The Role of Colchicine in Coronary Artery Disease

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Abstract: There is increasing experimental and clinical evidence that inflammation appears to play an important role in atherosclerosis and coronary artery disease. Treatment of coronary artery disease currently involves management of cardiovascular risk factors, lipid-lowering strategies and antiplatelet medications. Inflammation seems to be central to the pathogenesis of atherosclerotic plaque development, instability, and rupture seen in coronary artery disease. Colchicine, a well-known and relatively inexpensive drug, has unique anti-inflammatory properties, which is generating considerable interest in its potential role in reducing cardiovascular morbidity and potentially mortality. This review discusses the mechanism of action of colchicine in preventing and treating atherosclerosis as well as the literature from recent clinical studies supporting its use in coronary artery disease. (Curr Probl Cardiol 2021;46:100690.)

Introduction

Colchicine is a well-known medication indicated for the treatment for acute gout, Behcet's disease, familial Mediterranean fever, and acute and recurrent pericarditis.[1] Although colchicine is

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considered an anti-inflammatory agent, it does not share the same mechanism of action of nonsteroidal anti-inflammatory drugs or glucocorticoids, involving the arachidonic acid pathway.[2] Various clinical and experimental trials have investigated the anti-inflammatory activity of colchicine in atherosclerosis and coronary artery disease (CAD). The encouraging results in recent clinical trials have generated considerable interest in further exploration of the potential indications of colchicine in treating and preventing CAD. The purpose of this review article is to discuss the mechanism of action of colchicine in atherosclerosis and recent clinical studies investigating colchicine in CAD.

We identified relevant literature by conducting a search of the databases of PubMed and United States National Library of Medicine clinical trial database (http://www.clinicaltrials.gov) using the terms "colchicine" AND "cardiovascular disease" OR "coronary artery disease" OR "acute coronary syndrome" OR "myocardial infarction."

Inflammation in Atherosclerosis and Coronary Artery Disease

Current management of CAD consists of lifestyle modification, lipid regulation, and controlling thrombosis.[3] Currently there is no treatment exclusively directed against plaque formation and instability. Inflammation is a contributing factor leading to the instability of atherosclerotic plaques, which represents a potentially suitable target for treatment with anti-inflammatory drugs.[4,5] Several anti-inflammatory drugs have been investigated with regards to reducing inflammation in cardiovascular disease.[6] Statins are known to have anti-inflammatory properties in addition to their lipid lowering effect. Large clinical trials have found that statin therapy reduces hs-CRP (high-sensitivity C-reactive protein), independent of its lipid-lowering effects, which may contribute to improved clinical outcomes.[7,8] Corticosteroids have potent anti-inflammatory properties and therefore have been investigated as a potential agent for reducing inflammation in atherosclerosis and CAD. However, studies have demonstrated mixed results. Steroids appear to be athero-protective, but the benefit is likely offset by inducing cardiovascular risk factors such as hypertension and diabetes mellitus. Another signal for harm was described in a study showing increased risk for cardiac wall rupture as a result of impaired wall healing after myocardial infarction (MI).[9,10] Nonsteroidal anti-inflammatory drugs (NSAIDs), with the exception of aspirin, were found to increase the risk of subsequent MI in a nationwide

cohort study, and, as such, the NSAID class carries a boxed warning for increased risk of cardiovascular events.[11]

Other anti-inflammatory agents such as canakinumab, losmapimod, pexelizumab, inclacumab, varespladib, darapladib, and methotrexate, have also been studied in cardiovascular clinical trials with mixed results.[12-21]

Canakinumab, a human monoclonal antibody targeted against interleukin-1 β (IL1β) was studied in the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS).[12] CANTOS was a large, phase III, randomized trial that evaluated whether canakinumab in addition to optimal medical treatment would prevent recurrent cardiovascular events in patients with residual inflammatory risk. At a median follow-up of 3.7 years, canakinumab significantly reduced the composite endpoint of nonfatal MI, nonfatal stroke, and cardiovascular death by 15% compared to placebo. However, canakinumab also increased the risk of fatal infection or sepsis, and ultimately did not gain Food and Drug Administration approval.[12,13] More recently, methotrexate was evaluated in the Cardiovascular Inflammation Reduction Trial, which included 4786 patients with prior MI or multivessel CAD who also had type 2 diabetes mellitus or metabolic syndrome. Unlike data from CANTOS, methotrexate did not demonstrate a reduction in MI, stroke, or cardiovascular death compared to placebo.[21] Incidence of adverse events were more frequent with methotrexate, specifically cancer ($P = 0.02$), elevated transaminase ($P < 0.001$), and leukopenia ($P < 0.001$). Despite the promise of targeting inflammation in CAD, the results of these did not translate to routine use in clinical practice.

Mechanisms of Action of Colchicine

Colchicine displays unique properties as an anti-inflammatory drug, largely due to its differing mechanism of action than that of corticosteroids and NSAIDs, which involves the arachidonic acid pathway. To the contrary, there are several proposed mechanisms by which colchicine mediates its effects.

Colchicine impairs microtubule function and subsequent cellular activities involving microtubules such as cell division, exocytosis, phagocytosis, and neutrophil motility. At lower concentrations, colchicine binds to unpolymerized tubulin units forming a complex that inhibits the activity of microtubules. At higher concentrations, colchicine will cause depolymerization of microtubules.[22]

Colchicine reduces the adhesion of neutrophils to the endothelium, as seen in in vitro experiments. Selectins are a type of cell surface molecule

that are involved in the recruitment of neutrophils and adhesion to the endothelium during inflammation. The expression of selectins on the cell surface is mediated by microtubules. As a result of inhibiting microtubule function, colchicine diminishes the expression and the function of E-selectin (expressed on endothelial cells) and L-selectin (expressed on neutrophils) and impairs neutrophil migration to the site of injury.[23]

Another novel action of colchicine is that it inhibits the activation of the NLRP3 inflammasome by multiple pathways. Inflammasomes are a family of intracellular multimeric protein complexes that play an important part in the body's inflammatory response to injury. Activation of inflammasome NLRP3 leads to increased production of pro-inflammatory mediators such as interleukin 1β and interleukin-18 (IL-18). Cholesterol crystals are one of the activators of the NLRP3 inflammasomes and the resultant release of cytokines leads to the formation of atherosclerotic plaques and eventually progression, instability, and rupture. In addition to atherosclerosis, abnormal regulation of inflammasomes has been also associated with other chronic inflammatory conditions such as MI, reperfusion injury, and autoimmune diseases.[24-26]

In addition, colchicine has been observed to alter the levels of different inflammatory mediators. It increases the levels of human leukocyte cyclic adenosine monophosphate. Cyclic adenosine monophosphate prevents lysosomal degranulation and also increases the release of Prostaglandin E2, an inhibitor of leukocyte activity. Colchicine has is reported to reduce the production of other cytokines such as leukotriene B4, thromboxane A2, and cyclooxygenase 2.[2,27] Colchicine, with its unique anti-inflammatory mechanism and potential for long-term use, is therefore an attractive option to target inflammation associated with CAD.

Colchicine in stable Coronary Artery Disease

The risk for secondary events in the months to years following a coronary event is markedly elevated when compared to the general population.[28] Because inflammation and its mediators are thought to be associated with progression of both de novo and established CAD, several studies have investigated colchicine's effects on cardiovascular events in clinically stable patients with CAD[29] (Refer to Table 1).

Colchicine is widely used for the prophylaxis and treatment of acute flares of gout. Additionally, patients with gout have a high prevalence of diabetes, hypertension, metabolic syndrome, and obesity as compared to the general population and therefore have a greater risk of cardiovascular disease. Two retrospective studies explored the possibility of additional cardiovascular

Table 1. A summary of important clinical studies looking at the role of colchicine in coronary artery disease

Study	Study design	Sample size	Clinical setting	Colchicine dose and duration of treatment	Primary outcome and results	Adverse events
Retrospective studies on cardiovascular effects in gout						
Crittenden et al[30]	Retrospective cross-sectional study	1288 patients Colchicine (n = 576) Controls 712	Patients with gout	————	*Prevalence of MI* Colchicine 1.2% Control group 2.6% *P* = 0.03 There was reduced mortality and CRP levels in the colchicine group, but it was not statistically significant	Side effects not reported
Solomon et al[31]	Retrospective matched cohort study	1002 patients Colchicine (n = 501) Controls 501	Patients with gout	————	*Primary CV events (Composite of MI, stroke, TIA)* Colchicine 28 events Controls 82 events Adjusted HR 0.51 (95% CI 0.30 - 0.88) *P*= 0.016 *All-cause mortality* Colchicine 43 events Controls 103 events HR 0.27 (95% CI 0.17-0.43) *P*< 0.0001	Side effects not reported

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Table 1. (*continued*)

Study	Study design	Sample size	Clinical setting	Colchicine dose and duration of treatment	Primary outcome and results	Adverse events
Colchicine and stable CAD						
Nidorf et al[34]	Single center open label pilot study	64 patients Colchicine (n = 44) Control 20	Stable CAD with hs-CRP ≥2.0 mg/L	0.5 mg twice daily for 4 weeks	*Change in Plasma hs-CRP level* *- Final hs-CRP level* Colchicine 1.78 ± 1.23 mg/L Control 3.70 ± 2.30 mg/L *P*<0.002 *Decrease in hs-CRP (%)* Colchicine − 60% Control − 11% *P*<0.001	No significant side effects reported
Nidorf et al LoDoCo trial[35]	Prospective randomized observer blinded endpoint trial	532 patients Colchicine (n = 282) Controls 250	Stable CAD	0.5 mg daily for a median of 3 years	*Composite incidence of ACS, out-of-hospital cardiac arrest, or noncardioembolic ischemic stroke.* Colchicine 5.3% Controls 16% *P*< 0.001	**Early GI side effects** Colchicine 32 (11%)
Colchicine and ACS						
Raju et al (COOL study)[36]	Single-center prospective double-blind randomized controlled trial	80 patients Colchicine (n = 40) Placebo 40	ACS or acute ischemic stroke	1 mg daily for 30 days	*Median hs-CRP levels at 30 days* Colchicine 1.0 mg/L Control 1.5 mg/L *P*= 0.64	*Diarrhea* Colchicine 14 patients (35%) Placebo 7 patients (17.5%) *P*= 0.04

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Table 1. (*continued*)

Study	Study design	Sample size	Clinical setting	Colchicine dose and duration of treatment	Primary outcome and results	Adverse events
Akodad et al COLIN trial[37]	Single center prospective open label randomized controlled study	44 patients Colchicine (n = 23) Controls 21	STEMI successfully treated with PCI	1 mg daily for 1 month	*CRP peak value during hospitalization* Colchicine 29.03 mg/L Controls 21.86 mg/L *P*= 0.36	*GI side effects* Colchicine 10 patients (43%)
Hennessy et al LoDoCo-MI[38]	Single center prospective double-blinded randomized placebo control	237 patients Colchicine (n = 119) Placebo 118	Acute MI within 7 days	0.5 mg daily for 30 days	*Number of patients with a residual hs-CRP level ≥2 mg/L after 30 days of treatment.* Colchicine 44% Placebo 50% p =0.35	GI side effects: Colchicine 12 (11%) Placebo 6 (5%) *P*= 0.147
Martinez et al[39]	Single center prospective open label randomized control	83 patients ACS (n = 40) Stable CAD(n = 33) Controls 10	ACS, stable CAD	1 mg followed by 0.5mg within 24 hours before coronary artery sampling	*Transcoronary (coronary sinus-arterial) gradient of IL-1β, IL-6, IL-18 levels.* IL-1β *P*= 0.028 IL-18 *P*= 0.032 IL-6 *P*= 0.032	Not reported as the study was only short term and not designed to assess side effects.
Deftereous et al[40]	Two center prospective double-blinded randomized placebo control	151 patients Colchicine (n = 77) Placebo 74	STEMI treated with Primary PCI	Loading dose of 2 mg, then 0.5 mg twice daily for 5 days. Patients with <60 kg body weight given 0.5 mg daily.	*Area under the curve of CK-MB concentration over 72 hours after admission.* Colchicine 3144 $ng{\cdot}h^{-1}{\cdot}mL^{-1}$ Controls 6184 $ng{\cdot}h^{-1}{\cdot}mL^{-1}$ *P*< 0.001	*Diarrhea* Colchicine 15 patients (19%) Placebo 1 patient (1%) *Nausea/vomiting* Colchicine 3 patients (4%) Controls 0 patients

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Table 1. (*continued*)

Study	Study design	Sample size	Clinical setting	Colchicine dose and duration of treatment	Primary outcome and results	Adverse events
Vaidya et al[41]	prospective nonrandomized observational study	80 patients Colchicine (n = 40) Control 40	Recent ACS <1 month	0.5 mg daily for 1 year	*Reduction in low attenuation plaque volume (LAPV) on CT coronary angiography* Colchicine 15.9 mm^3 Controls 6.6 mm^3 *P*= 0.008	**Diarrhea** Colchicine 1 patient (2.5%)
Tardiff et al (COLCOT)[42]	Multicenter prospective randomized double blinded placebo control	4745 patients Colchicine (n = 2366) Placebo 2379	Within 30 days of MI	0.5 mg daily. Median duration: 22.6 months	*Composite mortality from CV causes, MI, CVA, resuscitated cardiac arrest, or urgent hospitalization for angina leading to coronary revascularization.* Colchicine 5.5% Placebo 7.1% *P*= 0.02	GI side effects Colchicine 408 (17.5%) Placebo 414 (17.6%) *P*= 0.9 **Diarrhea** Colchicine 225 (9.7%) Placebo 208 (8.9%) *P*= 0.35 *Infection* Colchicine 51 (2.2%) Placebo 38 (1.6%) *P* = 0.15 *Pneumonia* Colchicine 21 (0.9%) Placebo 9 (0.4%) *P*= 0.03

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Table 1. (*continued*)

Study	Study design	Sample size	Clinical setting	Colchicine dose and duration of treatment	Primary outcome and results	Adverse events
Colchicine and PCI						
O'Keefe et al[43]	Double-blind prospective randomized placebo control	197 patients Colchicine (n = 130) Placebo 67	Elective balloon angioplasty	0.6 mg twice daily for 6 months	*Angiographic restenosis at 6 months* *Restenosis (% of lumen diameter narrowing)* Colchicine 47 % Placebo 46% *P*= NS *Restenosis in at least 1 lesion* Colchicine 41 % Placebo 45% *P*= NS	*Diarrhea* Colchicine 36 (28 %) Placebo 3 (5%) *P* = 0.001
Freed et al[44]	Open-label pilot	50 patients Colchicine (n = 50)	Plain balloon angioplasty	0.6 mg twice daily for at least 4 months	*Restenosis rate after PTCA.* Colchicine 53% (No significnat effect on restenosis after PTCA compared to typical angioplasty population)	Diarrhea Colchicine 18%
Deftereos et al[45]	Prospective double-blind randomized placebo-control	196 patients Colchicine (n = 100) Placebo 96	Diabetic patients with PCI with bare-metal stent implantation	0.5 mg twice daily for 6 months	*In-stent restenosis rate by angiography* Colchicine 16% Placebo 33% *P*= 0.007. *Intravascular ultrasound-defined in-stent restenosis rate (IVUS defined ISR)* Colchicine 24% Placebo 43% *P*= 0.006	*GI symptoms* Colchicine 16% Placebo 7% *P* = 0.058

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Table 1. (*continued*)

Study	Study design	Sample size	Clinical setting	Colchicine dose and duration of treatment	Primary outcome and results	Adverse events
Shah et al COLCHICINE-PCI[46]	Single center prospective, randomized, double-blinded, placebo-control	400 patients Colchicine (n = 206) Placebo 194	Pre-procedural for patients undergoing PCI	1.2 mg, one to two hours before PCI followed by 0.6 mg 1 hour later	*Number of patients with peri-procedural myocardial injury* Colchicine 57.3 % Placebo 64.2% *P* = 0.19 *30 days MACE* Colchicine 11.7% Placebo 12.9 % *P* = 0.82 (Colchicine significantly reduced the rise in levels of IL-6 and hs-CRP 24 hours post PCI)	*Chest pain* Colchicine 9.0% Placebo 7.2% *GI symptoms* Colchicine 9.3% Placebo 3.2%

Abbreviations: ACS, acute coronary syndrome; CAD, coronary artery disease; CK-MB, creatine kinase-myocardial brain fraction; CRP, C-reactive protein; CT, computerized tomography; CV, cardiovascular; CVA, cerebrovascular accident: GI, gastrointestinal; hs-CRP, high-sensitivity C-reactive protein; HR, hazard ratio; IL, interleukin; MACE, major adverse cardiovascular events; MI, myocardial infarction; NS, not significant; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; STEMI, ST elevation myocardial infarction; TIA, transient ischemic attack.

benefit in patients who had been prescribed colchicine for gout.[30,31] These retrospective analyses of Medicare claims data and a Veterans' Affair population suggest an approximate 50% reduction in cardiovascular events, including MI.[30,31] Meta-analysis and systematic reviews of colchicine in cardiac disease have also suggested benefit.[32,33] A Cochrane review of cardiovascular outcomes in 4992 patients across 39 randomized trials revealed no effect on all-cause mortality. Yet there was some limited evidence based on 2 trials suggesting a reduction in the risk of MI (relative risk, 0.20; 95% CI, 0.07-0.57).[32]

The first prospective trial evaluating colchicine in the stable CAD population evaluated colchicine's effect on hs-CRP in 64 consecutive ambulatory patients.[34] Patients with an elevated hs-CRP were assigned to colchicine 0.5 mg twice daily or no treatment in addition to high intensity statin and aspirin. After 4 weeks, patients receiving colchicine saw a larger reduction in hs-CRP than those assigned to no treatment (−60% vs −11%, respectively; $P< 0.001$). Neither adverse effects nor therapy discontinuation was reported. This proof of concept pilot study led to the "Low-Dose Colchicine" (LoDoCo) trial[35]. LoDoCo randomized 532 patients with angiographically proven, stable CAD to colchicine 0.5 mg daily in addition to the patient's pre-existing CAD treatment or to no change in therapy. The sample included mostly males with a mean age of 67 years and nearly all patients were receiving a single antiplatelet agent in combination with a high intensity statin. In the intention to treat analysis, the primary composite endpoint of acute coronary syndrome (ACS), out-of-hospital cardiac arrest, and noncardioembolic ischemic stroke occurred in 5.3% of patients who received colchicine and 16% patients assigned to control ($P< 0.001$) after a median follow-up of three years. This result was mainly driven by a reduction in ACS, of which, more than one half were episodes of unstable angina with or without subsequent revascularization. Colchicine's effect on the primary outcome was similar in the per-protocol analysis (4.5% vs 16%; $P< 0.001$). Overall, 11% of patients discontinued colchicine during the first month and 11% discontinued therapy after initially tolerating the medication for at least 1 month.[35]

Colchicine in Acute Coronary Syndrome

ACS is the result of an atherosclerotic plaque that becomes unstable leading to plaque rupture followed by activation and aggregation of platelets, ultimately resulting in thrombus formation and blockage of the coronary artery. Inflammation has a major role in the development and progression of atherosclerosis.[28,29] On this basis, colchicine with its anti-inflammatory properties, has generated considerable interest in the

management of ACS. Several clinical studies have looked at the effect of colchicine in ACS (Table 1).

In the Colchicine Compared With Placebo to Reduce Hs-CRP in Patients With Acute Coronary Syndromes Targeting Inflammation in Atherosclerosis Trial (COOL), investigators evaluated the effect of colchicine on the inflammatory marker, high-sensitivity C-reactive protein (hs-CRP) and platelet function tests.[36] A total of 80 patients with ACS or acute ischemic stroke were randomized to colchicine 1 mg daily for 30 days vs placebo. Colchicine did not significantly reduce hs-CRP levels or affect platelet function tests. However, there was an increased incidence of diarrhea with colchicine use.

With the prior study evaluating a heterogeneous population, a subsequent evaluation was performed in the Interest of COLchicine in the Treatment of Patients With Acute Myocardial INfarction and With Inflammatory Response (COLIN) trial.[37] Forty-four patients with ST-elevation myocardial infarction (STEMI) successfully treated with PCI were randomized to colchicine 1 mg daily for 1 month or standard therapy. Despite exclusively limiting enrollment to ACS patients, this trial yielded the same outcome regarding colchicine's effect on CRP. There was no statistical difference in mean peak CRP value during the index hospitalization between the 2 groups. Additionally, there was no difference in major adverse cardiovascular events; however, the trial was not powered for this endpoint.

The Low Dose Colchicine after Myocardial Infarction (LoDoCo-MI) study randomized a total of 237 patients with acute MI within 7 days to colchicine 0.5 mg daily for 30 days or placebo.[38] Similar to prior studies, colchicine did not significantly reduce the CRP level to <2 mg/L at 30 days follow-up compared to placebo. There was also no significant reduction in the median level of hs CRP between both groups.

Another study looked at the effect of colchicine on inflammatory markers other than CRP. In this randomized open label trial, brief colchicine administration significantly reduced the intracardiac production of the inflammatory cytokines (IL-1β, IL-6, IL-18) in patients with ACS.[39]

Although the aforementioned studies showed a mixed impact on laboratory markers, perhaps colchicine's effect could be assessed physiologically by imaging studies. In 151 STEMI patients treated with primary percutaneous coronary intervention (PCI), subjects were randomized to colchicine 2 mg once followed by 0.5 mg twice a day or placebo for a total of 5 days to determine the impact on myocardial injury and infarct size.[40] Colchicine significantly reduced creatinine kinase myocardial brain fraction levels measured up to 72 hours after admission. A subset of 60 patients underwent magnetic resonance imaging and found that infarct

size was significantly reduced following colchicine treatment. Interestingly and contrary to the prior studies, maximal CRP levels were significant reduced in the colchicine group and with a significant correlation to relative and indexed infarct size. Furthermore, a prospective observational study of 80 patients who experienced an ACS event within 1 month prior to enrollment were allocated to colchicine 0.5 mg daily for 1 year vs optimal medical therapy (OMT) alone in attempt to evaluate coronary plaque modification through coronary computed tomography angiography.[41] Low attenuation plaque volume assessed by computed tomography angiography was chosen as the primary endpoint because of robust evidence suggesting the presence reflects plaque instability and a strong predictor of major adverse cardiac events. Colchicine treatment significantly reduced low attenuation plaque volume (mean 15.9 mm^3 [−40.9%] vs 6.6 mm^3 [−17.0%]; P= 0.008) in patients with OMT. Likewise, there was a significant reduction in hs-CRP levels with colchicine (mean −1.10 mg/L [−37.3%] vs −0.38 mg/L [−14.6%]; P< 0.001) vs OMT. Only 1 patient experienced a gastrointestinal adverse event with colchicine and no deaths or MIs reported in the follow-up period.

The previously described studies had relatively small sample size with a maximum follow-up of only 6 months and these evaluations focused on surrogate markers of ACS rather than clinical outcomes. The Colchicine Cardiovascular Outcomes (COLCOT) trial sought to evaluate these meaningful outcomes in 4745 patients who experienced an MI within 30 days from enrollment and who were also receiving OMT.[42] Subjects were randomized to colchicine 0.5 mg daily or placebo. After a medical follow-up of 22.6 months, the primary composite end point of cardiovascular death, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina leading to coronary revascularization was occurred in 5.5% of patients in the colchicine group compared to those in the 7.1% of patients in placebo group (P= 0.02). The primary outcome was driven mainly by reductions in stroke and urgent hospitalization for angina, with no significant reductions in cardiovascular death or MI. Discontinuation rates were high in both arms, occurring in 18.4% of patients in the colchicine group and 18.7% of those in the placebo group. Gastrointestinal side effects were the most commonly reported. Diarrhea occurred in 9.7% of patients in the colchicine group and in 8.9% in the placebo arm. A nonsignificant increase in infection was observed in the colchicine group (2.2 %) compared to the placebo group (1.6%); however, pneumonia rates was significantly higher with colchicine (0.9% vs 0.4%; P= 0.03).[42]

Colchicine in Coronary Angioplasty and Stenting

Coronary artery restenosis after PCI remains an important complication. Restenosis involves inflammation and neointimal hyperplasia. Since colchicine has anti-inflammatory properties, it may have a role in prevent restenosis after PCI.[2] The effect of colchicine in coronary angioplasty and stenting has been investigated in several clinical studies (Table 1).

In the setting of coronary angioplasty, colchicine was evaluated against placebo in 197 patients with stable CAD undergoing elective balloon angioplasty to assess angiographic restenosis.[43] Patients randomized to colchicine 0.6 mg twice daily or placebo were found to have no significant difference in the rates on restenosis over a medium follow-up period of 5.5 months. An open label pilot study of 50 patients also found that colchicine 0.6 mg twice daily (in addition to lovastatin and enalapril) had no effect on restenosis rates following balloon angioplasty.[44] In both the studies, colchicine associated diarrhea was more frequent.

Compared to balloon angioplasty, the introduction of bare-metal and drug-eluting stents have lowered the rates of restenosis in CAD. However, in-stent restenosis remains a problem in certain populations such as diabetics.[45] To evaluate colchicine in this population, 196 diabetic patients receiving bare metal stents were randomized to colchicine 0.5 mg twice daily or placebo for 6 months.[45] In-stent restenosis was assessed via both angiography and intravascular ultrasound. Angiographic in-stent restenosis occurred in 16% of patients treated with colchicine compared to 33% with placebo (P= 0.007). While these studies evaluated more long-term outcomes, it is unclear how colchicine may effect periprocedural or short term outcomes. The recent Colchicine-PCI trial examined whether colchicine administration of 1.8 mg prior to PCI reduces PCI-related myocardial injury, as compared to placebo, in 400 patients referred for coronary angiography with the potential for PCI.[46] There was no difference in periprocedural myocardial injury or any major adverse cardiovascular events at 30 days post-PCI. However, colchicine did significantly attenuate the increase of inflammatory biomarkers (IL-6 and hs-CRP) measured 24 hours post-PCI.

Ongoing Studies on Colchicine in Coronary Artery Disease

Currently, several phase III clinical trials examining the effect of low-dose colchicine in patients with CAD are underway. The LoDoCo2 trial

is a highly anticipated follow-up to the aforementioned LoDoCo study with results expected shortly. LoDoCo2 focuses on secondary prevention of cardiovascular disease with enrollment of over 5000 patients with stable CAD randomized to colchicine 0.5 mg daily or placebo with a planned follow-up of 3 years.[47] The primary endpoint consists of a composite of cardiovascular death, MI, ischemic stroke, and unstable angina requiring revascularization.

The CLEARSYNERGY (OASIS-9; Colchicine and Spironolactone in Patients With STEMI/SYNERGY Stent Registry) study is designed to investigate the effect of colchicine 1 mg per day vs placebo and spironolactone 25 mg per day vs placebo in a 2×2 factorial design.[48] The primary outcome is a composite of cardiovascular death, recurrent MI, or stroke. The study population will include 4000 patients with STEMI who have undergone primary PCI.

These large trials will provide more guidance to identify populations in which colchicine's anti-inflammatory and plaque stabilizing effects may have a potential benefit.

Discussion

Current evidence recommends proposes a multimodal approach to slow the natural progression of atherosclerosis in CAD. This is best achieved by controlling risk factors including dyslipidemia, hemostasis, as well as inflammation and oxidative stress of the atherosclerotic plaque.[3] Standard treatments such as aspirin and statins are the staples of secondary prevention in CAD and likely contribute beneficial effects in attenuating inflammation. However, there is no drug currently that targets inflammation exclusively. Several drugs with anti-inflammatory properties including statins, corticosteroids, and NSAIDs have been tested with the intention to modulate immune response by regulating inflammatory biomarkers in patients of CAD have failed to establish a clear benefit.[2]

Colchicine has gained increased interest with its unique anti-inflammatory properties. A number of studies signaled the potential for cardiovascular benefit with colchicine. Large outcome studies are still needed to confirm the optimal setting for its use. In the LoDoCo trial, colchicine had a number needed to treat of 9 patients to prevent 1 event of the primary outcome, largely driven by a reduction in ACS events, namely unstable angina.[35] Now more recently, the COLCOT trial further supported colchicine in an ACS population, with a number needed to treat of approximately 63 to prevent 1 event of the primary composite outcome.[42] Unlike LoDoCo, the benefit of colchicine was

driven by a lower incidence stroke and urgent hospitalization for angina leading to revascularization. The differences in the findings of these studies may be a result of patient selection, the patient population of stable CAD vs ACS, or sample size. An recent meta-analysis that included the COLCOT trial found that colchicine did not reduce major adverse cardiac events (relative risk, 0.64; 95% CI, 0.36-1.14, P= 0.13) but significantly increases gastrointestinal adverse events (relative risk, 2.66; 95% CI, 1.21-5.87, P= 0.02).[49] To date, there is no universal consensus or recommendations for the use of colchicine in secondary prevention of CAD or with ACS. While the majority of the evidence suggests that colchicine may provide a cardiovascular benefit, more studies with large populations and longer follow-up is necessary to properly identify a population with greatest benefit. LoDoCo2 and CLEARSYNERGY may provide us with those answers in the near future.[47,48]

Conclusion

Current evidence shows that inflammation is a critical component in the pathogenesis of coronary atherosclerosis. Drug therapy directed against inflammation may have a role in treating and preventing CAD. With recently published clinical trials and data, there is a growing interest in colchicine in the management of stable CAD, ACS, and PCI. While currently no guidelines recommend its use, clinicians might consider colchicine in patients with repeat cardiovascular events or to prevent in-stent restenosis following PCI, in populations that were evaluated in the primary literature. Colchicine is relatively safe but may be limited by gastrointestinal adverse events and in some cases increased rates of infection. Future studies are highly anticipated to provide stronger evidence regarding the potential role of this low-cost drug in reducing morbidity and potentially mortality associated with cardiovascular disease.

Authors contribution

Dr. Asra Khalid Butt contributed to conceptualization of the project, performed the review of the literature, and drafted the entirety of the manuscript text. Dr. Brandon Cave, Dr. Miguel Maturana & Dr. William F. Towers contributed to data curation and critical revision of the article. Dr Rami Khouzam, as faculty adviser, contributed to conceptualization of the project, critical revision and editing of the article, and gave final approval.

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