX inhibitors) increase all-cause mortality and the risk of myocardial infarction. Results of the largest published metaanalysis that included 280 studies of NSAIDs vs. placebo (124,513 patients) showed an about 30% increased coronary event risk in subjects using coxibs (relative risk [RR] 1.76, 95% confidence interval [CI] 1.31–2.37; p = 0.0001), diclofenac (RR 1.70, 95% CI 1.19–2.41; p = 0.0032), and ibuprofen (RR 2.22, 95% CI 1.10–4.48; p = 0.0253). This effect was not showed for naproxene which was the only of these drugs that did not increase cardiovascular mortality [6]. Avoidance of NSAIDs is currently recommended for 3–6 months after an acute coronary syndrome (ACS) and in patients with advanced congestive heart failure. Of note, however, NSAIDs and particularly ibuprofen are recommended for the treatment of pericarditis (class I B) in the European Society of Cardiology guidelines [7].

The class of NSAIDs also includes salsalate, which affect NF-κB similarly to ASA but their effect on outcomes in patients with CVD has not been studied. In the Targeting Inflammation Using Salsalate for Type 2 Diabetes (**TINSAL-T2D**) study, these compounds showed an inhibitory effect on inflammatory process by reducing the number of circulating leukocytes, neutrophils, and lymphocytes [8]. Thus, these inexpensive and relatively safe drugs still require careful evaluation of their potential use in the treatment of CVD.

Statins

In addition to a significant reduction of low-density lipoprotein cholesterol (LDL-C) level and a well-established reduction of cardiovascular mortality, statins are also characterised by a significant anti-inflammatory effect [9]. The Rosuvastatin to Prevent Vascular Events in Men and Women with Elevated C-Reactive Protein (**JUPITER**) study showed that statin therapy prevented cardiovascular events and mortality not only in patients with hyperlipidaemia but also in those with normal LDL-C level and elevated CRP level (≥ 2.0 mg/L), at the same time reducing serum CRP level [5].

Based on these and other statin trials, Ridker and Braunwald suggested that cholesterol lowering per se is associated with some anti-inflammatory effect [3, 9, 10]. Of note, however, the effect of statins on inflammation is complex and multidirectional. First, statins increase endothelial nitric oxide

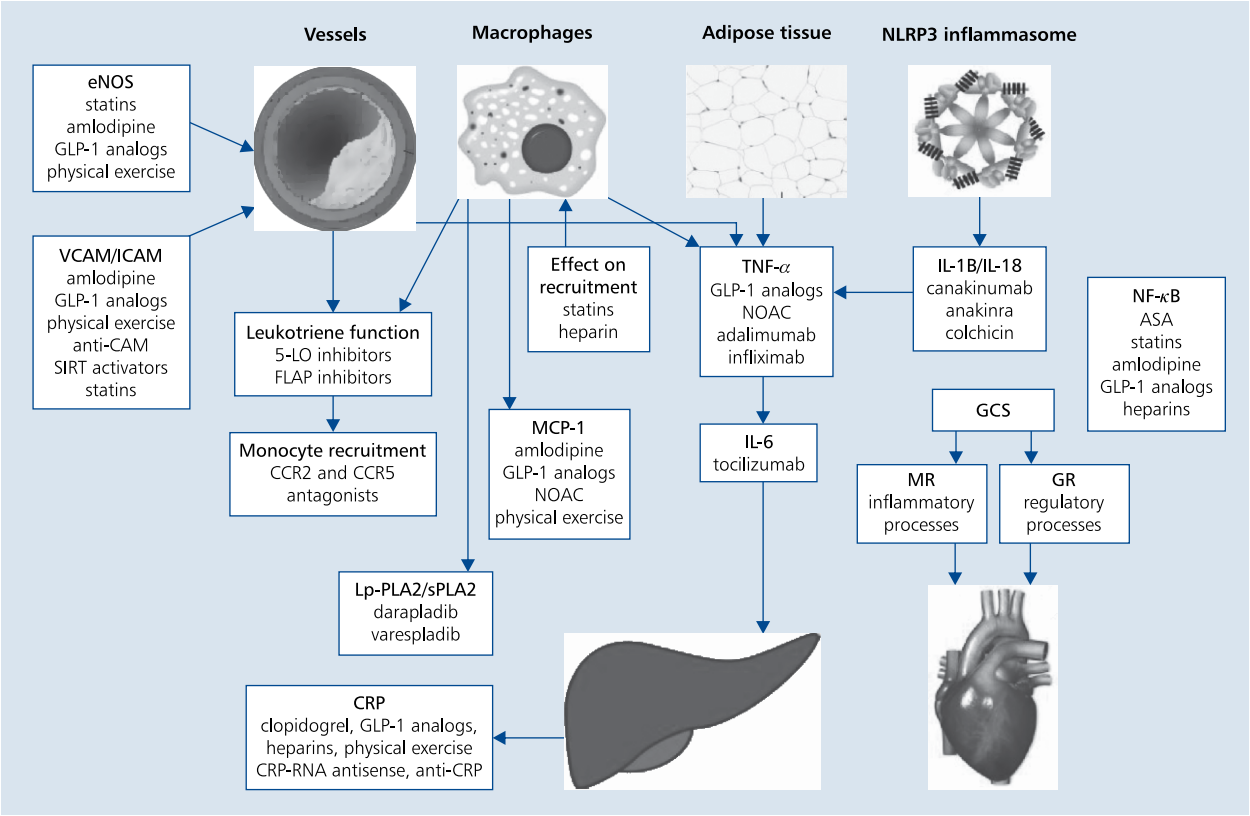

Figure 2. Anti-inflammatory drugs in the treatment of cardiovascular disease; ASA — acetylsalicylic acid; CAM — cell adhesion molecules; CCR — CC-chemokine receptor; CRP — C-reactive protein; eNOS — endotelial nitric oxide synthase; FLAP — 5-lipoxygenase-activating protein; GCS — glucocorticosteroids; GLP-1 — glucagon-like peptide 1; GR — glucocorticoid receptor; ICAM — intercellular adhesion molecule; IL — interleukin; 5-LO — 5-lipoxygenase; Lp-PLA2 — lipoprotein-associated phospholipase A2; MCP-1 — monocyte chemoattractant protein-1; MR — mineralocorticoid receptor; NF-κB — nuclear factor kappa B; NOAC — non-vitamin K antagonist oral anticoagulants; SIRT — sirtuin; sPLA2 — secretory phospholipase A2; TNF-α — tumour necrosis factor alpha; VCAM — vascular cellular adhesion molecule. Modified based on: Ridker PM, Luscher TF. Anti-inflammatory therapies for cardiovascular disease. Eur Heart J, 2014; 35: 1782–1791

synthase expression and thrombomodulin via the Kruppel like factor 2 (KLF-2) which is a transcription factor participating in the regulation of inflammatory and proliferative processes [9]. Statins also act by inhibiting formation of proinflammatory helper Th-1 lymphocytes and promote formation of anti-inflammatory Th-2 lymphocytes, thus regulating the course of the inflammatory response [11]. Another important mechanism involves inhibition of proinflammatory factors such as NF-κB and activator protein 1 (AP-1), leading to a reduced expression of vascular cellular adhesion molecule 1 (VCAM-1), E-selectin, P-selectin, and tissue factor [11].

Glucocorticosteroids

Glucocorticosteroids (GCS), steroid hormones released cyclically and in response to stress by the adrenal cortex and acting via the glucocorticoid receptor (GR), affect nearly all human tissues. An important role of GR in the maturation of cardiomyocytes and regulation of their function has been shown in a murine model [12]. In contrast, absence of this receptor is associated with developmental anomalies and myocardial dysfunction.

The effect of GCS on the myocardium is varied. On one hand, GCS may improve myocardial contractility and reduce cardiomyocyte apoptosis induced by myocardial ischaemia [13]. On the other hand, a lot of evidence indicates that persistently increased GCS levels lead to myocardial hypertrophy and development of hypertension and metabolic syndrome, important CVD risk factors [14]. In addition to GR, mineralocorticoid receptors (MR) of a very similar structure are also present in myocardial cells. It has been shown the MR activation in the cardiovascular system stimulates inflammation and fibrosis and has a negative effect on cardiac function and patient survival after cardiac events [15].

Based on the available studies, it has been postulated that use of selective MR antagonists together with GR agonists may lead to a significant progress in the treatment of cardiac disease in the future, but further studies are necessary to confirm these hypotheses [12]. In the past, use of GCS in acute myocardial

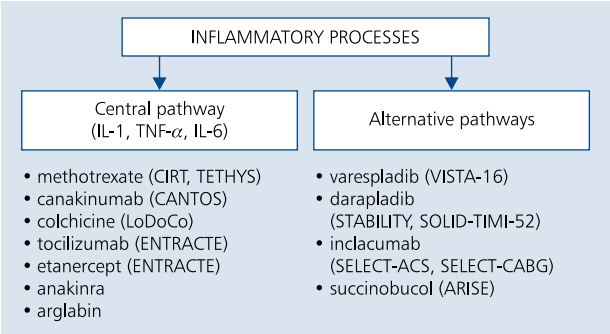

Figure 3. Inflammatory processes and new drugs in clinical trials (study acronyms in parentheses)

infarction was associated with an increased risk of mechanical complications of infarction, including cardiac rupture.

NEW ANTI-INFLAMMATORY DRUGS IN CLINICAL TRIALS

Anti-inflammatory drugs currently evaluated in studies testing their effect on the cardiovascular risk may be divided into compounds affecting the central inflammatory pathway (IL-1, TNF-α, IL-6) and those acting independently of that pathway (Fig. 3).

DRUGS AFFECTING THE CENTRAL INFLAMMATORY PATHWAY

Methotrexate

Methotrexate, used since the 1950s, may prove to be a breakthrough drug in the treatment of CVD. Its low doses (15–20 mg per week) were shown to reduce CRP and IL-6 levels, increase plasma high-density lipoprotein (HDL) levels, inhibit expression of adhesion molecules including intercellular adhesion molecule type 1 (ICAM-1) and VCAM-1 that are involved in the progression of atherosclerosis, modify purine metabolism that is of a major importance for the regulation of the immune response, and inhibit cytokine binding with their receptors, particularly interleukin 1β (IL-1β) binding with its receptor (IL-1R) [16].

Although methotrexate in low doses modifies inflammation parameters, it has no effect on plasma LDL-C level, haemostasis, and platelet function. It is thus an ideal candidate to test the hypothesis of an effect of anti-inflammatory therapy on the cardiovascular risk and progression of atherosclerosis without concomitant modification of other risk factors commonly used for the stratification of CVD mortality risk [3].

Among patients with rheumatoid arthritis or psoriasis at an increased cardiovascular risk treated with low doses of methotrexate, a decrease in cardiovascular mortality was found compared to methotrexate non-users [17]. Available data suggest that the reported cardioprotective effect of methotrexate may result from its effect on increased adenosine release and action on the A2A receptor, important for the reverse vascular cholesterol transport, and expression of adhesion molecules during the inflammatory response, including ICAM and VCAM [18].

The role of methotrexate in the treatment of CVD is currently evaluated in the Cardiovascular Inflammation Reduction Trial (**CIRT**) that began in 2013 and will recruit 7,000 patients with a history of myocardial infarction during the previous 5 years and diabetes type 2 and/or metabolic syndrome, testing low-dose methotrexate vs. placebo on top of the standard drug therapy. All patients in this study also receive 1 mg of folic acid. The primary endpoint includes recurrent myocardial infarction, stroke, and cardiovascular deaths [19]. Another study that is currently underway, The Effects of mETHotrexate Therapy on ST Segment Elevation MYocardial InfarctionS (**TETHYS**) trial, evaluates the effect of low-dose methotrexate on the cardiovascular risk in patient with an acute ST-segment elevation myocardial infarction (STEMI).

Colchicine

Colchicine, used in the treatment of acute gout since the antique times, is an alcaloid that exerts a number of anti-inflammatory actions. It inhibits cell division by binding with microtubules forming the karyokinetic spindle, and modifies the function of immune system cells, particularly leukocytes, by affecting their ability to phagocytose urate crystals; mobilisation, migration, and vascular wall adhesion; and intracellular lysosome degranulation [20]. It also has an effect on the inflammasome, a protein complex responsible, among others, for initiation of the inflammatory response to urate crystal deposition in tissues.

Colchicine not only significantly reduces plasma CRP level independent from statin or ASA use but also, as indicated by the Low Dose Colchicine for Secondary Prevention of Cardiovascular Disease (**LoDoCo**) study findings, its use in a dose of 0.5 g per day for at least 30 days was associated with a reduced risk of a combined endpoint that included recurrent acute myocardial ischaemia, cardiac arrest, and stroke (HR 0.33, 95% CI 0.18–0.59, p = 0.001) in all patients subgroups over 3 years of follow-up [21]. Of note, however, colchicine was withdrawn due to poor tolerance in over 20% of patients treated with this drug.

Canakinumab

Canakinumab is a human monoclonal antibody that inhibits IL-1β by directly binding with this cytokine and preventing its action via type I (IL-1β-RI) and type II (IL-1β-RII) receptors [22]. This drug has been approved for the treatment of systemic juvenile idiopathic arthritis and acute gouty arthritis, and it is evaluated in clinical trials for the treatment of rheumatoid arthritis. Available data suggest that dysregulation of the IL-1/IL-1Ra system may also underlie other common chronic inflammatory conditions such as diabetes type 2, arthritis, psoriasis, gout, and inflammatory bowel disease [23]. Among

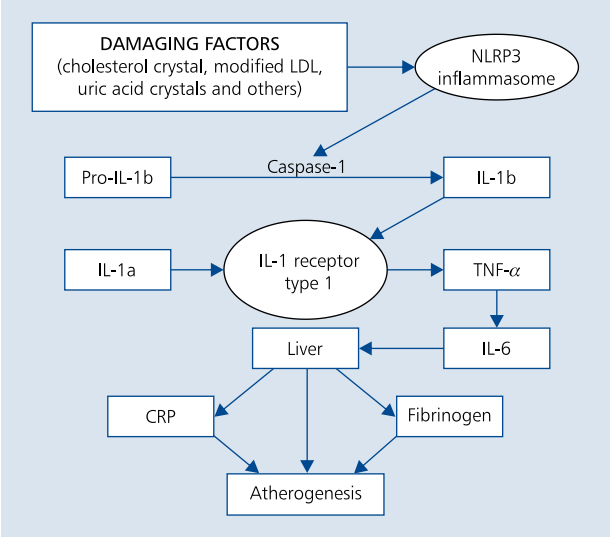

Figure 4. Central inflammatory pathway and progression of atherosclerosis. Damaging factors (including cholesterol crystals, modified low-density lipoproteins [LDL], asbestos, hydroxyapatite crystals, uric acid crystals and others) activate NLRP3 inflammasome which regulates proteolysis of inactive prointerleukin-1 beta (pro-IL-1b) by caspase-1 to active interleukin-1 beta (IL-1b). IL-1b binds with IL-1 receptor type 1 and activates inflammatory and atherogenic processes via tumour necrosis factor alpha (TNF-α) and interleukin-6 (IL-6); CRP — C-reactive protein; IL-1a — interleukin-1 alpha. Modified based on: Ridker PM. Closing the loop on inflammation and atherothrombosis: why perform the cirt and cantos trials? Transactions of the American Clinical and Climatological Association, 2013; 124: 174–190

all cytokines involved in the pathogenesis of atherosclerosis, IL-1 plays a particularly important role as it mediates the central inflammation pathway along with TNF-α and IL-6 (Fig. 4). In patients with diabetes type 2 who received once weekly subcutaneous canakinumab, IL-1β inhibition was associated with a rapid, dose-related reduction of the acute phase of the inflammatory response, resulting in a significant, persistent reduction in fibrinogen, IL-6, and CRP levels without an effect on plasma lipid levels [22].

Similarly to methotrexate, canakinumab exerts a selective anti-inflammatory effect without affecting other risk factors involved in the development of atherosclerosis and thus allows evaluation of the role of autoimmune processes in the pathogenesis of CVD. For this purpose, the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (**CANTOS**) study was initiated in 10,000 patients with coronary artery disease and chronically elevated plasma CRP level (> 2 mg/L) despite standard therapy including statins. In addition to evaluation of cardiovascular mortality risk, it will be particularly important to evaluate the adverse effects of canakinumab which is a potent immunosuppressive agent and may increase the risk of serious infections.

OTHER BIOLOGICAL AGENTS

Anakinra, tocilizumab, etanercept

Anakinra is a biologic immunosuppressive agent produced by recombinant *Escherichia coli* used, among others, for the treatment of rheumatoid arthritis when standard methotrexate therapy is ineffective. This compound is an IL-1R antagonist. It was shown to improve left ventricular function as evaluated by echocardiography in this patient group, reduce IL-6 and CRP levels, and have a beneficial effect on blood glucose control, resulting in a significant reduction of HbA1c level in diabetic patients [23].

Other biologic agents evaluated in prospective randomised clinical trials for their effect on cardiovascular risk are an IL-6 antagonist tocilizumab and a TNF-α antagonist etanercept. Both these agents are compared in patients with moderate to severe rheumatoid arthritis in A Study of RoActemra/Actemra (Tocilizumab) in Comparison to Etanercept in Patients With Rheumatoid Arthritis and Cardiovascular Disease Risk Factors (**ENTRACTE**), scheduled to be concluded in the second half of 2016 [24].

It should be noted, however, that biological therapy is contraindicated in patients with chronic heart failure in the New York Heart Association (NYHA) functional class III–IV. The anti-TNF Therapy Against Congestive Heart Failure (**ATTACH**) clearly showed that a use of a monoclonal antibody TNF-α antagonist infliximab was associated with an increased mortality in patients with moderate to severe chronic heart failure [25].

Arglabin

In January 2015, a report was published in "Circulation" on the use of an inflammasome inhibitor arglabin to induce regression of aortic atherosclerotic lesions in a murine model. This compound exerted an anti-inflammatory effect also by increasing phagocytosis by macrophages and altering expression of their surface adhesion molecules. Arglabin also resulted in beneficial changes of the lipid profile [26]. These promising observations will surely lead to more experimental and clinical studies to evaluate the efficacy and safety of this agent over the next few years.

DRUGS AFFECTING ALTERNATIVE INFLAMMATION PATHWAYS

Phospholipase inhibitors varespladib and darapladib

Phospholipase A2 (PLA2) is an enzyme responsible for phospholipid hydrolysis leading, among others, to the formation of potentially atherogenic lipid fractions and an increased vessel wall exposure to oxidative stress [27]. Data obtained in more that 80,000 patients suggest that plasma PLA2 activity and level is associated with an increased risk of cardiovascular mortality [28]. Based on these observations, two PLA2 inhibitors varespladib and darapladib were developed. However,

randomised clinical trials did not confirm a beneficial effect of PLA2 inhibition on outcomes in patients with advanced atherosclerosis (**VISTA-16**, **STABILITY**, and **SOLID TIMI** 52 studies). In clinical trials evaluating the effect of PLA2 inhibitors on inflammatory markers, no association was also seen between the use of varespladib (**FRANCIS**, **PLASMA I**, and **PLASMA II** studies [29]) or darapladib (**IBIS-B2** study [30]) and CRP and IL-6 levels. Interestingly, darapladib was reported to significantly reduce plaque necrotic core volume by virtual histology ($p = 0.01$), which may potentially suggest a stabilising effect of this drug on atherosclerotic plaques [30].

Adhesion molecule inhibitors: inclacumab

Adhesion molecules such as VCAM-1 and ICAM-1 play a key role in an initial step of plaque formation, leukocyte adhesion to the vessel wall and their migration through the endothelium. Among known adhesion molecules, the most important role in the development of CVD is probably played by P-selectin, a glycoprotein that interacts with P-selectin glycoprotein ligand-1 (PSGL-1), thereby activating multiple inflammation pathways, and thus may lead to the development of thromboembolic complications [31]. Promising results of preclinical studies led to a prospective randomised phase III trial, Effects of the P-selectin Antagonist Inclacumab on Myocardial Damage after Percutaneous Coronary Intervention for Non-ST-Segment Elevation Myocardial Infarction (**SELECT ACS**), in which the use of a recombinant monoclonal antibody against P-selectin, inclacumab, at 20 mg/kg body weight, administered in a continuous infusion over 1 h in 544 non-ST segment elevation myocardial infarction (NSTEMI) patients was associated with less myocardial damage as expressed by serum troponin and creatine kinase-MB levels as compared to the placebo group [32].

5-lipoxygenase inhibitors

Leukotrienes are arachidonic acid metabolites that play an important role in the development of inflammatory and allergic conditions such as asthma, rheumatoid arthritis, inflammatory bowel disease, psoriasis, and allergic rhinitis. An interesting observation has also been made that excessive leukotriene synthesis by 5-lipoxygenase may significantly contribute to progression of atherosclerosis. Patients with unstable coronary artery disease show an increased 5-lipoxygenase activity, and 5-lipoxygenase-activating protein gene polymorphism has been reported to affect the risk of myocardial infarction [33]. In a study conducted in ACS patients, a 5-lipoxygenase inhibitor atreleuton (VIA-2291) resulted in a significant reduction of plasma leukotriene level compared to the placebo group, and in a subgroup of 60 patients evaluated using computed angiotomography of the coronary arteries before and after 12-week therapy with atreleuton, 5-lipoxygenase inhibition was associated with a lower rate of new atherosclerotic plaques [34]. Hard endpoint data on the effect of this treatment are not available yet.

Serpins and sirtuins

Serpins are a class of serine inhibitors responsible for the regulation of multiple protease pathways associated with haemostasis, inflammation, and immune modulation. Currently, 2 mammalian serpins are used in the clinical practice: antithrombin III and alpha1-antitrypsin. Research focuses mostly on serpins derived from myxoma viruses, including Serp-1 which inhibits activation of tissue and urokinase-type plasminogen activator and Serp-2 which participates in the regulation of apoptosis and inflammation by affecting multiple enzyme families such as caspase and granzymes. In a group of 48 ACS patients, a significant reduction in myocardial damage biomarkers was shown in patients receiving Serp-1 compared to those receiving placebo [35]. However, the difference in all-cause mortality was not significant.

Another group of proteins are sirtuins, histone deacetylases of which SIRT1 has been indicated as the most important regulator of vascular homeostasis, stimulating endothelial and smooth muscle regeneration processes. In addition, SIRT1 modulates monocyte adhesion to the endothelium and formation of foam cells, and exerts a vasodilatory action by activating nitric oxide synthase and affecting NF-κB [3, 36]. In view of multiple promising studies, the role of sirtuins in CVD and other aging-related disease will continue to be evaluated in the near future [3].

DRUGS WITH A RECENTLY DISCOVERED ANTI-INFLAMMATORY POTENTIAL

Heparins

An increasing attention is drawn to anti-inflammatory properties of heparins which have become a subjects of interesting research reports during the last few years. In a prospective randomised study, Comparison of Effects on Markers of Blood Cell Activation of Enoxaparin/dalteparin/UHF in Patients with Unstable Angina Pectoris or NSTEMI (**ARMADA**), use of a low-molecular-weight heparin (LMWH) was associated with significantly lower plasma CRP level in patients with unstable angina or NSTEMI compared to unfractionated heparin (UFH) [37], while a similar anti-inflammatory effect of both drugs was observed in STEMI patients. A decrease in CRP level following treatment with UFH or LMWH was also seen in patients with atrial fibrillation [38] but no large trials are currently available that would evaluate pleiotropic effects of this drug class. With anti-inflammatory effects suggested for UFH and LMWH, it may be reasonably expected that the same properties are also shared by pentasaccharides, i.e. fondaparinux.

Interesting data were obtained in initial studies with the use of a heparin derivative characterised by a reduced anticoagulant effect, 2-O,3-O-desulfated heparin (ODSH),

which showed a protective effect on the endothelium in a rat model of myocardial infarction [39], and its reduced anticoagulant effect was confirmed in humans [40]. Further studies are necessary to clarify the role of ODSH in the treatment of acute and chronic CVD.

Non-vitamin K antagonist oral anticoagulants

In addition to its established role in haemostasis, thrombin also affects inflammatory responses [41]. By activating peroxisome proliferator-activated receptors (PPAR), present on leukocytes and platelets, thrombin initiates an intracellular signalling cascade leading to an increased expression of NF-κB. The latter transcription factor stimulates production of proinflammatory and procoagulant cytokines including TNF-α and IL-6, important for the regulation of inflammatory processes, and IL-1b, responsible for cellular proliferation. In view of an important role of thrombin in the pathogenesis of atherosclerosis and inflammatory processes, research was directed to potential anti-inflammatory effects of direct thrombin inhibitors and factor Xa inhibitors, commonly referred to as non-vitamin K antagonist oral anticoagulants (NOAC).

In mice, the use of small doses of rivaroxaban resulted in plaque stabilisation by increasing thickness of the fibrous cap, and reduced plasma IL-6 and TNF-α levels [42]. In a recent in vitro study, rivaroxaban resulted in a significantly increased release of IL-10, an anti-inflammatory cytokine, from human leukocytes stimulated with lipopolysacccharide. Due to a relatively short experience with these drugs, long-term data on the anti-inflammatory effect of NOAC in humans are not available yet, and it is not known whether this effect is shared by all NOAC regardless of their mechanism of action.

Antiplatelet agents

An anti-inflammatory effect of clopidogrel and other P2Y12 receptor antagonists is also a subject of research interests. In the Aspirin Versus/Or Clopidogrel in Aspirin-resistant Diabetics inflammation Outcomes (**AVOCADO**) study in patients with coronary artery disease and diabetes type 2, clopidogrel was found to reduce high-sensivity CRP and CD40 ligand, responsible for the activation of multiple inflammatory processes involved in atherogenesis and ACS [43]. On the other hand, Ramadan et al. [44] showed in a 6-week prospective, randomised, placebo-controlled study that apart from a significant CD40 ligand level reduction, clopidogrel did not affect other inflammation markers, endothelial status, and parameters of oxidative stress.

Similarly to clopidogrel, an effect of prasugrel was shown on the reduction of the number of leukocytes migrating to the ischaemic area, protection from left ventricular wall rupture, and reduced cardiac remodelling in a rat model of myocardial infarction. Studies by Liverani et al. [45] which evaluated the effect of prasugrel on neutrophil activation in vitro, showed that this drug reduces the response of these cells to chemokines, inhibits their activation, and reduces the number of leukocyte-platelet aggregates. An effect of ticagrelor on the neutrophil population has been shown in septic shock.

Gatifloxacin and other antibiotics in the treatment of cardiac disease

Gatifloxacin, a fluorochinolone antibiotic, is of a large research interest due to its bactericidal activity against *Chlamydia pneumoniae*, a pathogen which may be of a major importance in the pathogenesis of atherosclerosis in humans. In a paper published in "The New England Journal of Medicine" in 2005, Cannon et al. [46] reported a prospective randomised trial conducted in 4,162 ACS patients who received placebo or 400 mg of gatifloxacin, initially daily for 2 weeks and later for 10 days each month over on average 2 years of follow-up. No effect of gatifloxacin on the rates of all-cause mortality, cardiovascular mortality, and myocardial infarction compared to placebo was revealed. However, a diabetogenic effect of gatifloxacin was observed which resulted in withdrawal of this drug from the clinical practice. Authors of the largest metaanalysis of 13 clinical trials indicated that there was no evidence of the efficacy of antibiotic therapy in the treatment of CVD and suggested that new studies in this area were unlikely to prove the contrary [47].

Glucagon-like peptide 1 analogs

One of the newest antidiabetic agents with an established effect on the reduction of CVD incidence, glucagon-like peptide 1 (GLP-1) analogs, also known as incretin mimetics, act via their GLP-1R receptors and exert not only insulinotropic and insulinomimetic effects but also affect endothelial function, leukocyte adherence to the vascular wall, and inflammation markers. In a metaanalysis of liraglutide studies, the drug reduced high-sensitivity CRP level by 23% [48]. Liraglutide in doses larger than those used in the treatment of diabetes shows a potential for body weight reduction and has been recently approved for this indication.

OTHER RESEARCH DIRECTIONS

An interesting research avenue in the drug treatment of CVD are studies using vaccines to inhibit atherosclerosis progression by formation of antibodies against, among others, LDL-C, oxidised LDL, and apolipoprotein B-100. Attempts have also been made to administer liposome-encapsulated GCS (Nanocort® system) and recombined HDL particles but the effect of such treatment on cardiovascular mortality still need to be evaluated in large prospective clinical trials.

Another research area involves agents that specifically affect plaque stabilisation. The authors work in a centre that was first to show the importance of tryptase as a marker of plaque instability [49]. Tryptase is released with degranulation of mast cells present in atherosclerotic plaques. It may be suggested that cromones, drugs that stabilise mast cell membranes, may

have a role in plaque stabilisation, similarly to their currently observed anti-inflammatory effect and mast cell stabilisation in the airways of patients with asthma. This therapeutic group includes disodium cromoglycate, nedocromil sodium, and ketotifen, which are organic cromone (1,4-benzopirone) derivatives, mostly belonging also to the flavonoids. Early studies have suggested their cardioprotective effect [50].

SUMMARY

Previous research confirmed an important role of inflammatory processes in the pathogenesis of atherosclerosis, postulated as early as at the turn of the 19th century. These observations, however, did not result in any effective treatment of coronary artery disease that would be selectively targeted at anti-inflammatory effects. Although available data indirectly indicate that inhibition of the inflammatory response might lead to a reduced risk of cardiovascular mortality, studies on the direct effect of anti-inflammatory treatment on outcomes are still unavailable. Large multicentre prospective clinical trials planned to recruit more than 20,000 patients are currently underway that will allow better evaluation of the hypothesis of the inflammatory background of atherosclerosis and will provide data on long-term efficacy and safety of inflammatory response inhibition in the prevention and treatment of CVD. If results of these studies are positive, the next years to come may bring another breakthrough in cardiology comparable to that associated with introduction of statin or antiplatelet therapy.

Conflict of interest: *none declared*

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