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Update on colchicine, 2017

Anastasia Slobodnick[1,2], Binita Shah[2,3], Svetlana Krasnokutsky[1,2] and Michael H. Pillinger[1,2]

Abstract

Colchicine is an ancient medication that is currently approved for the treatment of gout and FMF. However, colchicine has a wide range of anti-inflammatory activities, and studies indicate that it may be beneficial in a variety of other conditions. This paper reviews the evidence for the well-established use of colchicine in gout, as well as several other rheumatic diseases. In addition, we highlight the potential benefit of colchicine in cardiac disease, including coronary artery disease in patients both with and without gout.

Key words: colchicine, gout, cardiovascular disease, inflammation

Rheumatology key messages

- Colchicine's mechanisms of action are multiple, and more complex than previously appreciated.
- In rheumatic disease, colchicine is most useful for conditions driven by macrophages and neutrophils.
- Colchicine's anti-inflammatory effects hold promise for prevention/management of cardiovascular conditions, including acute coronary syndromes.

REVIEW

Introduction

Colchicine has been used to treat various ailments for thousands of years. The first-known description of colchicine appears in the Ebers papyrus of ancient Egypt in 1550 BC, in which it was described as a treatment for pain and swelling [1]. Colchicine is one of the few medications known from that time period whose use has survived to modernity. Today, colchicine is widely used for treatment of acute gout flares, prophylaxis against gout flares and treatment of other crystal diseases and FMF. In addition to its commonly known uses, colchicine has potential benefits in a wide range of other conditions because of its broad anti-inflammatory effect. In this review, we focus on the evidence for colchicine use in gout, as well as calcium pyrophosphate arthropathy and FMF. In addition, we review recent interest in the use of colchicine for the prevention and/or treatment of cardiovascular disease, both in the context of gout and independent of gout.

[1]Crystal Diseases Study Group, Division of Rheumatology, Department of Medicine, New York University School of Medicine, [2]Rheumatology and Cardiology Sections, VA New York Harbor Health Care System, U.S. Department of Veterans Affairs and [3]Division of Cardiology, Department of Medicine, New York University School of Medicine, New York, NY, USA

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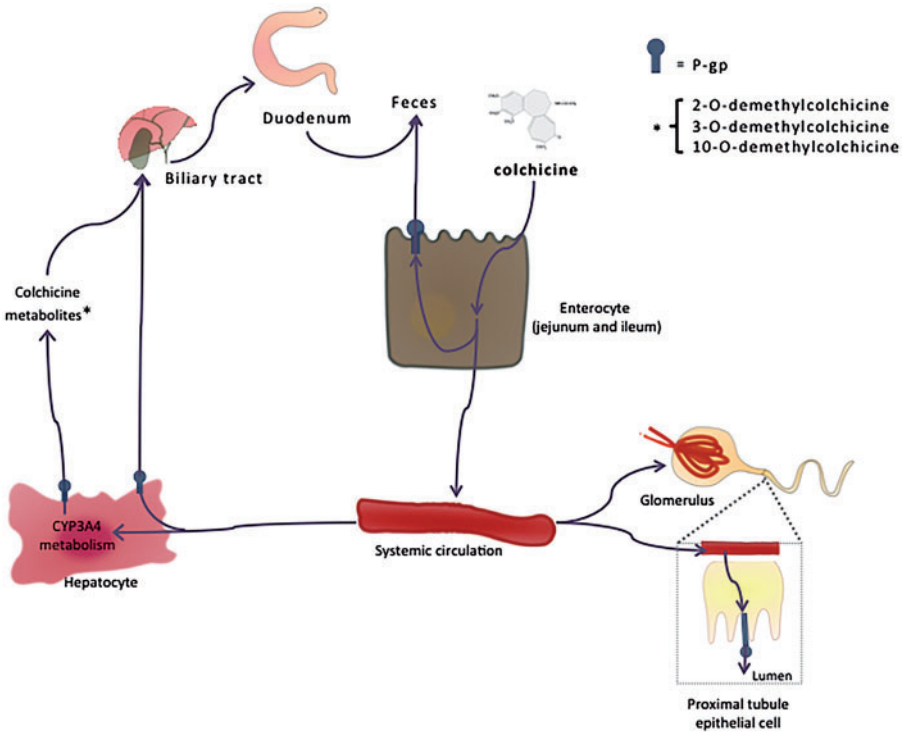
Correspondence to: Anastasia Slobodnick, Division of Rheumatology, NYU Hospital for Joint Diseases Suite 1410, 301 East 17th Street, New York, NY 10003, USA.
E-mail: anastasia.slobodnick@nyumc.org

Mechanisms of action

The mechanisms through which colchicine exerts its anti-inflammatory properties are multiple. Perhaps the best appreciated of these mechanisms is the ability of colchicine to bind to free tubulin dimers which, when incorporated into microtubules, block subsequent microtubule polymerization [2]. This dose-dependent mechanism appears to be directly responsible, at least *in vitro*, for the effects of colchicine on cell migration, cytokine release and intracellular trafficking, and plays an important role in the disruption of inflammatory cell activities by colchicine [3]. The extent to which this mechanism contributes to the effects of colchicine at clinically therapeutic doses is less well established. Colchicine inhibits neutrophil adhesion, extravasation and recruitment by altering neutrophil L-selectin expression and endothelial cell E-selectin distribution, and suppressing the release of the chemotactic agent leukotriene B_4 [4], as well as altering neutrophil deformability [5]. Colchicine also modulates leucocyte-mediated inflammatory activities, including inhibiting leucocyte production of superoxides and release of various cytokines and pyrogens [6, 7]. Whether all of these effects are secondary to the impact of colchicine on microtubules remains to be determined.

Fig. 1 Major mechanisms of colchicine metabolism and excretion



Colchicine is initially absorbed in the jejunum and ileum. P-Glycoprotein (P-gp) on the apical surface of enterocytes secretes a fraction of unchanged colchicine back into the lumen, from which it can be excreted. The remainder enters the systemic circulation and passes through the kidneys, where unchanged colchicine is excreted through glomerular filtration as well as through direct renal P-gp secretion into the proximal tubule. Within hepatocytes, colchicine undergoes demethylation into three distinct metabolites through the action of CYP3A4. These metabolites, along with a portion of unchanged colchicine, are secreted into the bile via hepatic P-gp, and thence into the duodenum for potential excretion.

More recently, colchicine has been found to suppress both monosodium urate (MSU)- and calcium pyrophosphate (CPP) crystal-induced activation of the Nod-Like Receptor Protein 3 (NLRP3) inflammasome, thereby suppressing caspase-1 activation and the subsequent release of IL-1β and IL-18 [8]. As the NLRP3 inflammasome is expressed largely in cells of the myeloid lineage [9], these observations are consistent with the clinical sense that colchicine is useful mainly in treating diseases associated with neutrophils and monocytes/macrophages (i.e. innate immune system) rather than those of the adaptive immune system. *In vitro* studies suggest that inflammasome suppression occurs only with clinically supratherapeutic levels of colchicine. However, as leucocytes accumulate colchicine, and intracellular neutrophil colchicine concentrations have been demonstrated to be much higher than plasma concentrations, clinically used colchicine doses may still be sufficient for inflammasome suppression [10, 11].

Metabolism and adverse effects

Colchicine is primarily eliminated from the body via transport by P-glycoprotein [P-gp, otherwise known as multidrug resistance protein 1 (MDR1) or ATP-binding cassette subfamily B member 1 (ABCB1)], which is expressed in hepatocytes (biliary excretion), proximal renal tubules (renal excretion), enteric cells (gut excretion), monocytes and cells of the blood–brain barrier (Fig. 1) [12]. P-Glycoprotein is encoded by the *MDR1* gene, and certain *MDR1* polymorphisms are associated with increased P-gp expression/activity and decreased serum colchicine concentrations [13, 14]. A smaller but significant portion of absorbed colchicine is metabolized by the hepatic P450 cytochrome CYP3A4, or directly cleared by the kidneys through glomerular filtration. All of these mechanisms are vulnerable to interaction with medications, which can therefore affect bloodstream levels [15]. Simultaneous use of colchicine with CYP3A4 inhibitors/competitors, including clarithromycin, many HIV medications, calcium channel blockers and azole antifungals, or with P-gp inhibitors/competitors such as ciclosporin and ranolazine, can lead to accumulation of colchicine, resulting in increased potential for toxicity (Table 1). The official prescribing guidelines for colchicine therefore recommend dose adjustments for patients taking these medications. A number of studies and/or case reports have also reported a potential interaction

Table 1 Common drugs that interact with colchicine

Strong CYP3A4 inhibitors	Moderate CYP3A4 inhibitors	P-glyco protein inhibitors
Clarithromycin	Cimetidine	Amiodarone
Cobicistat	Ciprofloxacin	Carvedilol
Diltiazem	Cyclosporine	Clarithromycin
Itraconazole	Erythromycin	Itraconazole
Ketoconazole	Fluconazole	Quinidine
Ritonavir	Fluvoxamine	Ranolazine
Telithromycin	Imatinib	Ritonavir
Voriconazole	Verapamil	Verapamil

between colchicine and certain statins, particularly atorvastatin and simvastatin, which are substrates for CYP3A4 [16–23]. Accordingly, when administering colchicine with a statin, it may be desirable to select a statin that is not metabolized by the CYP3A4 enzyme, such as pravastatin or rosuvastatin [24, 25]. The interaction between colchicine and statins is further complicated by the fact that both classes of drugs, independently, are recognized occasionally to cause muscle toxicity. Colchicine dose reduction is also recommended for patients with severe renal impairment, including patients on haemodialysis, as well as for patients with severe hepatic impairment [26, 27]. Among elderly patients, dosing is similar to that of other adults, and studies have found that it is not necessary to adjust the colchicine dose based on age alone, but practitioners should bear in mind that older patients may have renal insufficiency that could require dose adjustment [28].

Although generally well tolerated at prescribed doses, colchicine has a narrow therapeutic window, with reported fatalities with single doses as low as 7 mg [29]. In particular, fatalities have been reported in patients with chronic renal insufficiency taking unadjusted doses of colchicine, particularly when colchicine has been given i.v. or combined with CYP3A4 inhibitors [30–32]. The most common side-effects are gastrointestinal, including diarrhoea, vomiting and nausea, which may occur in $>20\%$ of colchicine users. Gastrointestinal toxicity is dose dependent and may improve by lowering the colchicine dose. Rarer acute adverse effects include myopathy, rhabdomyolysis and myelosuppression [33, 34]. A colchicine neuromyopathy may occur with chronic daily use, particularly in patients whose dose has not been appropriately adjusted for renal disease [35–37]. Symptoms of colchicine toxicity usually resolve within 1 week to several months of discontinuing the drug [10].

Colchicine in gout

Acute gout

Colchicine is effective for both treating and preventing acute gout flares. The first randomized controlled trial of colchicine effectiveness in acute gout was performed by Ahern *et al.* [38] in 1987, when 43 patients with crystal-proven acute gout were randomized to receive either colchicine (1 mg loading dose followed by 0.5 mg every 2 h until symptom response or onset of toxicity) or placebo. The patients presented an average of 38 h after symptom onset. This study found that at 48 h after initiation of treatment, 73% of joints in the colchicine group experienced a 50% or greater improvement in pain, compared with 36% of joints in the placebo group, and pain improved earlier among patients in the colchicine group. However, all 22 patients in the colchicine group developed diarrhoea over a median time period of 24 h, with a mean cumulative dose of 6.7 mg colchicine. Five patients in the placebo group also developed diarrhoea.

More recently, Terkeltaub *et al.* performed a double-blind, placebo-controlled trial, in which 575 patients with acute gout were randomized to receive a high dose of colchicine (loading dose of 1.2 mg, followed by 0.6 mg every hour for 6 h), a low dose of colchicine (loading dose of 1.2 mg, followed by 0.6 mg 1 h later) or placebo. Patients were told to initiate their medication within 12 h of symptom onset, and 185 patients had an eligible gout flare during the study period. After 24 h of follow-up, a similar proportion of patients in the high-dose and low-dose colchicine groups experienced a $\geqslant 50\%$ improvement in their joint pain (32.7% of patients in the high-dose group and 37.8% of patients in the low-dose group), whereas a significantly smaller proportion of patients in the placebo group (15.5%) experienced improvement. However, 19.2% of patients in the high-dose colchicine group experienced diarrhoea, whereas the proportion of patients who experienced diarrhoea or other adverse effects in the low-dose colchicine group was not significantly different from placebo [39]. These observations led both the ACR and EULAR to recommend the initiation of colchicine for acute gout treatment in a dosing regimen of 1.2 mg once (1.0 mg in the EULAR recommendations), followed by administration of 0.6 mg 1 h later (0.5 mg in the EULAR recommendations) [40, 41].

Current ACR and EULAR guidelines recommend that, when using colchicine as a first-line therapy in acute gout flare, it should optimally be administered early after the onset of the acute attack. Although ACR guidelines recommend colchicine initiation no longer than 36 h after the onset of the gouty flare, the EULAR guidelines suggest that the optimal time for initiation should be within 12 h of the flare onset [40, 41]. These recommendations are based on the conviction that colchicine is less effective once the gouty flare has become established. However, the evidence for this recommendation is limited and is mostly based on expert opinion that early initiation leads to better outcomes. Studies of gout have defined an acute attack as one with presentation within anywhere from 12 to 48 h of symptom onset, mostly in an attempt to reduce the confounding effect of spontaneous symptomatic improvement, which may also confound the data regarding colchicine efficacy [38, 39, 42–44]. After the initiation of acute treatment, both guidelines provide an option for follow-up therapy with 0.5–0.6 mg once or twice daily starting 12 h later (typically, the next day) until gout symptoms resolve [40, 41].

Gout prophylaxis

Patients undergoing the initiation of urate-lowering therapy (ULT) experience an extended period of increased risk of acute gouty flares, presumed to relate to the liberation of deposited crystals during the period of solid MSU dissolution [45]. Accordingly, most gout experts recommend extended daily treatment with an anti-inflammatory agent until the peak period of flare risk has subsided.

The first published study to evaluate colchicine for gout flare prophylaxis was conducted by Paulus *et al.* [46], in which 51 patients with gout, as defined by a serum urate concentration of >7.5 mg/dl and a history of typical attacks of acute arthritis, were randomized to either a combined tablet of probenecid 500 mg and colchicine 0.5 mg three times daily, or probenecid 500 mg with placebo three times daily. Thirty-eight of the 51 patients were included in the analysis, because the other patients did not demonstrate a clear reduction in their serum urate concentrations. Patients self-reported their acute gouty episodes, and they were classified as mild, moderate or severe by the investigators based on the patients' descriptions. Only those attacks that were judged to be moderate or severe were included in the analysis because of doubts about whether mild attacks were consistent with gout. Over the course of the study period, patients in the probenecid/colchicine group experienced an average of 0.19 gout attacks per month, while patients in the probenecid/placebo group experienced an average of 0.48 gout attacks per month. Adverse effects included mild to moderate gastrointestinal symptoms.

Borstad *et al.* [45] conducted the first study to evaluate the efficacy of concurrent colchicine use when initiating allopurinol for gout flare prophylaxis. Forty-three patients with crystal-proven gout who were starting allopurinol for gout prophylaxis were randomized to either colchicine 0.6 mg or placebo twice daily (patients with renal insufficiency or gastrointestinal side-effects received a once-daily dose). The two patient groups were similar in terms of baseline characteristics and allopurinol doses necessary to achieve therapeutic serum urate concentrations. Over a 6-month study period, patients in the colchicine group experienced a total of 12 acute gout flares, whereas those in the placebo group experienced 65 acute gout flares. Only 33% of patients in the colchicine group experienced at least one gout flare, compared with 77% of those in the placebo group. Patients in the colchicine group reported less severe gout flares than those in the placebo group. In addition, among patients in the colchicine group, those who took colchicine for the 6-month duration of the study period experienced significantly fewer gout flares than those who took colchicine for <6 months.

A study by Karimzadeh *et al.* [47] evaluated the optimal duration of colchicine therapy for gout prophylaxis. Two hundred and twenty-nine patients who had a diagnosis of gouty arthritis for $\geqslant 1$ year were randomized into one of three groups. All groups received allopurinol and 1 mg colchicine daily. Group 1 received colchicine for 3–6 months, group 2 for 7–9 months and group 3 for 10–12 months. After 1 year of follow-up, 54% of patients in group 1 had experienced at least one acute gouty attack, 27.5% of patients in group 2 experienced at least one acute gouty attack and 23% of patients in group 3 experienced at least one attack. Among the patients who experienced acute gout attacks, the mean time to an acute attack was 8 months in group 1, 11 months in group 2 and 11 months in group 3. The prevalence of side-effects was found to be similar in all three groups. Based on this study, the investigators concluded that 7–9 months was the optimal duration for colchicine prophylaxis with initiation of ULT. However, this study had several limitations. For example, there was no placebo, the number of gout flares per patient was not reported (only the time to the first flare), and there was no report of how patients had been proved to have gout.

Most recently, a *post hoc* analysis of three phase III clinical trials of febuxostat evaluated the optimal duration of gout flare prophylaxis [48]. In this study, 4101 patients received either colchicine 0.6 mg daily or naproxen 250 mg twice daily for either 8 weeks or 6 months when initiating ULT. Prophylactic regimens were not randomized or blinded, but were chosen by the investigators based on patients' renal function and medication tolerance. The study found that patients on the 8-week regimens of either colchicine or naproxen experienced a sharp increase in the rate of acute gout flares at the end of 8 weeks, whereas flare rates were consistently low at the end of 6 months of prophylaxis. The incidence of adverse effects did not differ between the 8-week and 6-month colchicine groups, although both of the colchicine groups experienced more adverse effects than the naproxen groups. Supporting the notion that a prophylaxis duration of $\sim$6 months is appropriate for most patients initiating ULT is the observation by Becker *et al.* [49] that, in patients undergoing urate lowering in the absence of colchicine, the risk of acute flares returns to baseline after $\sim$6 months.

Based largely on these studies, as well as expert opinion, ACR guidelines recommend colchicine 0.5–0.6 mg once or twice daily as a first-line prophylactic therapy in patients who are being initiated on ULT, with the recommended duration of therapy being the longest of three options: 6 months, 3 months after achieving the target serum urate concentration for a patient without tophi on physical examination, or 6 months after achieving the target serum urate concentration in patients with resolution of tophi previously seen on physical examination [40]. All three options presume the absence of ongoing attacks at the time of colchicine discontinuation. EULAR guidelines more simply recommend colchicine as first-line prophylaxis for the first 6 months of ULT, with a recommended dose of 0.5–1 mg daily [41].

Colchicine in other rheumatic diseases

Calcium pyrophosphate deposition disease

In contrast to patients with gout, who often receive ULT to treat their underlying metabolic condition, no causally

directed therapy currently exists for patients with calcium pyrophosphate deposition disease (CPPD). Colchicine is routinely used in CPPD, for both acute flares and suppressive flare prophylaxis. Although formal evidence for its efficacy in this setting is scant, the common mechanisms of activation in urate and CPPD crystal-induced inflammation support the logic of such an approach. EULAR recommends cautious use of colchicine 0.5 mg up to three or four times daily for acute CPPD attacks, with or without a 1 mg loading dose, as well as colchicine 0.5–1 mg daily for CPPD prophylaxis, a recommendation based largely on expert opinion and extrapolation from studies of colchicine use in gout [50].

Several small studies have focused on the efficacy of colchicine in acute CPPD. In 1980, Spilberg *et al.* [51] reported that 14 out of 17 patients with acute crystal-proven CPPD who received 1–2 mg of colchicine i.v. experienced improvement in their pain after 2 h, with the greatest effect being seen in patients who received colchicine within 24 h of symptom onset. Another study [52] from approximately the same era reported that seven patients with acute CPPD who received colchicine 2 mg i.v. followed by 0.5 mg i.v. every 6 h until resolution of symptoms all experienced an improvement in their pain, swelling, redness, tenderness and warmth. A third study evaluated the benefit of colchicine in patients with knee OA and persistent inflammation caused by CPPD. Thirty-nine patients were randomized to either colchicine (0.5 mg twice daily for 8 weeks then as needed until 20 weeks) or placebo and were followed for 5 months. At the end of the study period, patients in the colchicine group reported significantly improved symptoms and function compared with those in the placebo group [53].

Two studies have evaluated the efficacy of colchicine in CPPD prophylaxis. A 1987 case series reported that among 12 patients who received colchicine 1 mg daily for 1 year, the average number of acute CPPD attacks declined from 9.3 attacks in the year before treatment to 2.4 in the year following treatment [54]. In another study, 10 patients with recurrent CPPD received colchicine 0.6 mg twice daily for 1 year. The patients experienced a total of 32 episodes of acute arthritis in the year before treatment, and only 10 episodes in the year following initiation of colchicine [55].

FMF

FMF is an autosomal recessive autoinflammatory syndrome, with prevalence highest in patients of Mediterranean origin. A common thread between the pathophysiology of gout, CPPD disease and FMF appears to be increased responsiveness of the inflammasome, with overproduction of IL-1 [8, 56–58]. Patients with FMF experience recurrent episodes of fever and painful serositis that are usually self-limited, often monthly, and last 12–72 h. The most serious chronic complication of FMF is renal amyloidosis, which may progress to end-stage renal disease if left untreated.

Although the mechanisms by which colchicine exerts its effects in FMF are still being elucidated, it is widely accepted as the first-line therapy for children and adults based on clinical data [59, 60]. In multiple observational studies and randomized controlled trials, daily colchicine use was associated with significant improvement in the frequency and severity of FMF attacks in 85–90% of patients, with many patients achieving complete disease remission [61–65]. Importantly, colchicine 2 mg daily use is associated with prevention of amyloidosis and progression to renal failure among FMF patients, as well as prevention of recurrent amyloidosis in patients post renal transplant [65–67].

Colchicine and cardiac conditions

The past decade has seen a rapid increase in both the study and use of colchicine in a range of cardiac diseases, consistent with the burgeoning understanding that inflammation plays a key role in the development and propagation of many such conditions. The impact of colchicine on cardiac disease is of particular significance for patients with gout, both because gout patients have markedly increased cardiovascular risk compared with the general population, and because colchicine is a drug already routinely used in gout patients. The mechanisms of increased cardiovascular risk in gout patients are not fully understood, but are thought by some authors to relate, at least in part, to the increased acute and chronic systemic inflammation that gout patients experience [68–71]. Thus, the anti-inflammatory effects of colchicine may be explicitly relevant.

Coronary artery disease

Studies have found that many of the inflammatory mechanisms that are targeted by colchicine play a role in the pathogenesis of coronary artery disease (CAD). NLRP3 inflammasome activation has been noted in cardiac fibroblasts after a myocardial infarction (MI), and is thought to mediate myocardial ischaemia–reperfusion injury [72, 73]. Colchicine may also improve cardiac survival and left ventricular remodelling by inhibiting granulocyte accumulation within infarcts, and possibly by upregulating anti-inflammatory M2 macrophages while suppressing pro-inflammatory M1 macrophages [74]. A study by Shah *et al.* [75] found that both *in vitro* and *in vivo*, therapeutic levels of colchicine had no effect on pure platelet aggregation, but were associated with decreased neutrophil–platelet and monocyte–platelet aggregation [75]. These data suggest that colchicine may have the potential to reduce the size or propagation of clots that occur in the setting of inflammation, such as during MI, without impairing the ability of platelets to perform their clotting function in the setting of non-inflammatory lesions, such as acute skin breaks.

Multiple studies offer promising results for the prophylactic use of colchicine in patients with stable CAD or at high risk of cardiovascular events. One prospective, randomized, observer-blinded end-point trial of patients with stable, angiographically proven CAD demonstrated that the addition of colchicine 0.5 mg daily to optimal medical therapy (aspirin and/or clopidogrel, statin) significantly

decreased the composite primary outcome of acute coronary syndrome, out-of-hospital cardiac arrest and non-cardioembolic ischaemic stroke compared with no colchicine (5.3 *vs* 16%, $P < 0.001$; 67% relative risk reduction) [76].

Our group reported a retrospective, cross-sectional study that showed colchicine use in gout patients, a population at high cardiovascular risk, was associated with a decreased prevalence of MI compared with gout patients who did not use colchicine (1.2 compared with 2.6%, $P = 0.03$; 54% relative risk reduction) [77]. Importantly, the benefit of colchicine was lost during periods of colchicine non-compliance. A more recent retrospective study of gout patients found that colchicine use was associated with a 49% relative risk reduction in a composite primary outcome of MI, stroke and transient ischaemic attack compared with patients who did not use colchicine, as well as a 73% relative risk reduction in all-cause mortality [78]. A Cochrane review of colchicine for the prevention of cardiovascular events found that the use of colchicine was associated with a lower risk of MI (1.2 *vs* 5.8%, $P = 0.0003$), but not all-cause mortality [79].

Finally, a study by Deftereos *et al.* [80] suggests that colchicine may be beneficial in the setting of acute coronary syndrome. The study randomized 151 patients with ST-segment elevation MI to receive either colchicine (2 mg loading dose followed by 0.5 mg twice daily for 5 days) or placebo. Patients in the colchicine group were found to have a significantly lower area under the curve of creatine kinase-MB concentration, a marker of infarct size, compared with patients receiving placebo (3144 *vs* 6184 ng × h/ml, $P < 0.001$). A subgroup of patients ($n = 60$) also had a cardiac MRI 6–9 days after MI, and patients in the colchicine group were found to have a significantly lower average infarct size compared with patients in the placebo group (18.3 *vs* 23.2 ml/m^2, $P = 0.019$) [80].

Conclusion

Colchicine is one of the oldest known medications, yet there is still much to learn about its mechanisms of action. Studies continue to uncover its benefits in an ever-growing variety of diseases. In addition to its well-established roles in treating gout and FMF, colchicine has more recently demonstrated benefit in a variety of cardiac diseases, including pericarditis and CAD. Novel uses for colchicine are continuously being explored. Given its relatively good safety and tolerability profile when used carefully and appropriately, it is likely that colchicine will continue to be a part of the anti-inflammatory armamentarium for many years to come.

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