Why Colchicine Should Be Considered for Secondary Prevention of Atherosclerosis: An Overview

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ABSTRACT

Purpose: Colchicine is a widely available, inexpensive drug with a range of antiinflammatory properties that may make it suitable for the secondary prevention of atherosclerosis. This review examines how past and contemporary approaches to antiinflammatory therapy for atherosclerosis have led to a better understanding of the nature of the disease and sets out the reasons why colchicine has the potential to become a cornerstone therapy in its management.

Methods: We performed a literature search using PubMed, the Cochrane library, and clinical trial registries to identify completed and ongoing clinical studies on colchicine in coronary artery disease, and a PubMed search to identify publications on the mechanism of action of colchicine relevant to atherosclerosis.

Findings: A large body of data confirms that inflammation plays a pivotal role in atherosclerosis. The translation of this extensive knowledge into improved clinical outcomes has until recently been elusive. Findings from statin trials support the possibility that targeting inflammation may be beneficial, but this evidence has been inconclusive. Direct inhibition of atherosclerotic inflammation is being explored in current clinical trials. Targeted inhibition of interleukin 1β with canakinumab provided the proof of principle that limiting inflammation can improve outcomes in atherosclerotic vascular disease, but long-term treatment with a monoclonal antibody is unlikely to have widespread uptake. Other approaches using agents with a wider set of targets are being explored. Findings from observational studies suggest that methotrexate may reduce cardiovascular risk in patients with rheumatoid arthritis, but CIRT (Cardiovascular Inflammation Reduction Trial) demonstrated that methotrexate provided no cardiovascular benefit in patients with atherosclerotic vascular disease. Recent demonstration that cholesterol crystals trigger the NLRP3 (nucleotide oligomerization domain–, leucine-rich repeat–, and pyrin domain–containing protein 3) inflammasome and the release of inflammatory cytokines that also drive uric acid crystal–induced inflammation indicates that the multiple actions of colchicine that make it effective in gout may be relevant to preventing inflammation and limiting inflammatory injury in atherosclerosis. The ongoing LoDoCo2 (Low Dose Colchicine2) and COLCOT (Colchicine Cardiovascular Outcomes Trial) trials and several other planned large-scale rigorous trials will determine the long-term tolerability and efficacy of low-dose colchicine for secondary prevention in patients with coronary disease.

Implication: Colchicine holds promise as an important, accessible drug that could be successfully repurposed for the secondary prevention of atherosclerotic cardiovascular disease should its tolerability and cardiovascular benefits be confirmed in ongoing clinical trials. (*Clin Ther*. 2019;41:41–48)
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Keywords: atherosclerosis, cardiovascular disease, colchicine, prevention.

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INTRODUCTION

Colchicine is a widely available, inexpensive drug with a range of antiinflammatory properties that may make it suitable for the secondary prevention of atherosclerosis. This review examines how past and contemporary approaches to antiinflammatory therapy for atherosclerosis have led to a better understanding of the nature of the disease and sets out the reasons why colchicine has the potential to become a cornerstone therapy in its management.

MATERIALS AND METHODS

Using the key terms colchicine, atherosclerosis, coronary artery disease, and prevention, we performed a literature search using PubMed, the Cochrane library, and clinical trial registries to identify completed and ongoing clinical studies on colchicine in coronary artery disease. A PubMed search was also used to identify articles on the mechanism of action of colchicine relevant to atherosclerosis, published between xxx and xxx.

RESULTS

Lessons From Past and Contemporary Approaches to Antiinflammatory Therapy for the Secondary Prevention of Cardiovascular Disease

Over the past 20 years, a large body of data has amassed confirming that inflammation plays a pivotal role in atherosclerosis.[1,2] Three main lines of evidence have supported the concept. First, the work of pathologists Ross in United States[1] and Davies in United Kingdom[3] showed that infiltration of atheroma with inflammatory cells was an invariable part of the initiation and growth of atherosclerotic plaque. Second, Libby[4] demonstrated that enhanced accumulation of inflammatory cells was commonly seen in unstable plaques, suggesting that inflammation was potentially causal as a final step of plaque rupture. Finally, Ridker and others[5,6] demonstrated in multiple cohorts that high-sensitivity C-reactive protein (hs-CRP), a nonspecific biomarker of inflammation produced in the liver in response to interleukin (IL)-6, could be used to identify groups of patients with stable coronary disease who are at high risk for acute coronary events.

The translation of this extensive knowledge into improved clinical outcomes has until recently been elusive. Evidence to support the antiatherosclerotic efficacy of agents including corticosteroids, NSAIDs, and some biologic disease-modifying anti-rheumatic drugs that specifically target a number of inflammatory mediators (eg, tumor necrosis factor α, IL-6, and IL-1) not only failed to demonstrate any clear benefit on cardiovascular outcomes but raised the possibility that targeting such pathways may be associated with an increased risk for adverse off-target events.[7,8]

Indeed, until 5 years ago, only indirect evidence from statin trials continued to support the possibility that directly targeting inflammation in atherosclerosis might truly have merit. Trials of statins in both primary[9] and secondary[10] prevention demonstrated that patents who achieved not only the lowest low-density lipoprotein (LDL) but also the lowest hs-CRP levels on treatment had the lowest cardiovascular risk. However, these data did not conclusively demonstrate that the effect of statins on hs-CRP was truly independent of their low-density lipoprotein—lowering effect.[11]

In order to address this issue, Ridker and others launched 2 large-scale, Phase III, randomized, placebo-controlled trials to test the hypothesis that antiinflammatory therapy could truly improve clinical outcomes in patients with proven coronary artery disease over and above optimal medical therapy, including statins and antiplatelet therapy.

At the time, they chose 2 distinct strategies based on their understanding of the underlying pathophysiology of atherosclerosis. The first trial to launch was CIRT (Cardiovascular Inflammation Reduction Trial)[12] of methotrexate, an effective and generally well-tolerated oral therapy for rheumatoid arthritis (RA), known for its ability to reduce the expression of IL-6. The second to launch was the CANTOS (Anti-inflammatory Therapy with Canakinumab for Atherosclerotic Disease) trial of canakinumab as a highly targeted antiinflammatory strategy with an injectable monoclonal antibody aimed solely at inhibiting the effect of IL-1β, a pivotal cytokine in the inflammatory cascade upstream from IL-6, tumor necrosis factor α, and hs-CRP. IL-1β is the circulating form of IL-1, produced as a precursor (pro—IL-1β) and activated by caspase produced after the activation of NLRP3 (nucleotide oligomerization domain—, leucine-rich repeat—, and pyrin domain—containing protein 3) inflammasome, an innate immune-signaling complex found in proinflammatory macrophages and endothelium that is activated in a broad range of inflammatory diseases, including gout.[13]

The first trial to complete was the CANTOS trial.[14] It examined the effects of 3 doses of canakinumab injected every 3 months in 10,061 patients with a history of acute coronary syndromes and a level of hs-CRP of >2 mg/L.[8] At a median duration of follow-up of 3.7 years, the hazard ratios for the primary outcome (a composite of nonfatal myocardial infarction, nonfatal stroke, and cardiovascular-related death) were 0.93 with the 50-mg dose (P = NS), 0.85 with the 150-mg dose (P = 0.021), and 0.86 with the 300-mg dose (P = 0.031). There was no effect on all-cause mortality. Canakinumab was associated with a small but statistically significant risk for fatal infection (0.31 vs 0.18 events per 100 person-years; P = 0.02). Further analysis demonstrated that patients in the treatment arm whose hs-CRP fell below 2 mg/L at 3 months remained at low risk over the duration of the follow-up period; however, the investigators did not report whether the outcomes in these patients were improved compared with those in patients in the placebo arm of the trial with a level of hs-CRP of <2 mg/L at 3 months.[15]

The CANTOS trial was important as a proof of principle that inhibiting IL-1β can improve clinical outcomes in patients with coronary disease; however, large gaps remain in translating the results of CANTOS to clinical care.[16] Specifically, it was disappointing that the effect on the primary outcome was only modest, that there was no effect on mortality, that there was no clear dose response, and that treatment was associated with a significant risk for fatal infection. In addition, the need for the injection of a monoclonal antibody every 3 months over decades, at an estimated cost of almost $200,000 per annum,[17] were clear signals that canakinumab would never be used in routine clinical practice for secondary prevention in patients with coronary heart disease. Of further relevance is that while canakinumab is widely approved for the treatment of rare periodic fever syndromes in which there is abnormal production of IL-1β, and is approved in Europe for the treatment of active systemic juvenile RA, its demonstrated effects were insufficient to gain approval from the US Food and Drug Administration (FDA) for use in the treatment of flares of gouty arthritis due to tolerability concerns predominantly related to the increased risk for serious infection.[18] More recently still, the FDA rejected an application for canakinumab to be registered for use in the treatment of atherosclerotic vascular disease.[19]

CIRT was the subsequent trial to be reported.[20] It demonstrated that, contrary to observations in largely retrospective, uncontrolled studies in RA, methotrexate provided no cardiovascular benefit in patients with established atherosclerotic vascular disease (without RA). Furthermore, in this population, methotrexate had no effect on circulating levels of IL-1β, IL-6, or CRP.

Both CANTOS and CIRT were pivotal trials that together suggested that the dominant inflammatory pathways involved in atherosclerosis have more in common with those seen in gout than in RA, and this realization has clear therapeutic implications.

Why Colchicine Should Be Considered for the Secondary Prevention of Cardiovascular Disease

In the past decade, new insights into the process of atherosclerosis have emerged. Specifically, there has been significant progress in understanding the inflammatory cascade related to activation of the NLRP3 inflammasome[21] and an increased awareness of the role that cholesterol crystals (CCs) play in the pathogenesis of the disease.[22] Although CCs have been identified in atherosclerotic plaque for over 150 years, their role in the development and progression of atherosclerosis remained largely ignored until recently as the mechanisms by which they can cause inflammatory injury have become clear (Fig. 1).

CCs develop in atherosclerotic plaque in response to changes in the physiochemical environment of the cholesterol-rich core that may be brought about by alterations in temperature, pH, hypoxia, or the addition of cellular debris due to apoptosis. In some circumstances the process of crystallization can be rapid and unchecked, leading to massive expansion and unheralded rupture of the plaque.[23] Most often, CC growth is less dramatic; however, even microscopic CCs have the potential to trigger injury due to their ability to promote an inflammatory response that is akin to, albeit weaker than, that seen in gout. In circumstances in which CCs are not rapidly cleared by resident scavenger cells, the inflammatory process may persist and be sufficiently intense to disrupt the vascular endothelium, leading to atherothrombosis.[24] In most instances, however, CCs are effectively cleared, and in these circumstances,

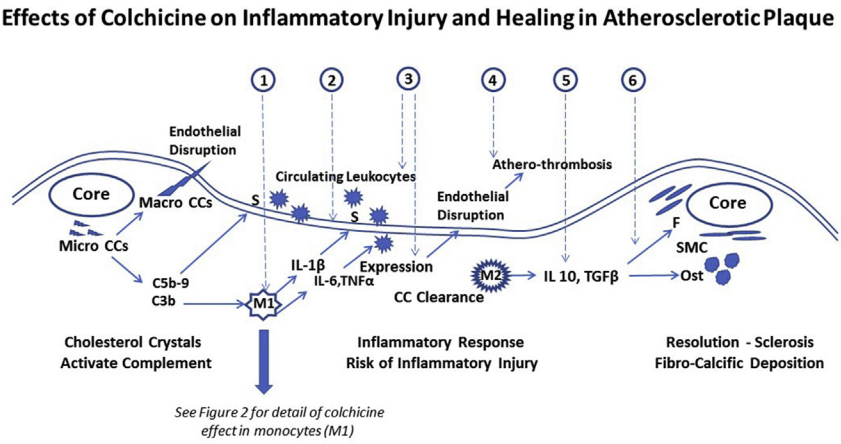

Fig. 1. The formation of cholesterol crystals (CCs) in atherosclerotic plaques may lead to injury. Once formed, microscopic CCs may enlarge to form macroscopic CCs, which can cause sudden unheralded disruption of the endothelium, or they may activate complement to trigger an inflammatory response by promoting the entry of circulating leukocytes into the vascular bed by either directly activating endothelium to produce selectins (S) or by stimulating proinflammatory macrophage (M1) to release interleukin (IL)-1β, which also acts to enhance the recruitment of inflammatory cells into the vascular bed. If the CCs are not rapidly cleared, the inflammatory response can persist, increasing the risk for inflammatory injury that may disrupt the endothelium and lead to atherothrombosis. As CCs are cleared, antiinflammatory macrophages (M2) begin to dominate the milieu and release of antiinflammatory cytokines, including IL-10 and transforming growth factor (TGF)-β, that suppress proinflammatory signals and promote the ingrowth of smooth muscle cells (SMCs), fibrocytes (F), and osteophytes (Ost), leading to the formation of fibrocalcific plaques. Colchicine inhibits the proinflammatory response to CCs by: (1) reducing macrophage expression of IL-1β and the release of various cytokines, including tumor necrosis factor (TNF)-α; (2) reducing endothelial expression of selectins; and (3) inhibiting the actions of circulating leukocytes, including suppressing their ability to release lytic enzymes (eg, matrix metalloproteinase and superoxide). In addition, colchicine: (4) impairs platelet—leukocyte interactions that promote athero-thrombosis, and it can promote resolution and healing by (5) stimulating the expression of IL-10 and TGF-β and by (6) limiting the growth of SMCs, fibroblasts, and osteophytes, which if unchecked leads to vascular thickening, deformity, and calcification.

antiinflammatory macrophages begin to dominate the milieu and release antiinflammatory cytokines, including IL-10 and transforming growth factor β, that suppress proinflammatory signals and promote the ingrowth of smooth muscle cells, fibrocytes, and osteophytes, which leads to the formation of fibrocalcific plaques and sclerosis of the vessel wall.

Like uric acid crystals, CCs trigger inflammation by directly activating complement. Factor C3b[25–27] stimulates proinflammatory macrophages to assemble the NLRP3 inflammasome to produce IL-1β,[28,29] which then incites the endothelium to express E-selectin, and factor C5b-9 directly incites endothelial cells to express E-selectin. Hence, 2 independent pathways activated by complement promote the ingress and activation of circulating leukocytes, including neutrophils, into the atherosclerotic bed. This is important as it indicates that selective inhibition of IL-1β may be insufficient for complete dampening of the inflammatory response to CCs because of the ability of C5b-9 to induce the vascular endothelium to express E-selectin and allow continued ingress of circulating leukocytes into the vascular bed. In addition, it is known that crystal-induced inflammation is also driven by mechanisms other than inflammasome, including necroptosis,

necroinflammation, frustrated phagocytosis, granuloma formation, and tissue fibrosis, and that inhibition or genetic deletion of NLRP3 does not affect crystal cytotoxicity in neutrophils.[30] So, while specifically targeting IL-1β may be highly effective in some periodic fevers, it may be less effective in preventing crystal-induced inflammation as seen in gout and atherosclerosis. Indeed, this is a compelling reason why colchicine, with its broader range of cellular effects, may prove to be of greater value in the secondary prevention of cardiovascular disease than is canakinumab.

Colchicine is already widely used and known to be well tolerated and effective for the secondary prevention and treatment of acute gout and familial Mediterranean fever (FMF).[31] Recently it was also demonstrated to be useful in the management of pericarditis and atrial fibrillation.[32] Experience in the treatment of these conditions has confirmed that, aside from early gastrointestinal intolerance, which may limit its use in some patients, colchicine is well tolerated when used continuously, especially at doses of <1 mg/d. The efficacy of colchicine in both gout, in which uric acid crystals activate the same pathways as CCs, and in FMF, in which there is a genetic anomaly that results in overproduction of the NLRP3 inflammasome, speaks clearly to mechanisms by which it may also be of benefit in atherosclerosis.[33]

Effects of Colchicine in Inflammatory Injury and Healing

Within hours of oral ingestion, colchicine is widely distributed and rapidly taken up by a range of cells throughout the body, becoming most highly concentrated in endothelial cells and leukocytes and especially in neutrophils and macrophages. On entry into the intracellular environment, colchicine irreversibly binds to tubulin, thereby interfering with the production of a range of proteins essential for cellular function.[34,35] There are at least 6 separate modes of action of colchicine relevant to atherosclerosis, as summarized in Figs. 1 and 2.

Although there is evidence that regular colchicine treatment results in suppression of the complement classic pathway functional activity in patients with FMF,[36] it is generally believed that the major therapeutic effects of colchicine are related to its ability to alter cellular function. Specifically, in proinflammatory macrophages, colchicine impairs the cellular apparatus required for the assembly of proinflammatory mediators, including matrix metalloproteinase and tumor necrosis factor α. It also affects the assembly of the NLRP3 inflammasome, thereby reducing the release of IL-1β and a range of other interleukins, including IL-6, that are formed in response to danger signals (Fig. 2). In neutrophils, it

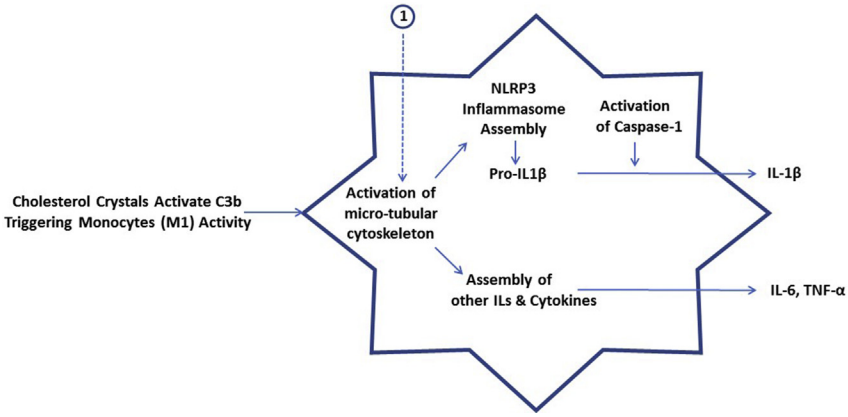

Fig. 2. Detail of the effects of colchicine on monocyte activation. The effects of colchicine on tubulin inhibit the assembly of the NLRP3 (nucleotide oligomerization domain–, leucine-rich repeat–, and pyrin domain–containing protein 3) inflammasome, resulting in upstream inhibition of the interleukin (IL)-1β pathway and the expression of other pivotal proinflammatory cytokines and interleukins. TNF = tumor necrosis factor.

impairs the cellular apparatus required for mobility, adhesion, and the formation and release of cytotoxic substances, including superoxide and a range of proteolytic enzymes. In endothelial cells, colchicine inhibits the production of IL-1β and the expression of E-selectin required for neutrophil adhesion.[35] In addition, colchicine dampens the effects of mast cells[37] and T cells[38,39] that are also pivotal in mediating the response to injury induced by (cholesterol) crystals and can impair the platelet–leukocyte interactions that are important in promoting atherothrombosis.[40] Finally, colchicine can limit the extent of inflammatory injury by promoting antiinflammatory macrophages to release IL-10, TGB- β, and other antiinflammatory cytokines that act to suppress proinflammatory signaling and promote favorable healing by dampening the growth of vascular smooth muscle cells,[41] fibrocytes, and osteophytes, which, if unchecked, may lead to excessive fibrosis, calcification, and deformity of the arterial wall.[42]

Evidence Supporting the Use of Colchicine in Cardiovascular Disease

Recent evidence suggests that the cellular effects of colchicine may translate into clinical benefits in patients with coronary disease. Specifically, it has been demonstrated that colchicine can rapidly and reliably reduce hs-CRP,[43] have favorable effects on the morphology of coronary atherosclerotic plaque,[44] reduce the risk for in-stent stenosis,[45] and reduce the risk for cardiovascular events without tolerability concerns.[46] (A detailed assessment of this evidence is presented in this issue.[47,48])

Of relevance in patients with cardiovascular disease, colchicine 0.5 mg/d does not affect lipid levels, bleeding time, or blood pressure; it is not proarrhythmic; and it has never been reported to cause any clinically important drug interaction when prescribed with the full range of medications commonly used in the treatment of cardiovascular disease. Of the potential drug interactions between colchicine and drugs eliminated via hepatic cytochrome P-450 isozyme 3A4, only the interaction with clarithromycin appears clinically important, and only when colchicine is administered at a dose of >1 mg/d. In addition, colchicine does not directly affect kidney or liver function, and it is well tolerated at low doses in patients with kidney and liver disease.[49,50] Although colchicine has no direct myotoxic effects, myotoxicity has been reported at a dose of >1 mg/d soon after the commencement of statin therapy in patients with moderate renal impairment.[51] Finally, significant bone marrow toxicity and death related to colchicine use have been reported only in the setting of intentional overdose or coadministration with clarithromycin.[52]

The promise of colchicine 0.5 mg/d in patients with coronary disease is currently being explored in several large-scale, rigorous trials, including LoDoCo2 (Low Dose Colchicine2; Australian and New Zealand Clinical Trial Registry identifier: ACTRN12614000093684) in ~5500 patients with stable coronary disease, COLCOT (Colchicine Cardiovascular Outcomes Trial; ClinicalTrials.gov identifier: NCT02551094) in ~4800 patients with recent acute coronary syndromes, and CLEAR-Synergy (Colchicine and Spironolactone in Patients with ST Elevation Myocardial Infarction/ Synergy Stent Registry [OASIS-9]; ClinicalTrials.gov identifier: NCT03048825) in ~4000 patients with ST elevation myocardial infarction undergoing percutaneous coronary intervention.

CONCLUSIONS

Colchicine is a unique, sophisticated agent that has the potential to be successfully repurposed beyond its existing widespread role in the secondary prevention of acute inflammatory flares in gout and FMF. Should ongoing trials confirm its tolerability and benefits in patients with coronary disease, it will likely become a cornerstone therapy in the secondary prevention of cardiovascular disease with the potential to impact the global burden of cardiovascular disease.

Conflicts of Interest

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clinthera.2018.11.016.

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