Reviews

The Role of Colchicine in Acute Coronary Syndromes

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ABSTRACT

Purpose: Because inflammation is a key process implicated in the pathogenesis of atherosclerosis at all stages, including plaque formation, progression, instability, and rupture, and because colchicine has unique anti-inflammatory properties, this review article summarizes the pathophysiologic mechanisms underpinning inflammation in atherosclerosis and acute coronary syndrome (ACS), outlines anti-inflammatory therapeutic approaches that have been tested thus far, and evaluates the evidence supporting the potential role of colchicine in improving outcomes and reducing cardiovascular morbidity and mortality in patients after ACS.

Methods: PubMed was searched for publications on colchicine and ACSs and atherosclerosis, and www.clinicaltrials.org was searched for completed and ongoing trials of colchicine use in ACSs.

Findings: Despite contemporary optimal medical therapy, patients remain at a high risk of future events after an ACS because of residual inflammation at culprit and nonculprit sites. Several attempts have been made to address this with targeted anti-inflammatory therapies, but until the recent promising results of canakinumab (an anti–interleukin-1β monoclonal antibody), most have failed to find any prognostic benefit in large clinical trials with hard end points. The pathogenic role of neutrophils and monocytes in atheroinflammation is well established, and a fundamental component in this process is the activation of the NOD-like receptor protein 3 inflammasome, a cytosolic multiprotein complex that, when activated by a stress signal such as cholesterol crystals, drives caspase-1–dependent release of 2 key proinflammatory cytokines, which are predictive of future adverse cardiovascular events: interleukin-1β and interleukin-18. Colchicine is a widely available, inexpensive, and well-tolerated medication that, among several anti-inflammatory mechanisms of action, inhibits activation of the NOD-like receptor protein 3 inflammasome complex. A seminal trial has found the beneficial properties of colchicine in reducing adverse cardiovascular events in the stable coronary artery disease population.

Implications: Despite promising results in small prospective observational and randomized trials, there is a need for more evidence evaluating the role of colchicine as a secondary preventive agent after ACSs. (*Clin Ther*. 2019;41:11–20)

Keywords: acute coronary syndrome, atherosclerosis, colchicine, coronary artery disease, inflammation.

INTRODUCTION

Atherosclerosis and its clinical manifestations, such as coronary artery disease (CAD) causing acute coronary syndrome (ACS), are leading causes of worldwide morbidity and mortality. Contemporary therapy emphasizes modulation of cardiovascular risk factors, lipid-lowering strategies (both dietary and pharmacologic), and antiplatelet medications to prevent thrombosis. However, there is an increasing body of evidence that implicates inflammation as a process central to the pathogenesis of atherosclerotic plaque

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development, instability, and rupture. Patients with an index ACS remain at an increased risk of recurrent cardiovascular events (up to 20% at 3 years),[1,2] in part because of residual coronary inflammation at culprit and nonculprit sites after ACSs,[3,4] despite current guideline-based medical therapy. Recurrent events in these patients are particularly worrisome because they are associated with significantly more morbidity and mortality than the index event.[2]

Statins, which are part of contemporary optimal medical therapy (OMT) after ACSs, are known to confer an anti-inflammatory benefit in addition to their lipid-lowering properties.[5,6] However, there is a now a shift toward developing therapies that specifically target inflammation to further improve outcomes in this high-risk group of patients. Until recently, the key role of inflammation in atherothrombosis remained a hypothesis based on clinical and experimental data, and there was no high-quality evidence that reducing vascular inflammation translates into reduced cardiovascular event rates. The Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS),[7] however, found that the anti-inflammatory canakinumab (at a dose of 150 mg every 3 months) reduced major adverse cardiovascular events (MACEs) in patients with a previous myocardial infarction (MI) and high-sensitivity C-reactive protein (hs-CRP) levels $\geq$2 mg/L. Canakinumab is a monoclonal antibody that specifically targets interleukin (IL)-1β, a key cytokine in the inflammatory cascade that drives the IL-6 signaling pathway. However, limitations to its widespread implementation include a higher rate of fatal infections and a prohibitively high cost. Therefore, there is a crucial need for new therapies in this high-risk patient cohort.

Colchicine is a widely available, tolerable, and inexpensive anti-inflammatory medication that prevents mitosis by inhibiting microtubule polymerization[1,8] but also interferes with several steps in the inflammatory process. It is used extensively in the management of gout, acute and recurrent pericarditis, and familial Mediterranean fever. Recent evidence also supports its role in cardiovascular disease prevention, and it may represent another potentially useful agent for investigating the inflammation hypothesis in atherothrombosis.[9] This review outlines the role of inflammation in ACS and provides an overview of other targeted anti-inflammatory approaches this far. It then details the evidence thus far supporting a role for colchicine as a secondary preventive agent after ACS and comments on trials currently under way to evaluate this.

INFLAMMATION IN ACS AND THE NLRP3 INFLAMMASOME

Extensive evidence supports a pathogenic role for local and systemic inflammation in ACS, and understanding the molecular and cellular mechanisms that drive this process can improve prognostic stratification and allow identification of novel therapeutic targets.[1,4,10] There have been important recent developments in understanding.

Endothelial activation by triggers, such as low-density lipoprotein cholesterol (LDL-C) or hemodynamic strain, promotes the release of proinflammatory cytokines, oxygen-free radicals, and matrix-degrading metalloproteinases, which amplify the local inflammatory process and reduce plaque stability through collagen-mediated weakening of the fibrous cap. Key proinflammatory cytokines play a role in endothelial activation and further inflammatory cell recruitment and activation and potentiate procoagulant properties of endothelial cells and neutrophils. Furthermore, plaque rupture causes blood contact with tissue factor, a potent procoagulant protein also produced by macrophages, which promotes thrombosis.[3,4,10–13]

Polymorphonuclear neutrophils are also increasingly being recognized as important contributors to atheroinflammation and plaque destabilization.[14–17] Neutrophils activated by cholesterol crystals can also expel neutrophil extracellular traps (NETs), which are weblike structures that contain DNA, histones, neutrophil elastase, and myeloperoxidase.[18]

A key player in the innate immune system is the NOD-like receptor protein 3 (NLRP3) inflammasome, a cytosolic multiprotein complex present in myeloid cells, including neutrophils, monocytes, and eosinophils. Activation of the inflammasome is a 2-phase process. Exposure to various stress signal stimuli, such as cholesterol crystals in plaque, is sensed by the NLRP3 receptor, which primes the inflammasome complex, leading to the assembly of NLRP3, the adaptor protein apoptosis–associated specklike protein that contains the caspase recruitment domain, and the effector cysteine protease procaspase-1.[1,19,20] Activation is completed after a second signal (eg, adenosine triphosphate), leading to caspase-1 activation

and secretion of active IL-1β and IL-18. Therefore, exposure of monocytes and neutrophils to stimuli, such as cholesterol crystals, which are found in higher concentrations in unstable plaque (resulting in higher inflammasome activity), triggers the NLRP3 inflammasome. This in turn promotes caspase-1−dependent release of 2 key inflammatory cytokines (IL-1β and IL-18), both of which are predictive of future cardiovascular events and are key mediators in plaque development, progression, and destabilization.

IL-1β is a proinflammatory cytokine involved in the promotion of monocyte and leukocyte adhesion to vascular endothelial cells, growth of vascular smooth muscle cells, and procoagulant activity induction.[7,21,22] The activation of IL-1β also stimulates the downstream IL-6 receptor signaling pathway, which elicits the acute-phase response that drives expression of atherothrombosis mediators, such as fibrinogen and plasminogen activator inhibitor. Patients with ACS also have the highest transcoronary (coronary sinus aortic) gradients of IL-1β, IL-18, and IL-6 compared with those with stable CAD and no CAD, indicating increased local cardiac production due to active atheroinflammation.[23]

Hence, it is clear that the transformation of a silent atherosclerotic lesion to a ruptured unstable plaque causing ACS is critically mediated by activated immune and inflammatory cells that destabilize the lesion and cause subsequent thrombosis and ischemia. However, there is substantial evidence that inflammation associated with ACS is a diffuse pan-coronary process and not confined to a culprit plaque.[4,11,24] A study of 65 patients found widespread activation of neutrophils across the coronary vascular bed in patients with unstable angina, regardless of the location of the culprit lesion.[25] These studies, along with others, support the concept that a widespread coronary inflammatory process is the substrate for individual plaque instability, with thrombosis and ischemia developing at sites where such a process is most intense.[11]

TARGETING INFLAMMATION IN ACS

An appreciation of the role of inflammation in ACS has generated interest in the development of novel anti-inflammatory therapies to alleviate the high rate of recurrent events and adverse prognosis in these patients. However, despite promising early preclinical and mechanistic studies and Phase II trial results, many of these have failed to find benefit in a large, Phase III trial examining hard clinical outcomes.[21,26]

Statins are known to have pleiotropic anti-inflammatory properties that act synergistically with their lipid-lowering properties. The mechanism of action is multifactorial and includes inhibiting T-cell activation, macrophage infiltration, and leucocyte adhesion, as well as reducing reactive oxygen species generation and enhancing endothelial nitric oxide production.[3,4] Several large clinical trials have found that statin therapy reduces hs-CRP, independent of its lipid-lowering effects, translating into improved clinical outcomes.[6,27] The Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trial[6] randomized 3745 patients with ACS to moderate or intensive lipid-lowering statin therapy and found that patients with a CRP level <2 mg/L after statin therapy had lower event rates (recurrent MI or death due to CAD) than those with higher levels (2.8 vs 3.9 events per 100 person-years, $P = 0.006$). Importantly, this effect of better clinical outcomes was present irrespective of the level of LDL-C achieved on treatment. Furthermore, the cumulative incidence of events at follow-up for patients with CRP levels <2 mg/L but LDL-C levels >1.8 mmol/L was almost identical to those with CRP levels >2 mg/L but LDL-C levels <1.8 mmol/L (3.2 vs 3.1 per 100 person-years), supporting the value of attenuating inflammation after ACS along with lipid lowering. Similarly, the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT)[28] randomized 18,144 patients stabilized after ACS to simvastatin or ezetimibe/simvastatin and measured LDL-C and hs-CRP at baseline and 1 month after randomization. Again, similar to the PROVE-IT trial, there were an almost identical proportion of patients who met the primary composite end point (cardiovascular death, ACS, coronary revascularization within 30 days, or nonfatal stroke) in the group who achieved hs-CRP levels <2 mg/L but LDL-C levels >1.8 mmol/L and the group with hs-CRP levels >2 mg/L but LDL-C levels <1.8 mmol/L (33.4% vs 33.7% at 7 years). A series of more specific anti-inflammatory agents have been investigated in randomized controlled trials, generally with negative results.

Corticosteroids were investigated as an early logical choice for anti-inflammatory therapy after ACS. A meta-analysis of 11 trials (2646 patients) found a 26% decrease in mortality (odds ratio = 0.74, $P = 0.015$), but sensitivity analyses limited to large studies and randomized trials found a lack of

efficacy.[29] Furthermore, steroids were abandoned after a concerning signal of impaired wall healing after MI, resulting in cardiac rupture.[30]

Nonsteroidal anti-inflammatory drugs were all (except aspirin) found to increase the risk of subsequent MI in patients with CAD and increased mortality (hazard ratio [HR] = 1.63) in patients after MI during a 5-year period.[31]

Pexelizumab was another early example of an anti-inflammatory therapy for ACS. Pexelizumab is a single-chain fragment of a humanized monoclonal antibody that binds to the C5 component of the complement cascade, preventing its cleavage into C5a and C5b-9, which are proinflammatory and activate endothelial cells and leucocytes. On the basis of promising proof-of-concept and early animal studies, 2 Phase II placebo-controlled studies were commenced in patients with ST-elevation MI (STEMI), assessing the effect of pexelizumab after fibrinolytic reperfusion therapy or primary percutaneous coronary intervention (PCI).[21] These studies suggested that pexelizumab may modulate the subacute inflammatory consequences of ischemia and infarct healing. On the basis of this signal, a Phase III trial[32] randomized 5745 patients to placebo or pexelizumab (bolus and infusion), but no difference was found in mortality or the composite end point of death, shock, or heart failure. Because of these results, combined with a subsequent meta-analysis confirming no benefit in patients with STEMI, development and investigation of the drug were discontinued.[21]

Varespladib was also developed to function as a nonspecific inhibitor of secretory phospholipase A2 (PLA2) activity. Secretory PLA2 is an enzyme implicated in atheroinflammation by interacting with tumor necrosis factor α receptor signaling and hydrolyzing LDL-C, resulting in lipid accumulation within macrophages, oxidative stress, and downstream inflammation.[21] In a Phase II randomized trial of 625 patients with ACS, varespladib and atorvastatin significantly reduced LDL-C, hs-CRP, and secretory PLA2 levels at 8 and 24 weeks after ACS compared with placebo and atorvastatin, but there was no difference in MACEs between the 2 groups.[33] In a large, follow-up, randomized, placebo-controlled trial of 5145 patients with ACS, daily treatment with varespladib for 4 months after ACS lowered LDL-C and hs-CRP levels but was associated with a higher rate of the composite primary outcome, resulting in early termination because of potential harm.[34]

Darapladib, on the other hand, is a direct selective inhibitor of lipoprotein-associated PLA2. Lipoprotein-associated PLA2 activity hydrolyzes oxidized LDL-C, which produces pro-inflammatory byproducts and is highly expressed in necrotic cores of vulnerable and ruptured plaque. Moreover, higher lipoprotein-associated PLA2 levels are associated with an increased risk of coronary events.[21,26] After no treatment effect was found in a large, randomized, placebo-controlled trial of 15,828 patients with stable CAD,[35] a similar trial of 13,026 patients with ACS[36] recruited within 30 days of non-STEMI (NSTEMI) or STEMI, with a median follow-up of 2.5 years. Again, no difference was found in the primary composite end point (cardiovascular death, MI, or urgent revascularization) between the darapladib and placebo groups (16.3% vs 15.6%, $P = 0.93$), and no difference was found in all-cause mortality or any of the individual components of the primary end point. Thereafter, lipoprotein-associated PLA2 was abandoned as a therapeutic target to improve cardiovascular outcomes.[21]

Inclacumab is a highly specific human recombinant monoclonal antibody against P-selectin, a cell adhesion molecule that plays a crucial role in leukocyte and platelet recruitment, tethering, and adhesion. Higher levels of P-selectin are found in patients with ACS and are associated with increased rates of cardiovascular mortality.[21] After promising animal models, a Phase II trial of 544 patients with NSTEMI was performed in which patients were randomized to an infusion of placebo, 5 mg/kg of inclacumab, or 20 mg/kg of inclacumab before PCI.[37] The primary outcome was a change in troponin I level from baseline and at 16 and 24 hours. Although no significant difference was found between the placebo and 5-mg/kg group, a difference was found between the placebo and 20-mg/kg group at 24 hours (–23.8%, $P = 0.05$). However, a Phase III trial examining hard clinical outcomes remains to be conducted.

Losmapimod is a selective inhibitor of the p38 intracellular mitogen-activated protein kinase signaling cascade. p38 mitogen-activated protein kinase regulates the transcription of inflammatory cytokines, such as TNF-α, IL-1, IL-6, and IL-8, and potentiates the generation of reactive oxygen species.[21] The Phase II trial randomized 535 patients to losmapimod or placebo within 18 hours of presenting with a NSTEMI and at least 2 hours before PCI.[38] The mean hs-CRP level at 72 hours was lower in the losmapimod group than in the

placebo group ($P = 0.0009$), but no difference was found at 12 weeks. Mean troponin I AUC values also did not differ. However, markers of ventricular function or remodeling suggested benefit, with similar mean B-type natriuretic peptide levels at 72 hours but significantly lower at 12 weeks in the losmapimod cohort ($P = 0.04$). After this, a large, randomized, placebo-controlled Phase III trial was commenced in which 3503 patients hospitalized with an acute MI were randomized to losmapimod or placebo for 12 weeks then followed up for an additional 12 weeks.[39] Although the losmapimod group had significantly lower levels of hs-CRP and B-type natriuretic peptide after drug therapy initiation compared with the placebo group, this did not translate into any difference in the primary composite end point of cardiovascular death, MI, or recurrent ischemia (HR = 1.16, $P = 0.24$); therefore, the trial was not expanded to recruit larger numbers.

Finally, canakinumab has earned significant attention recently as a human monoclonal antibody targeted at IL-1β. A Phase II trial of canakinumab (monthly injections for 4 months) in 556 patients with diabetes and high cardiovascular risk found that IL-1β inhibition with canakinumab significantly reduced plasma levels of IL-6 and hs-CRP, without affecting LDL-C levels, compared with placebo.[40] CANTOS[7] was a large, Phase III, randomized trial that sought to evaluate whether canakinumab on top of OMT could prevent recurrent vascular events in patients with residual inflammatory risk by recruiting 10,061 patients with previous MI and hs-CRP levels ≥2 mg/L. At 48 months, the median reduction in hs-CRP from baseline compared with placebo was 26%, 37%, and 41% in the 50-, 150-, and 300-mg dose groups accordingly, with no significant reduction in lipid levels in any canakinumab groups compared with placebo. At a median follow-up of 3.7 years, in the 150-mg group the event rate for the primary outcome (nonfatal MI, nonfatal stroke, cardiovascular death) was 15% lower than the placebo group (HR = 0.85, $P = 0.021$), which was better than both the 50-mg (HR = 0.93, $P = 0.30$) and 300-mg (HR = 0.86, $P = 0.0031$) groups. The 150-mg cohort also met statistical significance for the secondary outcome, which included the primary end points plus unstable angina leading to urgent revascularization (HR = 0.83, $P = 0.005$). No significant difference was found in all-cause mortality (HR = 0.94, $P = 0.31$) for canakinumab compared with placebo. These results finally affirmed the inflammatory hypothesis in atherothrombosis and have set the stage for a new era of anti-inflammatory cardiovascular therapeutics.[22]

The Cardiovascular Inflammation Reduction Trial is a randomized, double-blinded, placebo-controlled trial that will investigate whether low-dose methotrexate (target dose, 15-20 mg/wk) will reduce rate of MI, stroke, and cardiovascular death among patients with type 2 diabetes mellitus or metabolic syndrome and a documented history of MI or past evidence of multivessel CAD by angiography. It will aim to recruit 7000 patients with a mean follow-up period of 3 to 5 years and is currently under way.[41]

THE ROLE OF COLCHICINE

Colchicine is an anti-inflammatory medication with a well-established adverse effect profile and is widely available and inexpensive. Common (>1%) adverse effects are gastrointestinal (eg, diarrhea, nausea, vomiting), with rarer adverse effects (<0.1%) that include hypersensitivity, hepatitis, myoneuropathy, rhabdomyolysis, and blood dyscrasias. Major interactions are with strong CYP3A4 inhibitors, calcineurin inhibitors, and statins, such as pravastatin, and major precautions are found in patients with renal disease, hepatic disease, and pregnancy.[1,42]

Along with its effect on mitosis by binding to tubulin and promoting microtubule depolymerization, colchicine inhibits the activation of the NLRP3 inflammasome protein complex.[42] There are several purported mechanisms by which colchicine can suppress NLRP3 inflammasome activation, including direct monocyte caspase-1 inhibition, inhibition of the *MEFV* gene preventing inflammasome assembly, inhibition of colocalization of inflammasome cytoplasmic proteins, and inhibition of P2 × 7-mediated pore formation, which is a key step in NLRP3 inflammasome response to adenosine triphosphate .[1,43] Ex vivo monocytes from patients with ACS receiving short-term colchicine (1 mg followed by 0.5 mg 1 hour later) therapy exhibited a marked reduction in intracellular and secreted levels of IL-1β compared with pretreatment levels. There was also a significant reduction in procaspase-1 mRNA levels and secreted caspase-1 protein levels in treated patients, suggesting that short-term colchicine intensely and markedly suppressed monocyte caspase-1 activity, thereby reducing monocyte IL-1β secretion.[43] In addition, in these patients, the same colchicine regimen

significantly reduced transcoronary levels of the key caspase-1–mediated cytokines (IL-1β and IL-18) and downstream IL-6 by 40% to 88% (P = 0.028, 0.032, and 0.032, respectively).[23] These findings are consistent with the concept that local activation of cholesterol crystal-induced inflammation within atherosclerotic plaque drives plaque instability, and that it may be possible to modify future outcomes of patients by blocking NLRP3 inflammasome activation with low-dose colchicine.[44]

Indirect support for a beneficial effect of colchicine on cardiovascular disease comes from 2 retrospective studies that have reported reduced incidence of cardiovascular disease, especially ischemic heart disease, in patients with continuous colchicine use for the treatment of gout and familial Mediterranean fever.[8,42,45,46] Furthermore, a study of 64 patients found that low-dose colchicine (0.5 mg BID) effectively and independently decreased hsCRP levels in patients with stable CAD.[47] The pivotal LoDoCo trial of 532 patients with stable CAD followed up during a median of 3 years found that colchicine 0.5 mg/d administered in addition to high-dose statin therapy and OMT was effective in the prevention of MACEs (HR = 0.33, $P < 0.001$) compared with placebo.[48]

In the setting of plaque rupture, an initial small study followed up 80 patients for 30 days after ACS or acute ischemic stroke and found no difference in hsCRP or platelet aggregation in the group given colchicine (1 mg/d) compared with placebo (Table).[49] However, this study did not specify how soon after the ACS diagnosis colchicine was administered, and by 30 days after the index event, acute inflammatory processes would have subsided even in the control group, rendering these findings difficult to interpret. A trial of 151 patients presenting with STEMI (treated with PCI) randomized them to colchicine (loading dose of 2 mg then 0.5 mg BID) or placebo for 5 days and sought to test the hypothesis that a short course of colchicine could reduce infarct size (Table).[50] The creatinine kinase–MB AUC was nearly half that of the placebo group ($P < 0.001$), indexed cardiac magnetic resonance imaging–defined infarct size was 18.3 mL/1.73 m^2 versus 23.2 mL/1.73 m^2 in the colchicine and placebo groups, respectively ($P = 0.019$), and the relative infarct size as a proportion of left ventricular myocardial volume was 13.0% and 19.8%, respectively ($P = 0.034$). These results suggested a benefit of short-course colchicine in reducing infarct size in patients with STEMI treated with PCI. A smaller study of 44 patients, however, with a follow-up of 1 month, randomized patients with STEMI to colchicine 1 mg/d plus OMT or OMT alone and found no difference in mean peak CRP value during the index hospitalization between the 2 groups (Table).[51]

In a prospective, observational study of 80 patients with ACS allocated in a 1:1 ratio to OMT alone or OMT with colchicine 0.5 mg/d for 12 months, computed tomography coronary angiography was performed at baseline and 12 months (Table).[8] OMT involved risk factor optimization and statin intensification therapy aiming at an LDL-C level <1.8 mmol/L. The primary outcome was change in low attenuation plaque (LAP) volume, and secondary outcomes were change in hsCRP level and change in other computed tomography coronary angiography parameters, including total atheroma volume. LAP has been consistently found in large clinical trials and intracoronary imaging comparison studies to represent a powerful predictor of future ACS and MACEs. A significant mean reduction in LAP volume of 41% and 17% was found in the treatment and control groups, respectively, during the 12-month period, with a significant difference ($P = 0.008$) between the 2 groups. Similarly, there was a significant mean reduction in hsCRP levels in both groups (37% and 15% in the treatment group and controls, respectively) from baseline, and again there was a compelling statistically significant difference ($P < 0.0001$) between the 2 groups. A linear regression and correlation analysis found a highly significant linear relationship ($R^2 = 0.158$, $P < 0.001$) and strong positive correlation ($r = 0.578$) between change in LAP volume and change in hsCRP level. Finally, both groups achieved successful statin intensification therapy after ACS, with a substantial mean reduction in LDL-C of 0.5 and 0.4 mmol/L from a baseline of 2.4 and 2.3 mmol/L in the control (–20%) and treatment (–19%) groups, respectively. However, no difference was found between the 2 groups here, with similar percentage reductions in both groups. A multivariate linear regression analysis of the primary and secondary outcomes retained statistical significance for reduction in LAP volume ($P = 0.04$) and hsCRP level ($P = 0.004$). This study found, for the first time to our knowledge, that regular low-dose colchicine therapy has a substantially more powerful coronary plaque–stabilizing effect than OMT alone. These changes were seen independent of substantial reductions

Table. Main studies evaluating colchicine in ACS.

Study	No. of Patients	Population	Colchicine Regimen	Outcomes
Raju et al[49]	80	ACS or acute ischemic stroke	1 mg/d vs placebo for 30 days	Colchicine did not significantly reduce absolute hs-CRP at 30 days (1.0 vs 1.5 mg/L, $P = 0.22$) or difference in hs-CRP from baseline to 30 days (7.0 vs 7.1 mg/L, $P = 0.64$). No difference in platelet function either using various assays.
Deftereos et al[50]	151	STEMI treated with PCI	1.5 mg immediately, then 0.5 mg 1 hour later, then 0.5 mg BID vs placebo for 5 days	The CK-MB AUC was nearly half that of the placebo group ($P < 0.001$). Indexed CMR-defined infarct size was smaller in the colchicine group (18.3 vs 23.2 mL/1.73 m^2, $P = 0.019$), and the relative infarct size as a proportion of LV myocardial volume was smaller in the colchicine group (13.0% vs 19.8%, $P = 0.034$) compared with placebo.
Akodad et al[51]	44	STEMI treated with PCI	1 mg/d for a month vs no treatment	No significant difference in mean CRP peak value between the colchicine and control groups (29.0 vs 21.9 mg/L, $P = 0.36$) even after adjustment for the culprit artery (27.0 vs 25.0 mg/L, $P = 0.79$).
Martínez et al[23]	83	ACS (m = 40), stable CAD (n = 33), controls (n = 10)	1 mg followed by 0.5 mg within 24 hours before coronary sinus sampling vs no treatment	Transcoronary gradients for IL-1β, IL-18, and IL-6 were highest in patients with ACS ($P = 0.08$, 0.03, and 0.01, respectively), and colchicine administration significantly reduced these gradients by 40%–88% ($P = 0.03$, 0.03, and 0.03, respectively).
Vaidya et al[8]	80	Recent ACS (< 1 month)	0.5 mg/d vs no treatment for a year	Colchicine significantly reduced LAP volume (–41% vs –17%, $P = 0.008$) and hs-CRP (–37% vs –15%, $P < 0.001$) vs controls. Reductions in LDL-C ($P = 0.21$) and total atheroma volume ($P = 0.28$) were comparable in both groups.

ACS = acute coronary syndrome; CAD = coronary artery disease; CK-MB = creatinine kinase–MB; CMR = cardiac magnetic resonance; hs-CRP = high-sensitivity C-reactive protein; IL = interleukin; LAP = low attenuation plaque; LDL-C = low-density lipoprotein cholesterol; LV = left ventricle; PCI = percutaneous coronary intervention; STEMI = ST-elevation myocardial infarction.

in LDL-C during 12 months, which were comparable between the treatment and control groups, representing successful statin intensification therapy in both groups. This process was likely driven by the properties of colchicine, which allow it to attenuate atherosclerosis-associated inflammation in vulnerable plaque, as seen by the proportionally greater reduction in hsCRP level in the treatment group, the lack of effect of colchicine on total atheroma volume, and the strongly positive linear correlation between change in LAP volume and hsCRP level.

Two large randomized trials are upcoming that aim to evaluate the role of colchicine in the setting of an ACS and whose results could be potentially practice changing if they find that colchicine's putative plaque-stabilizing effects translate into improved patient outcomes. The Colchicine Cardiovascular Outcomes Trial aims to recruit 4500 patients with an acute MI within the last 30 days and will compare colchicine 0.5 mg/d for 2 years versus placebo.[1] The primary outcome will be a composite of cardiovascular death, resuscitated cardiac arrest, acute MI, stroke, and hospitalization for angina requiring revascularization. The Colchicine and Spironolactone in Patients with STEMI/SYNERGY Stent Registry trial is not yet under way but will aim to recruit 4000 patients with a STEMI who have undergone PCI and assess outcomes after randomization to colchicine versus placebo and spironolactone versus placebo in a 2×2 factorial design. The primary outcome will be MACEs defined as death, recurrent target vessel MI, stroke, or ischemia-driven target vessel revascularization.

FUTURE DIRECTIONS

The knowledge that inflammation is a critical process in the pathogenesis of atherosclerosis offers new opportunities for the prevention and treatment of CAD and its sequelae of ACS, which result in significant patient morbidity and mortality. During the past several years, multiple therapies have targeted inflammatory pathways involved in ACS and atherosclerosis to attempt to improve patient outcomes, with many failing to translate into therapeutic benefit when tested in large, randomized clinical outcomes trials. Patients who have had an ACS remain at a substantial residual risk of MACEs despite contemporary OMT because of the progression of atherothrombotic disease within and beyond the culprit site, representing an unmet therapeutic need. However, with the advent of CANTOS and several other trials currently under way, the next decade will no doubt define the role of inflammation as a target of cardiovascular risk reduction. Colchicine in particular has recently gained traction in cardiovascular medicine and may have the potential to dampen the inflammatory milieu that causes plaque instability and atherothrombosis, thereby reducing the rate of recurrent cardiovascular events and improving patient outcomes.

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DECLARATION OF INTERESTS

There are no conflicts of interest to declare.

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