Anti-inflammatory Therapy in Atherosclerosis: The Past and the Future

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Since 1847 when Vogel, an eminent German pathologist, first observed that cholesterol was present in arterial plaques, atherosclerosis (AS) has been regarded as a cholesterol storage disease characterized by a passive deposition of cholesterol in the artery wall. One decade later, Virchow, a renowned pathologist, stated that AS is not really “a consequence of a fatty process but a direct product of inflammation”. Unfortunately, these early observations did not attract much attention from the cardiovascular community. It was not until the end of 19 century that pathologists began to recognize AS as an inflammatory disease, after many years of research in the new field of vascular biology by a number of groups, notably the one by Libby. From this moment, the discovery of a safe and effective anti-inflammatory therapy for AS has been a Holy Grail, but in reality a tough battle, for many physicians and scientists working in this field.

Five battles against inflammation in atherosclerosis

The first battle against inflammation in AS occurred in the 1960s to 1980s, in which physicians logically used corticosteroids to suppress inflammation in patients with acute myocardial infarction (AMI). However, most of these early studies were nonrandomized and unblinded trials conducted in small samples of patients, and the results were inconclusive. A meta-analysis published in 2003 involving 11 clinical trials and 2646 patients with AMI found that corticosteroid therapy reduced mortality by 26% with a hazard ratio (HR) of 0.74 (95% confidence interval [CI]: 0.59-0.94), but further sensitivity analysis limited to randomized and controlled trials showed lack of efficacy with HR of 0.95 (95% CI: 0.72-1.26). A major concern with corticosteroid therapy in patients with AMI was an inhibited healing of the infarcted myocardium and increased risk of cardiac rupture. Thus, corticosteroid therapy for AMI was finally given up. Later on, in a small study involving 67 patients with active rheumatoid arthritis (RA) who were randomized to either prednisolone or no prednisolone treatment, the carotid intima-media thickness, prevalence of atherosclerotic plaques and endothelial function showed no significant difference between the two groups of patients after 5 years of follow-up. In 2010, a randomized, controlled study enrolled 375 non-diabetic patients with coronary artery disease and no contraindications to dual antiplatelet treatment or corticosteroid therapy. The patients were allocated into bare-metal stent group, bare-metal stents followed by a 40-day prednisone treatment group, and drug-eluting stent group. The primary endpoint was the event-free survival of cardiovascular death, myocardial infarction (MI), and recurrence of ischemia requiring repeated target vessel revascularization at the first year. The results showed that the primary endpoint was 80.8% in bare-metal stent group compared to 88.0% in the prednisone (P=0.040) and 88.8% in the drug-eluting stent groups (P=0.006), respectively. However, chronic administration of corticosteroid therapy in patients with stable coronary artery disease may induce hyperlipidemia and hyperglycemia, which may aggravate AS lesions.

The second battle against inflammation in AS focused on the effects of nonsteroidal anti-inflammatory drugs (NSAIDs) on the incidence of MI when a group of investigators reported in 2000 that the incidence of MI was lower among patients taking naproxen, a non-selective cyclooxygenase (COX) inhibitor, than those taking rofecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor in patients with RA. However, subsequent studies showed that all NSAIDs except for aspirin increased the risk of MI. The fundamental property of NSAIDs is to inhibit COX, which consists of two isoenzymes: COX-1 is expressed constitutively in most tissues, while COX-2 is induced only by inflammation. Platelets contain only COX-1 that converts arachidonic acid to thromboxane A2 (TXA2), and aspirin as a non-selective COX inhibitor prevents arterial thrombosis because of its ability to reduce COX-1-dependent production of platelet TXA2. In contrast, selective inhibition of COX-2 reduces endothelial production of prostacyclin while leaving the platelet production of TXA2 intact, which may increase the risk for cardiovascular thrombotic events. The Danish national survey involving 99,187 patients with first MI reported in 2012 that the HR of MI in 5 years was 1.63 (95% CI: 1.52–1.74) in users of NSAIDs versus non-users of NSAIDs. Thus, except for aspirin, NSAIDs are no longer recommended for pain relief in patients with atherosclerotic cardiovascular disease unless necessary.

The third battle against inflammation in AS included three trials of colchicine treatment from 2013 to 2020. The mechanism underlying the anti-inflammatory property of colchicine is complex but may involve the following aspects: (1) colchicine binds to tubulin, affecting mitosis and functions of microtubules; (2) a low dose of colchicine prevents microtubule polymerization while a high dose of colchicine promotes microtubule depolymerization, resulting in impaired chemotaxis of neutrophils to...
the inflamed endothelium; and (3) colchicine inhibits the activity of the nucleotide-binding oligomerization domain (NOD)-like receptor protein 3 (NLRP3) inflammasome and attenuates the release of interleukin-1β and interleukin-18.\[^{13}\] The first low-dosed Colchicine (LoDoCo) trial used a prospective, randomized, open and end blinded (PROBE) design and recruited 532 patients with stable coronary heart disease who were randomly divided into low dose colchicine (0.5 mg/day) and no colchicine treatment groups and followed for 3 years. The incidence of primary endpoints was 5.3% in the colchicine group and 16% in the no colchicine group with a HR of 0.33 and relative risk reduction (RRR) of 0.67.\[^{14}\] The therapeutic benefit almost twice that of intensive stain treatment. Although initially criticized as “too good to be true”, mainly due to the deficient trial design, LoDoCo trial was the first victory in anti-inflammatory battles against AS and thus called “a seminal trial”.\[^{15}\] The second trial, Colchicine Cardiovascular Outcomes Trial (COLCOT), with a randomized, double-blind, placebo-controlled design, enrolled 4745 patients with a history of MI more than 30 days who were randomly divided into small dose of colchicine (0.5 mg/day) or placebo groups and followed for nearly 2 years. The incidence of primary endpoints was 5.5% in the colchicine group and 7.3% in the no colchicine group with a HR of 0.77 and RRR of 0.23.\[^{16}\] The third trial, Low-dose Colchicine Trial 2 (LoDoCo 2), utilized a randomized, double-blind, placebo-controlled design and enrolled 4745 patients with chronic coronary disease, who were randomly divided into small dose colchicine (0.5 mg/day) or placebo groups, and followed for an average of 28.6 months. The incidence of primary endpoints was 6.8% in the colchicine group and 9.6% in the no colchicine group with a HR of 0.70 and RRR of 0.30.\[^{17}\] Compared with RRR of 0.67 in the first LoDoCo trial published in 2013, RRR of 0.30 in LoDoCo 2 trial published in 2020 was more realistic and convincing. Thus, all the three trials of colchicine treatment achieved rewarding results.

The fourth battle against inflammation in AS involved the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) published in 2017, which was the first trial demonstrating the efficacy of anti-inflammatory therapy in AS with robust evidence.\[^{18}\] This trial used a randomized, double-blind, placebo-controlled design that included 10,061 patients with chronic inflammation after MI (hs-CRP >2 mg/L) who were randomly divided into 3 doses (50, 150, and 300 mg) of canakinumab, a monoclonal antibody targeting interleukin-1β, and placebo groups, and followed for an average of 3.7 years. Positive efficacy was found only in the 150mg canakinumab group, with the incidence of primary endpoints being 3.86% in the 150mg group and 4.5% in the placebo group resulting in a HR of 0.85 and RRR of 0.15.\[^{19}\] By comparison, the therapeutic benefit of CANTOS was substantially lower than that by the COLCOT, but drug-related adverse effects were more common in the CANTOS than that in the COLCOT.

The fifth battle against inflammation in AS was Cardiovascular Inflammation Reduction Trial (CIRT) published in 2018.\[^{19}\] CIRT used a randomized, double-blind, placebo-controlled design and incorporated 4786 patients with previous MI or multivessel coronary disease with additional type 2 diabetes or metabolic syndrome. Patients were randomly divided into low dose methotrexate treatment and placebo groups and followed for more than 2 years. The incidence of primary endpoints was 4.13% in the methotrexate group and 4.31% in the placebo group with a HR of 0.96 (95% CI: 0.79–1.16). The failure of CIRT was attributed to the absence of increased hs-CRP (mean 6 mg/L in the study population) and the ineffectiveness of methotrexate treatment in reducing serum levels of interleukin-1β and other inflammatory factors in the enrolled patients.\[^{19}\]

### Further barriers to be conquered

The tortuous path underneath anti-inflammatory therapy for AS indicates the complexity of inflammatory mechanisms in the pathogenesis of AS. The success and failure of anti-inflammatory trials have posed several critical scientific questions. First, previous clinical trials enrolled patients with a history of MI or chronic coronary heart disease. It is unclear whether anti-inflammatory therapy at an early stage of AS is effective for preventing cardiovascular events. Lipid deposition in the arterial wall has long been considered as an early and passive process of AS, which instigates an inflammatory response in the artery. However, a recent study found that the B1 scavenger receptor (SR-B1) in endothelial cells binds plasma low-density lipoprotein (LDL) particles, which are delivered into the sub-endothelial space and engulfed by macrophages to form foam cells.\[^{20}\] If this novel finding can be reproduced in human studies, inhibition of SR-B1 in endothelial cells might attenuate lipid deposition and prevent inflammation in the arterial wall. Our previous studies demonstrated that early anti-inflammatory therapy may prevent the formation of AS plaques in an animal model of AS.\[^{21}\] Thus, it is likely that early intervention of the inflammatory process of AS may prevent or delay the occurrence of coronary artery disease. Second, it is well known that serum inflammatory factors surge in patients with acute coronary syndromes, and thus, it is possible to use anti-inflammatory therapy to inhibit systemic inflammation and reduce cardiovascular events in these patients? Third, available Mendelian randomization studies demonstrated a causal relationship between circulating interleukin-6 receptor level and increased risk of cardiovascular disease.\[^{22}\] Experimental studies showed that interleukin-1α played a similar pro-inflammatory effect as interleukin-1β.\[^{23}\] Thus, the exploration of effective and safe medications against interleukin-6 receptor and interleukin-1α is highly warranted. Fourth, canakinumab targets interleukin-1β, while colchicine modulates multiple targets. From the comparison of therapeutic benefits and adverse effects between CANTOS and COLCOT, multi-target anti-inflammatory therapy appears to be superior to single-target therapy, but this hypothesis remains to be confirmed. Fifth, despite the use of low doses of colchicine in COLCOT and LoDoCo 2 trials, many patients in these two trials had drug-related adverse effects. Thus, whether it is safer and equally effective to use an even lower dose of colchicine need to be explored in future trials. Sixth, although proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are recognized as a potent lipid-lowering agent, recent studies have provided evidence that PCSK9 induces the secretion of pro-inflammatory cytokines in macrophages, liver cells, and a variety of tissues.\[^{24}\] In addition, sodium-glucose co-transporter 2 inhibitors (SGLT-2i) are a new class of drugs targeting the renal proximal tubules to increase glucose excretion and have been proven effective in reducing cardiovascular events in patients with or without diabetes. However, recent studies found these drugs have potent anti-inflammatory effects.\[^{25}\] Thus, the relative contribution of the anti-inflammatory effects of PCSK9 inhibitors and SGLT-2i to the therapeutic benefits in patients with AS should be further examined. Finally, new anti-inflammatory clinical trials in patients with AS are undergoing. FLAVOUR is a phase IIa
study of AZD5718 in patients with a history of MI. Leukotrienes are synthesized by leukocytes in atherosclerotic lesions, and AZD5718 is a novel antagonist of 5-lipoxygenase activating protein that suppresses leukotriene biosynthesis. All enrolled patients receive standard care plus oral AZD5718 of 200 or 50 mg, or placebo once daily for up to 12 weeks. The primary efficacy outcome is urine leukotriene E4 levels, and the secondary efficacy outcome includes transhoracic Doppler-measured coronary flow velocity reserve and left ventricular systolic and diastolic function. It is my projection that with the resolution of these issues, anti-inflammatory therapy will fall into a greater milestone in the treatment of AS, after lipid-lowering therapy, antplatelet therapy, and control of risk factors (smoking, hypertension, and diabetes).

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**Conflicts of interest**

None.

**References**