



Colchicine: an affordable anti-inflammatory agent for atherosclerosis

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Purpose of review

Inflammation has been shown to be central to the development and progression of atherosclerosis. Despite detailed understanding of its central role and the cellular dynamics, which contribute to atherosclerotic inflammation, there has been slow progress in finding suitable agents to treat it. The recent CANTOS trial showed that the interleukin-1 β inhibitor canakinumab can improve outcomes after acute coronary syndromes. Being a monoclonal antibody, it is expensive and inconvenient to administer for long-term treatment. This review summarizes recent work in finding effective, affordable alternatives to canakinumab.

Recent findings

Statin drugs have anti-inflammatory properties but separating their LDL lowering effect from their anti-inflammatory effect has been difficult. Drugs acting on targets outside of the interleukin-1 β (IL-1 β) pathway have been tested without finding a suitable candidate. Following the proof of principle provided by the success of canakinumab, other candidates targeting the IL-1 β pathway are undergoing detailed evaluation. The most likely candidates are low-dose methotrexate and low-dose colchicine. The potential mechanisms and ongoing clinical trials are described.

Summary

Targeting the IL-1 β pathway has already been successful with canakinumab but its expense and inconvenience of administration may limit its widespread uptake for controlling inflammation in atherosclerosis. Low-dose methotrexate and low-dose colchicine are affordable and more accessible alternatives, currently undergoing detailed evaluation for safety and efficacy in large randomized controlled trials.

Keywords

canakinumab, colchicine, inflammation, interleukin-1 β , methotrexate

INTRODUCTION

Evidence that inflammation plays a central role in the initiation and progression of atherosclerosis has accumulated rapidly over the past two decades [1].

A highly influential article by US pathologist Ross [2] summarized the evidence accumulated during the 1990s. Ross's review, which has been cited an astonishing 28 519 times, eloquently summarized his own work [3] and that of others in identifying many of the inflammatory pathways leading to atherosclerotic plaque. Earlier, Davies [4] in UK had shown that unstable plaques were constituted not only of a large lipid core with a thin cap, but also were heavily infiltrated with monocytes and macrophages. Libby [5] and others had demonstrated the role of an inflammatory process as a final step towards plaque rupture and atherothrombosis. Ridker and others worked assiduously through the 1990s and early 2000s to demonstrate in multiple cohorts that high-sensitivity C-reactive protein (hs-CRP), was a useful nonspecific biomarker of

inflammation and elevated levels could predict increased risk of acute coronary events [6]. Although the role of CRP in identifying high risk incremental to other risk factors remains controversial [7], it has proven to be valuable marker of atherosclerosis-related inflammation.

Since this early work, there have been significant developments in understanding the inflammatory pathways, which initiate atherosclerosis and lead to plaque instability. These developments have guided a better understanding of potential targets for controlling inflammation-related atherosclerosis. The

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KEY POINTS

- Multiple sources of evidence (histopathology, imaging, biomarkers) indicate the importance of inflammation in the initiation and progression of atherosclerosis.
- A recent trial has demonstrated that selective targeting of the interleukin-1 β (IL-1 β) pathway with canakinumab can improve cardiovascular outcomes, whereas trials targeting non-IL-1 β pathways have been unsuccessful.
- The high cost and inconvenience of injectable canakinumab is likely to limit its widespread use in atherosclerotic disease.
- Colchicine and methotrexate are more affordable and not only target the IL-1 β pathway but also have other potentially important anti-inflammatory actions.
- Current trials of low-dose methotrexate and low-dose colchicine will clarify their long-term efficacy, safety and affordability in atherosclerotic patients on antiplatelet therapy and statins.

interleukin-1 β pathway has been identified as playing a central role in triggering the inflammatory cascade, which leads to release of pro-inflammatory interleukin-6 (IL-6) and tumour necrosis factor α (TNF α) [8,9^{*}]. Other, even newer concepts upstream and downstream from the IL-1 β pathway have widened the focus of efforts to target the inflammatory processes. Upstream, the important role of the NLRP3 inflammasome is now well recognized. Following an irritative stimulus, the NLRP3 inflammasome assembles within the activated macrophage, resulting in activation of caspase, which converts

pro-IL-1 β to active IL-1 β [10^{*}]. An increasing recognition of the role of cholesterol crystals has also led to the realization that cholesterol crystals are not a mere by-product of degeneration of the plaque. They can cause direct traumas to the vessel wall [11] and trigger inflammasome assembly providing a unique link between cholesterol and inflammation [12,13]. This crystal-initiated inflammation parallels the action of urate crystals in triggering the inflammatory cascade in gout [14]. Downstream from the IL-1 β pathway, the causal role of neutrophils in atherosclerosis, particularly in destabilization of the plaque, is being increasingly recognized [15]. A relatively new finding is neutrophil extracellular traps (NETs), which are released from neutrophils, which have been triggered by cholesterol crystals to prime macrophages to release cytokines [16].

Despite this extensive and rapidly expanding knowledge of the mechanisms linking inflammation and atherosclerosis, the translation to therapeutic use has been elusive.

It has become clearer that attempts to target pathways outside of the IL-1 β pathway are unlikely to be effective. Table 1 briefly summarizes the contributory role of statins, the negative results from targeting the non-IL-1 β pathways and then the apparent success in targeting the IL-1 β pathway.

STATINS

The antiatherosclerotic effects of statins have been amply demonstrated. Although most of the benefit has been attributed to the LDL-cholesterol-lowering effect, there is considerable evidence that statins

Table 1. Potential anti-inflammatory targets in atherosclerosis

Drug	Mechanism	Trial results
statins	LDL reduction, pleiotropic	Inconclusive
Non-IL-1 β pathways		
Corticosteroids	Nonspecific anti-inflammatory	Negative
NSAIDs	COX inhibition	Negative
Pexelizumab	Complement inhibition	Negative
Losmapimod	MAPK inhibitor	Negative
Darapladib, Varespladib	LpPLA2 inhibition	Negative
IL-1 β pathways		
CRP inhibitors	CRP inhibition	Not trialled
DMARDs	TNF α , IL-6 inhibition	Adverse effects
Methotrexate	IL-6, MULTIPLE sites	Results pending
Canakinumab	IL-1 β inhibition	Positive
Colchicine	Multiple sites incl inflammasome assembly	Encouraging

COX, cyclo-oxygenase; CRP, C-reactive protein; DMARDs, disease-modifying antirheumatic drugs; IL-1, interleukin-1; IL-6, interleukin-6; LDL-C, LDL-cholesterol; LpPLA2, lipoprotein-associated phospholipase A2; MAPK, mitogen-activated protein kinase; TNF, tumor necrosis factor.

have a significant anti-inflammatory effect in atherosclerosis [17]. In the PROVE-IT study comparing low-dose pravastatin with high-dose atorvastatin, better outcomes were seen in those with LDL cholesterol below 1.8 mmol/l and hs-CRP below 2 mg/l, but the best outcomes were seen when the low LDL and low hs-CRP groups were combined [18]. Similar findings were seen in the analysis of the JUPITER trial of rosuvastatin in primary prevention [19].

NON-INTERLEUKIN 1 β PATHWAYS

Anti-inflammatory trials in non-IL-1 β pathways are summarized in Table 1. These trials have been consistently negative.

Corticosteroids

Meta-analysis of trials of corticosteroids in myocardial infarction to 2003 did not show any harm or benefit [20]. A large case-control study 404 183 persons, 50–84 years old, compared 4795 hospitalized AMIs or CHD deaths with a random sample 20 000 controls showed an adverse effect [21]. Trials of corticosteroids are also unlikely because of anecdotal reports of an increased propensity to cardiac rupture [22].

NSAIDs

NSAIDs reduce hs-CRP and at one time, were considered as possible agents for treating inflammation in atherosclerosis [23]. In 2005, the results of the APPROVE study of rofecoxib in prevention of colonic polyps showed a dramatic increase in cardiovascular events [24], and shortly after, rofecoxib was withdrawn from the market. Subsequent investigations showed that the cardiovascular risk was not confined to rofecoxib and involved nonselective NSAIDs as well [25].

Complement inhibition with pexelizumab

The complement system plays a role in atherosclerosis [26]. Pexelizumab binds to the C5 component of the complement cascade, preventing its cleavage into pro-inflammatory C5a and C5b-9. Two phase 2 studies in ST-elevation myocardial infarction (STEMI) were encouraging but a phase 3 placebo-controlled trial of 5745 patients (APEX) was negative [27]. Development and investigation of the drug was discontinued.

Mitogen-activated protein kinase inhibition with Losmapimod

Losmapimod is a selective inhibitor of the p38 intracellular mitogen-activated protein kinase (MAPK) signalling cascade. A single encouraging

phase 2 study lowered brain natriuretic peptide (BNP), but a 3503 acute myocardial infarction (MI) study (LATITUDE) showed no difference in primary outcome at 12 weeks [28].

Lipoprotein-associated phospholipase A2 inhibition

Lipoprotein-associated phospholipase A2 (Lp-PLA2) produced primarily by macrophages and lymphocytes, bound to LDL. It is pro-inflammatory and proatherogenic. It is present in necrotic lipid plaque and is a biomarker of poor outcome in ACS. Darapladib is a selective Lp-PLA2 inhibitor. Two large trials, the SOLID trial in stable coronary heart disease [29] and the STABILITY trial in acute coronary syndromes [30], both failed to show any benefit. Varespladib is a nonspecific inhibitor of secretory phospholipase A2 (sPLA2) activity. It lowered CRP phase 2 study but the large VISTA randomized controlled trial showed a higher rate of the primary outcome, and the development of the drug was halted [31].

Other LDL-lowering agents

Probuco is an LDL-lowering agent with diverse anti-atherosclerotic effects. It has not found wide acceptance because of an HDL-lowering effect, an effect which, had been assumed to adversely affect outcomes. The validity of this assumption has been challenged and its role is currently being re-examined [32]. It has anti-inflammatory effects demonstrated in rabbits [33], but did not demonstrate any clear anti-inflammatory or antiatherosclerotic effect in a small clinical trial [34]. Other LDL-lowering agents including ezetimibe and PCSK9 inhibitors have only a limited effect on inflammatory biomarkers [35].

THE INTERLEUKIN 1 β PATHWAY

C-reactive protein inhibitors

CRP is an acute phase reactant released from the liver. It has been visualized in atherosclerotic plaques [36] and for a time speculation that it may have a direct role and to an interest in developing CRP inhibitors. Misinterpretation of technical laboratory artefacts [37], and a large Mendelian randomization study failed to demonstrate a direct causal link to CRP [38], and it is now unlikely that the development of CRP inhibitors will play any significant role.

Tumour necrosis factor α and interleukin-6 inhibitors

Inhibitors of TNF α and IL-6 have been successfully developed as disease-modifying antirheumatic

drugs (DMARDs). Trials of TNF α inhibitors such as etanercept have been attempted with negative and some adverse findings in five trials in cardiac failure [39], so it is unlikely that these will be trialled further. A 3080 trial of tocizumab, a specific IL-6 inhibitor, has been compared with etanercept without any difference in cardiovascular events over nearly 5 years [40], but a trial of tocilizumab against placebo has not been conducted.

Methotrexate

Widespread use of methotrexate as a DMARD in rheumatic diseases has resulted in a degree of familiarity with the use and side effects of the drug. It is taken weekly orally or by injection. Observational studies of patients taking methotrexate have shown encouraging trends to lower rates of cardiovascular events in some studies [41] but not in all [42]. As its mode of action includes inhibition of dihydrofolate reductase (DHFR), oral folate is routinely taken with methotrexate. It has multiple sites of action including IL-6 inhibition [43]. The NHLBI funded CIRT (Cardiovascular Inflammation Reduction Trial) [44] is comparing low-dose methotrexate (target dose 15–20 mg/week) against placebo. The trial had planned to recruit 7000 patients but recently announced that it had been stopped after 4786 patients of the planned 7000 patients had been enrolled. The only information publicly available is that there were no substantive safety concerns. It will report the final results in late 2018. Even if the results are positive, the negative feelings about methotrexate and its potential toxicity [45] and low long-term adherence [46] may limit its widespread adoption for the treatment of cardiovascular disease.

Canakinumab

The first trial to report its findings of testing the hypothesis that inhibiting inflammation in atherosclerosis was the CANTOS trial [47^{***}]. CANTOS evaluated the effect of specific inhibition of IL-1 β with canakinumab in patients with a history of acute coronary syndromes with a hs-CRP greater than 2 in 10 061 patients. At a median follow-up of 3.7 years, it showed a statistically significant effect on the primary outcome (nonfatal MI, nonfatal stroke, and cardiovascular death), no effect on all-cause mortality and a small risk of fatal infection. The CANTOS trial has been welcomed as a proof of principle that inhibiting inflammatory pathways, specifically IL-1 β , can improve outcomes of patients with coronary disease. However, its potential for registration and wide clinical acceptance received

a mixed reception [48^{*}]. The possibility of long-term therapy at an estimated annual cost of almost \$200 000 per year [49] indicated the need for more accessible, cheaper solutions.

Colchicine in various forms has been used for treatment of gout for centuries [50]. It has been used in cardiology for a range of conditions including pericarditis and perioperative atrial fibrillation [51]. Its primary side effect of diarrhoea is well known, and in high doses, it can be lethal [52]. However, low-dose colchicine has been widely used long-term in patients with Familial Mediterranean Fever and has Food and Drug Administration (FDA) approval for doses up to 2.4 mg daily in patients with this condition [53]. The multiple sites of action of colchicine in the inflammatory cascade have been well reviewed recently [54,55]. Colchicine is highly concentrated in neutrophils and macrophages prolonging its action [56]. Its ability to bind tubulin achieves multiple cellular actions, including inhibition of the assembly of the NLRP3 inflammasome [57]. In addition to its effect on neutrophils [50,51], colchicine impairs the release of IL-1 β into NETs [58]. Many of the actions have been demonstrated in patients with coronary disease [59,60^{*}].

The actions of colchicine relevant to atherosclerosis are summarized in Fig. 1.

In patients with coronary disease, low-dose colchicine rapidly reduces hs-CRP in patients taking statins [61], and has been shown to reduce coronary atherosclerotic plaque [62^{**}]. The 2013 publication of the LoDoCo trial demonstrated in a PROBE design that low-dose colchicine (0.5 mg/day) in patients on high-dose statins was well tolerated and was strongly suggestive of a marked benefit [63]. Importantly, no adverse effects were seen in the patients who were on moderate and high doses of statins.

The role of colchicine and the low risk of major side effects with low-dose colchicine have been described in a recent Cochrane systematic review of 39 trials with 4992 patients. There was a reduction in risk of myocardial infarction, but with unreliably wide confidence intervals [relative risk (RR) 0.20, 95% confidence intervals (CI) 0.07–0.57; two trials]. There was no effect on total adverse events but gastrointestinal intolerance was increased [64^{**}].

The use of low-dose colchicine is now being explored in trials totalling 15 000 patients. (Table 2). These include the LoDoCo2 trial in ~5500 patients with stable coronary disease [65], the COLPOT trial in 4800 patients with recent acute coronary syndromes [66], the CLEAR-SYNERGY (OASIS-9) in 4000 patients with STEMI undergoing percutaneous coronary intervention (PCI) [67], and the CONVINC trial in 2623 patients [68]. Table 2

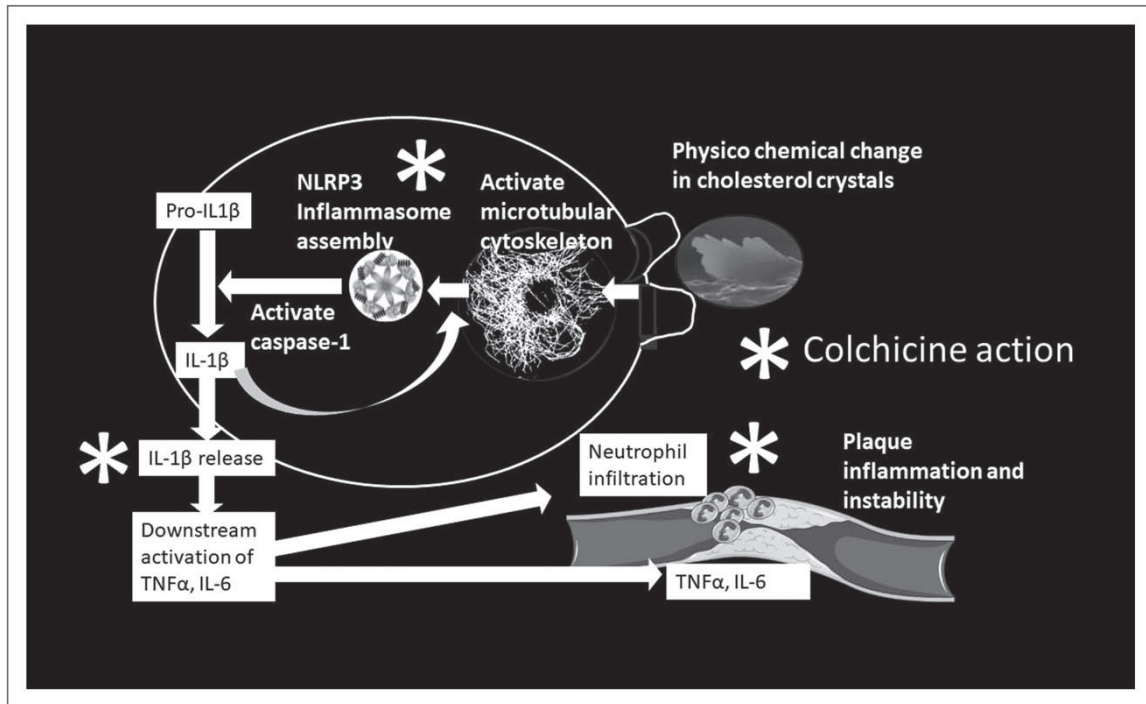


FIGURE 1. Multiple sites of action of colchicine relevant to atherosclerosis. IL-1 β , interleukin-1 β ; TNF α , tumour necrosis factor α ; IL-6, interleukin-6.

summarizes the trials ongoing with low-dose colchicine.

MONITORING THE EFFECT OF ANTI-INFLAMMATORY AGENTS IN ATHEROSCLEROSIS

A benefit on cardiovascular outcomes is the most relevant measure of an anti-atherosclerotic effect of

the new wave of anti-inflammatory agents. Although nonselective evidence-based prescribing can be justified, as in the approach adopted for statin therapy in the controversial 2013 US lipid control Guidelines [69], monitoring of anti-inflammatory and antiatherosclerotic effect is reassuring for patient and clinician. Monitoring the level of hsCRP is likely to remain widely used as it is inexpensive and widely available, and lowering the level

Table 2. Trials currently underway to test low-dose colchicine in atherosclerosis

Trial name and PI	Patients	Sample size	Dose	Clinical trial registration
Acute coronary syndromes				
Tardif <i>et al.</i> , Canada; COLCOT	Acute coronary syndrome	4500	Colchicine 0.5 mg/day vs. placebo	NCT025510 94
Jolly <i>et al.</i> , Canada, CLEAR-SYNERGY OASIS-9	Stent Registry ST elevation myocardial infarction	4000	Colchicine 1 mg/day and/or spironolactone 25 mg/day and/or placebo and/or SYNERGY stent (2 $\times$ 2 factorial design),	NCT030488 25
Stable coronary disease				
Nidorf <i>et al.</i> , Australia, Netherlands; LoDoCo2	Stable coronary artery disease	5500	Colchicine 0.5 mg/day vs. placebo	ACTRN1261 4000093684
Stroke or high-risk TIA				
Kelly <i>et al.</i> , Ireland; CONVINC	Stroke or high risk transient ischaemic attacks	2623	Colchicine 0.5 mg/day vs. placebo	NCT028986 10

See text for trial descriptions. TIA, transient ischemic attack.

of hsCRP was shown to correlate with benefit on outcomes in the CANTOS trial [70]. However, hsCRP is nonspecific biomarker and lowering of hsCRP levels, for instance with NSAIDs do not necessarily correlate with benefit [23]. Novel biomarkers have similar drawbacks [71]. Imaging approaches are being evaluated, the most promising being the use of combined magnetic resonance (MR) and PET [72].

CONCLUSION

The most promising targets for control of inflammation appear to lie within the IL-1 β pathway. The CANTOS trial with canakinumab provided proof of principle that inhibition of IL-1 β can improve outcomes. Canakinumab, being a monoclonal antibody and hence expensive, is unlikely to be widely adopted for long-term treatment. Of the available alternatives, re-purposing of methotrexate and colchicine show the best potential for affordable and accessible anti-inflammatory treatment in atherosclerosis. Ongoing trials are needed to establish their efficacy and safety.

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Conflicts of interest

There are no conflicts of interest.

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