Anti-inflammatory effects of non-statin low-density lipoprotein cholesterol-lowering drugs: an unused potential?

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ABSTRACT

Objectives. Inflammatory responses are closely knit with low-density lipoprotein (LDL)-cholesterol in driving atherosclerosis. Even if LDL-cholesterol is causative to atherosclerotic diseases and LDL-cholesterol lowering reduces hard clinical endpoints, there is a residual risk for clinical events, possibly driven by inflammatory processes, in accordance with its role in autoimmune diseases. *Design.* As LDL-cholesterol treatment targets are reduced, the use of non-statin lipid-lowering drugs will probably increase. Atherosclerotic plaques evolve through lipid infiltration and modification in the intima, furthermore infiltration of cells including monocytes, macrophages, T-lymphocytes and neutrophils initiating inflammatory signaling. Here we briefly review inflammation in atherosclerosis and the effects of the non-statin lipid-lowering drugs on inflammation. The review is limited to the most common non-statin lipid lowering drugs, i.e. proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors, bile acid sequestrants (BAS) and cholesterol absorption inhibitors. *Results.* PCSK9 inhibition is mostly studied together with statins and is associated with a reduction of pro-inflammatory cytokines. Furthermore, PCSK9 inhibitors seem to have an effect on monocyte migration trough CCR2. They also have an interaction with sirtuins, possibly offering a therapeutic target. BAS have several interesting effects on inflammation, including reduction of pro-inflammatory cytokines and a reduction of the number of infiltrating macrophages, however there are relatively few reports considering that these drugs have been on the market for decades. Ezetimibe also has effects on inflammation including reduction of pro-inflammatory cytokines and adhesion molecules, however these effects are usually accomplished in tandem with statins. *Conclusion.* This topic adds an interesting piece to the puzzle of atherosclerosis, indicating that PCSK9 inhibition, BAS and ezetimibe all affect thromboinflammation.

Introduction

Inflammatory responses are closely knit with low-density lipoprotein (LDL) -cholesterol in driving the atherosclerotic process [1]. Both innate and adaptive inflammatory responses are important in evolving atherosclerosis through a bidirectional interaction with lipids [2,3]. Recently a close cross-talk between hemostasis and inflammation has been described, named thromboinflammation, with a main potential for further research in defining targets for inhibiting this cross-talk [4,5].

There seems to be a residual risk for clinical events in a large proportion of patients with atherosclerotic diseases, possibly in part driven by inflammatory processes [6,7]. This hypothesis has recently been tested, and reduction of the pro-inflammatory interleukin (IL)-1b pathway by canakinumab reduced clinical endpoints [8,9]. On the other

hand, in a recent randomized controlled trial, low dose methotrexate did not reduce risk of cardiovascular disease, [10] illustrating the importance of targeting the driving inflammatory pathways when using an anti-inflammatory approach in atherosclerotic patients.

Several reviews have discussed the anti-inflammatory effects of statins [11–14], a subject which is beyond the scope of the present review. However, the recent discovery of the importance of the IL-1b pathway in atherosclerosis [8] raises new questions about how other lipid-lowering drugs affect inflammation. In the present article we briefly review the effects of the non-statin lipid-lowering drugs on the inflammatory arm of atherosclerosis. The review is limited to the most common non-statin lipid lowering drugs: Proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors, bile acid sequestrants (BAS) and cholesterol absorption inhibitors.
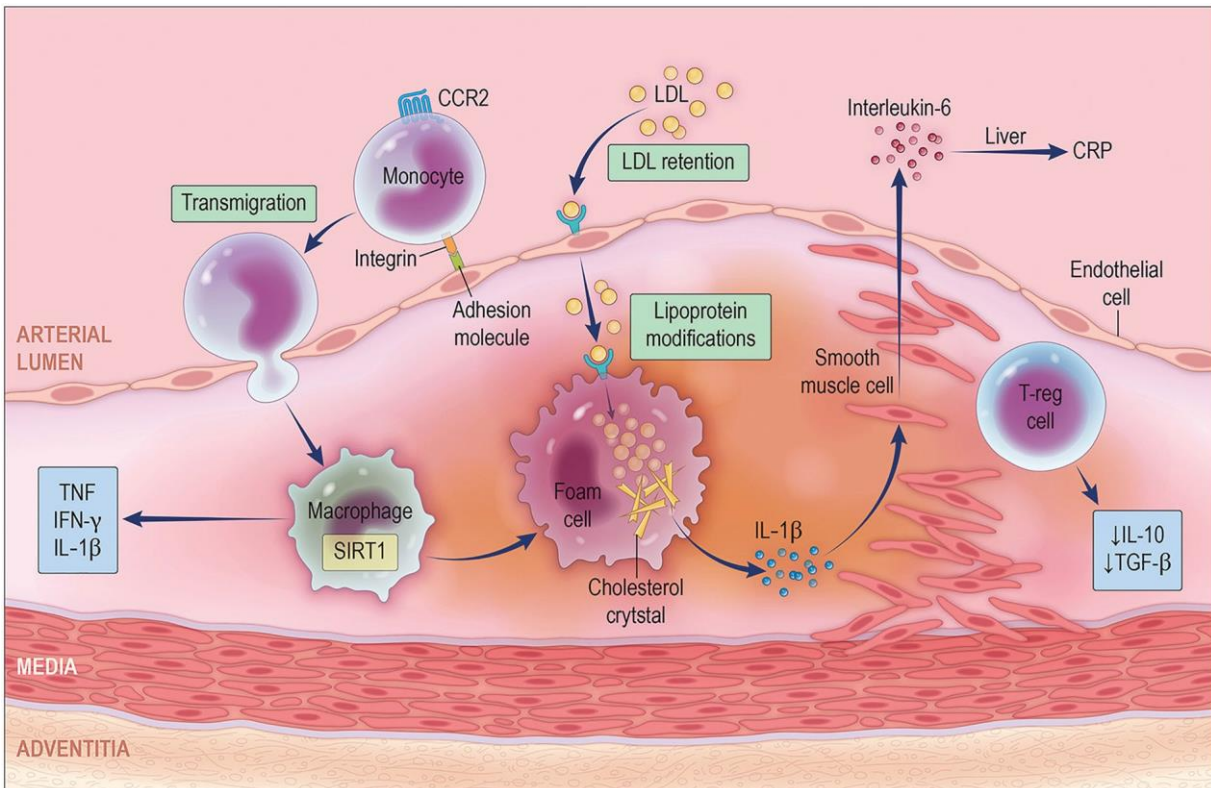
Figure 1. Monocytes enter the subendothelial space, and transform to different subsets of macrophages. LDL-cholesterol particles enter the intima and undergo modifications. Ultimately, lipid rich foam cells are formed being part of the atherosclerotic plaque. Several immunological responses are essential parts of the build-up of an atherosclerotic plaque. CCR2: C-C chemokine receptor type 2; LDL: low-density lipoprotein; CRP: C-reactive protein; TNF: Tumor necrosis factor; IFN: Interferon; IL: Interleukine; SIRT: Sirtuin; TGF: Transforming Growth Factor.

Inflammation and the immune system in atherosclerosis (Figure 1)

Already back in the mid nineteenth century, Virchow described the inflammatory nature of atherosclerotic plaques [15]. However, it was not until the late twentieth century that this research really picked up speed [16]. Inflammation is a major component of atherosclerosis [3,17], and cholesterol and inflammation have been described as partners in crime during atherogenesis [18]. In fact, like many other non-infectious disorders, atherosclerosis is characterized by a low-grade non-resolving inflammation with the interaction between inflammation and lipids as its hallmark.

In brief, lipoproteins are retained by matrix proteoglycans in the intimal layer of the arterial wall. These lipoproteins are prone to undergo oxidative modifications [19], and this event is followed by an immediate innate immune response [20]. Circulating monocytes migrate to atherosclerotic plaques, aided by a wide range of adhesion molecules and chemokine receptors [21]. Macrophages, prototypical cells in the innate immune system, have for several years been known to play a key role in lipid accumulation and inflammation during atherogenesis and more recent studies have delineated several macrophage subtypes within the lesion, such as pro-inflammatory M1 macrophages and the anti-inflammatory and pro-resolving M2 macrophages. This macrophage diversity has hampered targeted therapy directed against these cells in atherosclerotic disorders [22]. Moreover, we and others have shown that the NLRP3

inflammasome in macrophages play a major role in translating lipid-mediated (i.e. cholesterol crystals) signalling into inflammation with IL-1Þ and IL-18 as the major inflammatory outcome, and recent studies suggest that also complements are involved in these inflammatory responses [23]. Several other types of immune cells are also involved in atherosclerosis, including T and B cells [24,25]. Thus, whereas Th1 CD4Þ T cells and CD8Þ T cells seem to enhance atherogenesis, Th2 cells and in particular regulatory T cells seem to have anti-atherogenic properties at least partly related to the release of anti-inflammatory cytokines like IL-10 and for regulatory T cells, also transforming factor. A similar diversity seems also to exist within the B cells [26].

Furthermore, neutrophils are pivotal in inflammatory responses in atherosclerosis [27] including in the formation of neutrophil extracellular traps [28], and these cells seem to be of particular importance in relation to plaque erosion, an important mechanism for the development of non ST elevated myocardial infarction (NSTEMI). Also mutations of myeloid cells in the bone marrow may give rise to clones of myeloid cells in peripheral blood called clonal haematopoiesis of indeterminate potential increasing the risk atherosclerosis possibly by regulating expression of inflammatory genes [1,29]. Interestingly, the genes that are most often mutated in these patients (e.g. DNMT3A and TET2) are related to regulation of epigenetic modification, suggesting an important role for methylation and demethylation of genes in atherogenesis [30,31].

This complex interaction between lipids and inflammation include activation of a variety of both inflammatory and anti-inflammatory pathways, and how to modulate this complex network of interacting molecules in an anti-atherogenic direction is a major task in the management of patients with atherosclerotic disorders.

Even though LDL-cholesterol lowering therapy has proven its excellent value in several clinical trials with significant reductions in major clinical endpoints, patients with atherosclerotic diseases treated with such medication still have a residual increased risk for new events, and this is particular true in patients with residual untreated inflammation. Whereas specific anti-inflammatory therapy such as IL-1 directed therapy may be needed, LDL-lowering therapy may also modulate the inflammatory arm of atherosclerosis both indirectly by attenuated the LDL-cholesterol mediated inflammation, but potentially also by directly modulating inflammatory signalling. Whereas these mechanisms are widely studied in statins, the possible anti-inflammatory effects of other lipid lowering medication are less known.

Mechanisms of action, effect on LDL-cholesterol and clinical endpoints for commonly used lipid-lowering drugs beyond statins (Table 1)

PCSK9 inhibitors
The use of PCSK9 inhibitors increases steeply. Currently there are two monoclonal antibodies in clinical use that inhibit PCSK9; evolocumab and alirocumab. They lower LDL-cholesterol by 50−60% though inhibition of PCSK9 and hence increases LDL-receptor capacity [32,33]. This leads to a reduction in cardiovascular clinical endpoints [34,35]. In the recent European Guidelines on Dyslipidemias, PCSK9 inhibitors are recommended as the third lipid lowering agent if the treatment targets are not met by statins and ezetimibe [36].

Bile acid sequestrants (BAS)
The most commonly used BAS in LDL-cholesterol lowering are colestipol, colsevelam and cholestyramine. Even if sevelamer is a BAS and also lowers LDL-cholesterol, it is most commonly used as a phosphate binding drug in renal failure. BAS have been in clinical use for decades. They lower LDL-cholesterol by stimulating bile synthesis and lowering intestinal lipid absorption, and they also affect glucose homeostasis in type 2 diabetes [37]. LDL-cholesterol is lowered by 15−20%, and there is one primary prevention study showing effect on clinical endpoints [38]. However, endpoint studies have not been performed after the introduction of statins.

Cholesterol absorption inhibitors
Ezetimibe is the only clinically available cholesterol absorption inhibitor, however phytosterols also inhibit cholesterol absorption. Ezetimibe inhibits the Niemann-Pick C1-like protein in the small intestine [39], and the LDL-cholesterol lowering effect is 20−25% (fixed dose). In the IMPROVE-IT trial, clinical endpoints were reduced when adding ezetimibe to statins after acute coronary syndromes [40], and similarly in the EWTOPIA 75 primary prevention trial, ezetimibe reduced composite endpoints [41].

Effects on inflammation for commonly used lipid-lowering drugs

PCSK9 inhibitors
PCSK9 inhibitors as monotherapy or added to statins and ezetimibe efficiently reduce LDL-cholesterol, although CRP remains unchanged [42]. However, this does not exclude anti-inflammatory effects of PCSK9 inhibition that are not mirrored by CRP reduction.

Tang et al. interestingly demonstrated that oxidized LDL-cholesterol upregulated PCSK9 in macrophages as well as inflammatory markers including IL-1a, IL-6 and TNF. These markers were reduced when inhibiting PCSK9 with small interfering RNA PCSK9 through nuclear factor kappa-light-chain-enhancer of activated B cells [43]. The same group has also shown that PCSK9 is upregulated in murine atherosclerotic plaques, whereas downregulation leads to decreased plaques and decreased inflammation as measured by reduced concentrations of IL-1a, IL-6 and TNF [44].

Bernelot Moens et al. found that persons with familial hypercholesterolemia with grossly elevated LDL-cholesterol had a three-fold increase in expression of the pro-atherogenic chemokine receptor CCR2 compared to controls with normal LDL-cholesterol [45]. When these subjects were treated with PCSK9 inhibition, the levels of LDL were reduced as predicted, and notably, CCR2 expression and TNF production was reduced, while IL-10, commonly considered an anti-inflammatory cytokine, was increased [45]. This finding of reduced CCR2 expression with PCSK9 inhibition might indicate the possibility of reduced monocyte influx to atherosclerotic plaques [21]. In the cell model of vascular smooth muscle cells, Grune et al. have demonstrated that PCSK9 levels are linked to LDL-cholesterol receptor mediating CCR2 expression [46], again pointing to a possible effect of PCSK9 inhibition on monocyte influx.

Sirtuins are a highly conserved protein family of histone deacetylases that are of major importance for mediating the beneficial effects of calorie restriction on cardiovascular disease, and seem to be key enzymes in regulation of metabolic driven inflammation [47]. These effects are partly related to

Table 1. Mechanism of action and LDL-cholesterol lowering effect of lipid lowering treatment.

	Mechanism of action	Effect	Endpoint studies
PCSK9 Inh	Increases LDL-R activity	Up to 50–60%	Yes [33,34]
BAS	Increase hepatic LDL-C clearance	Up to 20%	Yes [38]
Ezetimibe	Inhibits intestinal LDL-C absorption	Up to 20–25%	Yes [30]

PCSK9 Inh: Proprotein convertase subtilisin-kexin type 9 inhibitors.
BAS: Bile acid sequestrant; LDL-C: low-density lipoprotein-cholesterol; LDL-R: low-density lipoprotein-receptor.
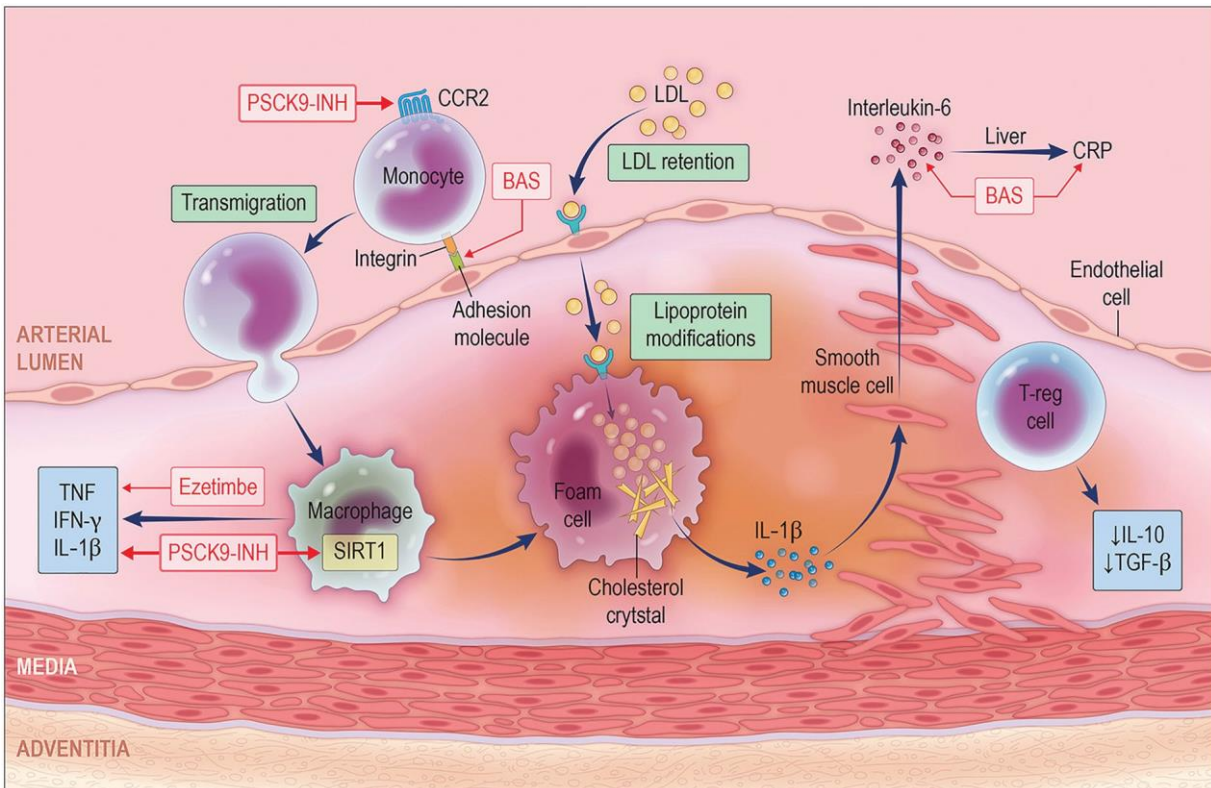
Figure 2. Suggested effects of non-statin lipid lowering drugs on inflammation. The atherosclerotic plaque is similar to the one in Figure 1, here possibly effects on inflammatory pathways are depicted. CCR2: C-C chemokine receptor type 2; LDL: Low-density lipoprotein; CRP: C-reactive protein; TNF: Tumor necrosis factor; IFN: Interferon; IL: Interleukine; SIRT: Sirtuin; TGF: Transforming Growth Factor.

epigenetic modification of relevant genes. Notably, PCSK9 seems to an important regulator of sirtuins, and accordingly, it is possibly that some of the anti-inflammatory effects of PCSK9 inhibition could be mediated through modulation of sirtuins.

Taken together, PCSK9 inhibition does not seem to reduce CRP, but have some promising effects that could modulate the inflammatory arm of atherosclerosis such as inhibiting monocyte influx into the atherosclerotic lesion by downregulating CCR2 expression and modulating the sirtuins in an anti-inflammatory direction. In addition, PCSK9 inhibition has been suggested to attenuate oxidative stress, enhance autophagy and modulate vascular smooth muscle cells to a less pro-atherogenic phenotype. Altogether, these effects that not necessarily will be mirrored by CRP, will have to be proven in larger clinical studies that also include advanced molecular analyses on clinical samples.

Bile acid sequestrants
Devaraj et al. demonstrated that colsevelam in addition to lowering LDL-cholesterol in mildly hypercholesterolemic subjects also significantly lowered CRP, and there was no correlation between CRP and LDL-cholesterol lowering [48]. McGettingan et al. used a murine model of liver steatosis demonstrating that sevelamer reduced the hepatic cell expression of pro-inflammatory genes including IL-1b, TNF and IL-6 [49]. Fuchs et al. have shown that in a murine model colsevelam reduced inflammation including reduction of the prototypical pro-atherogenic chemokines monocyte

chemoattractant protein 1 (MCP-1)/CCL2 and vascular cell adhesion molecule 1 [50]. In a study utilizing a human monocyte line, Mobraten et al. showed that bile acids activate the G-protein coupled receptor TGR5 in parallel with stimulating toll-like receptor 4, leading to an increase in inflammatory cytokines IL-6 and IL-8 [51], possibly indicating that BAS could affect this signaling. Altogether, although data are scarce, these studies may suggest a possible anti-inflammatory effect of BAS, potentially at least partly independent of LDL lowering.

Cholesterol absorption inhibitors
When ezetimibe is added to simvastatin after an acute coronary syndrome more patients get significant reductions in LDL-cholesterol and CRP, corresponding to a reduction in clinical endpoints [52]. Krysiak et al. showed that both ezetimibe and simvastatin reduced TNF and IFNc in people with elevated LDL-cholesterol, however only significant for simvastatin. The reduction in intracellular adhesion molecule 1 and CRP was strongest for the combination of simvastatin and ezetimibe [53]. Qin et al. used a macrophage model to demonstrate that ezetimibe downregulated the TNF gene and further reduced levels of TNF through nuclear factor kappa-light-chain-enhancer of activated B cells/mitogen-activated protein kinase pathway [54]. These in vitro data may suggest that the potential anti-inflammatory effects of ezetimibe are merely secondary to a reduction in LDL-cholesterol. Ghanim et al. observed that when obese persons were fed cream, several inflammatory markers

increased including IL-1b, TNF and matrix metallopepdidase 9. These markers were significantly reduced by the combination of simvastatin and ezetimibe [55], but this study did not examine the effects of statins and ezetimibe separately. Altogether, although there are some data suggesting that ezetimibe could have anti-inflammatory effects, the effects are most probably less than the effects of statins, and whether the anti-inflammatory effects of ezetimibe are at least partly independent of its effects on LDL-cholesterol is still unclear.

General considerations

Based on several epidemiological, clinical and experimental studies it seems to be of major importance to target both the lipid and the inflammatory arms of atherogenesis. In addition to therapeutic options that directly target inflammation, some lipid lowering medication may possess anti-inflammatory effects beyond that of LDL-cholesterol lowering that in itself will attenuate inflammation. Such effects are well known for statins. However, whereas current data do not support strong anti-inflammatory effects of BAS and ezetimibe, the anti-inflammatory effects of PSCK9 inhibition should be an area of future interest. In particular, based on the presumably lack of effects on CRP levels, PCSK9 inhibition may modulate other parts of the inflammatory response than statins, and the anti-inflammatory potential of the combination of these drugs should be further explored (Figure 2).

Anti-inflammatory properties – a resource unused?

As inflammation is a key player both in the initiation and the propagation of the atherosclerotic process, and as the CANTOS trial has shown that anti-inflammatory therapy can have an impact on clinical endpoints – how can we take advantage of the anti-inflammatory properties of drugs already in use and how should we include anti-inflammatory effects in the development of new drugs?

The positive results from the CANTOS trial should be explored deeper in relation to whether non-statin lipid lowering drugs have effects on IL-1b signaling and other anti-inflammatory pathways, especially as statin drugs may have different effects on IL-1b signaling in different cells [56]. This is important as the European Lipid guidelines recently advocated a reduction of LDL-cholesterol to below 1.4 mmol/L in patients with atherosclerotic diseases [36] necessitating non-statin drugs in addition to statins in order to obtain this treatment goal.

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Disclosure statement

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