Critical Care

Beyond Gout: Colchicine Use in the Cardiovascular Patient

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Colchicine is one of the oldest medications still in use today and is commonly used for the treatment of gout and familial Mediterranean fever. Its anti-inflammatory properties have raised the question of its utility in managing several cardiovascular diseases, including postoperative atrial fibrillation and pericarditis. This article will review the evidence for colchicine in these conditions and provide recommendations for use.

Colchicine is one of the oldest known drugs still prescribed today. It is US Food and Drug Administration (FDA)–approved for the treatment of familial Mediterranean fever and acute gout and for prophylaxis against gouty arthritis.¹ Colchicine exhibits both antiproliferative and anti-inflammatory actions, primarily via inhibition of microtubule self-assembly through the formation of tubulin-colchicine complexes. This action inhibits the movement of intercellular granules and the secretion of various inflammatory substances. Colchicine has also been found to impair neutrophil adhesion to vascular endothelium. Colchicine shows a preferential concentration for leukocytes, thus decreasing leukocyte motility and blunting the inflammatory response. Peak concentrations in leukocytes may be more than 10 times the peak concentration in plasma; therefore, a therapeutic effect can be seen at relatively low oral doses.²

In recent years, colchicine has been evaluated in the management of a number of cardiovascular diseases, most notably the treatment of acute and recurrent pericarditis and prevention of postoperative atrial fibrillation (POAF). In this article, we review the current evidence for colchicine's role in the treatment of cardiovascular disease and provide recommendations for use. All trials discussed are summarized in Table 1.

POSTOPERATIVE ATRIAL FIBRILLATION AND POSTPERICARDIOTOMY SYNDROME

POAF is the most common arrhythmia following cardiac surgery, with an incidence of 30% to 50%

reported in the literature.³ The burden of POAF is expected to increase with the escalating number of cardiac surgeries being performed in an aging population.⁴ Although often considered a self-limiting complication, POAF is associated with significant morbidity, including stroke, myocardial infarction, ventricular arrhythmias, renal failure, congestive heart failure, and prolonged hospitalization.⁵ The incidence of POAF is higher after valve surgery (40%) than coronary artery bypass graft (CABG) surgery (30%), and this risk escalates further with combined procedures (50%).^{3,6} In addition to multiple known predisposing patient characteristics, several perioperative factors are thought to contribute to the development of POAF. Pericardial inflammation, excess catecholamine production, and volume and pressure changes are all thought to alter atrial refractoriness, thereby providing a substrate for atrial fibrillation (AF) in the presence of a trigger (eg, an electrolyte imbalance or atrial premature contraction).^{3–5}

Similarly, the postpericardiotomy syndrome (PPS) occurs in 10% to 40% of patients 1 week to several months following cardiac surgery.^{7,8} Although a standardized definition and universal diagnostic criteria are lacking, this immune-mediated syndrome is characterized by the presence of 2 or more of the following signs or symptoms: noninfectious fever lasting beyond the first postoperative week, pleuritic chest pain, friction rub, pleural effusion, or new/worsening pericardial effusion. Most commonly resulting in increased patient morbidity and health care costs,

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Table 1. Literature summary of colchicine in cardiovascular disease

Trial (year)	N	Patient population	Intervention	Primary endpoint(s)	Primary result(s) (colchicine vs placebo)	Adverse effects (colchicine vs placebo)
<i>PPS and POAF</i>						
COPPS (2010) ⁸	360	Adults undergoing cardiac surgery without baseline liver, renal, or GI disease	Colchicine 1 mg bid on POD 3, followed by 0.5 mg bid ^a x 1 month vs placebo	Incidence of PPS at 12 months	8.9% vs 21.1%; $P = .002$ (NNT = 9)	8.9% vs 5%; $P = .212$
COPPS AF Substudy (2011) ⁴	336	COPPS patients in sinus rhythm at randomization (POD 3)	Colchicine 1 mg bid on POD 3, followed by 0.5 mg bid ^a x 1 month vs placebo	Incidence of POAF at 1 month	12.0% vs 22.0%; $P = .021$ (NNT = 11)	9.5% vs 4.8%; $P = .137$
COPPS-2 (2014) ¹²	360	Adults undergoing cardiac surgery in sinus rhythm at enrollment	Colchicine 0.5 mg bid ^a x 1 month starting 48–72 h before surgery vs placebo	PPS within 3 months POAF ^b	19.4% vs 29.4%; 95% CI, 1.1–18.7 (NNT = 10) 33.9% vs 41.7%; 95% CI, -2.2 to 17.6 (NS)	20.0% vs 11.7%; 95% CI, 0.76–15.9 (NNH = 12)
<i>Acute pericarditis</i>						
COPE (2005) ¹⁴	120	Adults with first episode of acute pericarditis and no C/I to colchicine therapy	Conventional therapy ^c plus colchicine 2 mg on day 1, then 1 mg daily x 3 months ^a vs placebo	Incidence of recurrent pericarditis	11.7% vs 33.3%; $P = .009$ (NNT = 5)	8.3% vs 6.7%; $P = \text{NS}$
ICAP (2013) ¹⁵	240	Adults with first episode of acute pericarditis and no C/I to colchicine therapy	Conventional therapy ^d plus colchicine 2 mg on day 1, then 1 mg daily x 3 months ^a vs placebo	Incidence of incessant or recurrent pericarditis	16.7% vs 37.5%; $P < .001$ (NNT = 4)	11.7% vs 10.0%; $P = .84$

(Continued)

Table 1. Literature summary of colchicine in cardiovascular disease (CONT.)

Trial (year)	N	Patient population	Intervention	Primary endpoint(s)	Primary result(s) (colchicine vs placebo)	Adverse effects (colchicine vs placebo)
<i>Recurrent pericarditis</i>						
CORE (2005) ²¹	84	Adults with first episode of recurrent pericarditis	Conventional therapy ^c plus colchicine 2 mg on day 1, then 1 mg daily x 6 months ^a vs placebo	Incidence of recurrent pericarditis at 18 months	24.0% vs 50.6%; 95% CI, 2.5-7.1; <i>P</i> = .02 (NNT = 4)	7.1% vs 14.3%; <i>P</i> = .48
CORP (2011) ²²	120	Adults with first episode of recurrent pericarditis	Conventional therapy ^d plus colchicine 2 mg on day 1, then 1 mg daily x 6 months ^a vs placebo	Incidence of recurrent pericarditis at 18 months	24.0% vs 55.0%; 95% CI, 0.13-0.46; <i>P</i> < .001 (NNT=4)	6.7% vs 6.7%; <i>P</i> > .99
CORP-2 (2014) ²³	240	Adults with ≥2 prior pericarditis recurrences	Conventional therapy ^e plus colchicine 0.5 mg bid ^a x 6 months vs placebo	Incidence of recurrent pericarditis at 18 months	21.6% vs 42.5%; 95% CI, 0.24-0.65; <i>P</i> = .0009 (NNT = 5)	11.7% vs 8.3%; <i>P</i> = .519

Note: BID = twice daily; C/I = contraindication; COPE = COLchicine for Acute PEricarditis; COPPS = COLchicine for the Prevention of the Postpericardiotomy Syndrome; COPPS-2 = COLchicine for the Prevention of Postpericardiotomy Syndrome and Postoperative Atrial Fibrillation; CORE = COLchicine for REcurrent pericarditis; CORP = COLchicine for REcurrent Pericarditis; CORP-2 = COLchicine for Recurrent Pericarditis 2; GI = gastrointestinal; ICAP = Investigation on Colchicine for Acute Pericarditis; NNH = number needed to harm; NNT = number needed to treat; NS = not significant; POAF = postoperative atrial fibrillation; POD = postoperative day; PPS = postpericardiotomy syndrome.

^a Doses halved (ie, 0.5 mg daily) in patients weighing <70 kg or intolerant to the highest dose.

^b Secondary endpoint.

^c Aspirin 800 mg every 6-8 hours for 7-10 days, followed by 3-4 week taper. Alternative: prednisone 1.0 to 1.5 mg/kg/day x 4 weeks with subsequent taper if contraindication.

^d Aspirin 800-1000 mg or ibuprofen 600 mg every 8 hours x 7-10 days, followed by 3-4 week taper. Alternative: prednisone 0.2-0.5 mg/kg/day x 4 weeks with subsequent taper if contraindication or intolerance.

^e Aspirin, ibuprofen, or indomethacin dosed by provider. Alternative: prednisone 0.2-0.5 mg/kg/day x 4 weeks with subsequent taper if contraindication or intolerance.

PPS can also progress to life-threatening complications including cardiac tamponade.^{7,8}

Multiple pharmacologic interventions have been studied for the prevention of POAF, including beta-blockers, antiarrhythmic agents, cardiac glycosides, and numerous anti-inflammatory agents. Among these, published guidelines endorse beta-blockers as the pharmacologic agents of choice.⁹⁻¹¹ Preoperative administration of amiodarone has similarly demonstrated efficacy in reducing the incidence of POAF in high-risk patients (class IIa recommendation); however, an extensive side-effect profile and unique pharmacokinetics may limit its utility, particularly in more emergent surgeries where planned preoperative loading cannot occur.^{10,11} Treatment options for PPS are limited to aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs); corticosteroids may also be considered in cases of NSAID contraindication or failure. Until recently, no therapies have been proven efficacious for the primary prevention of PPS.⁸

Two prospective, randomized, double-blind, placebo-controlled trials have sought to evaluate the role of colchicine in the prevention of PPS and POAF.^{4,8,12} The COPPS (Colchicine for the Prevention of the Postpericardiotomy Syndrome) study randomized 360 patients to receive placebo or colchicine at a dose of 1 mg twice daily on postoperative day (POD) 3, followed by 0.5 mg twice daily for 1 month.⁸ Doses were halved in patients weighing less than 70 kg or those intolerant to higher doses. The primary endpoint of PPS at 12 months was significantly reduced in patients receiving colchicine prophylaxis (8.9% vs 21.1%; $P = .002$). The secondary endpoint (combined rates of disease-related hospitalization, cardiac tamponade, constrictive pericarditis, and relapses) was similarly reduced (0.6% vs 5.0%; $P = .024$), with no significant difference in the incidence of adverse effects (8.9% vs 5.0%; $P = .212$). Gastrointestinal intolerance was the primary side effect documented in both study groups, which led to a nonsignificant increase in drug withdrawal in colchicine-treated patients (11.7% vs 6.7%; $P = .145$).

In a substudy of the COPPS trial, patients who were in sinus rhythm at the time of randomization (POD 3) were included in an analysis of POAF rates at 1 month following the treatment intervention.⁴ Among 336 patients, 22% of placebo-treated patients and 12% of colchicine-treated patients had a documented POAF event during the study period ($P = .021$). The duration of POAF (3.0 ± 1.2 vs 7.7 ± 2.5 days; $P < .001$), length of hospital stay (9.4 ± 3.7

vs 10.3 ± 4.3 days; $P = .04$), and length of rehabilitation stay (12.1 ± 6.1 vs 13.9 ± 6.5 days; $P = .009$) were significantly reduced with colchicine. Among colchicine- and placebo-treated patients, perioperative beta-blocker use was lower in patients with POAF compared with those who maintained sinus rhythm (32.7% vs 55.5%; $P = .003$). There were no significant differences noted in perioperative amiodarone use. A dilated left atrium was the only independent risk factor for POAF in multivariable analysis.⁴ Side effects (9.5% vs 4.8%; $P = .137$) and drug withdrawal rates (11.8% vs 6.6%; $P = .131$) were similar in the 2 treatment arms (colchicine vs placebo). While providing preliminary evidence of colchicine's safety and efficacy in POAF prevention, a major limitation of this trial was the delayed initiation of colchicine on POD 3. A majority of POAF cases typically occur during this same period, with a peak incidence on POD 2 to 3.^{3,5} Indeed, 43.3% of all episodes of POAF in COPPS study subjects occurred on POD 1 to 2, before the treatment intervention.⁴

In an effort to address these limitations, Imazio and colleagues¹² designed the COPPS-2 (Colchicine for the Prevention of Postpericardiotomy Syndrome and Postoperative Atrial Fibrillation) trial, a double-blind, placebo-controlled, randomized study of colchicine prophylaxis beginning 48 to 72 hours before cardiac surgery. Three-hundred sixty patients were randomized to colchicine 0.5 mg twice daily or placebo for 1 month following surgery. Again, a dose reduction was prespecified in low-body-weight individuals. The primary endpoint of PPS at 3 months was significantly reduced with colchicine (19.4% vs 29.4%; 95% CI, 1.1-18.7). No significant differences were observed between treatment arms for any of the secondary endpoints (POAF and postoperative effusions within 3 months, incidence of cardiac tamponade, need for pericardiocentesis or thoracentesis, recurrences of PPS, disease-related readmissions, stroke, and overall mortality). The incidence of adverse effects in COPPS-2 was twice that observed in the original COPPS trial (20% of colchicine-treated patients vs 11.7% of those receiving placebo; 95% CI, 0.76-15.9), owing largely to an increase in gastrointestinal intolerance. Authors attributed this discrepancy to the increased vulnerability of patients during the perioperative phase.¹² Despite the increased adverse effect profile with colchicine, discontinuation rates remained similar in the 2 arms (21.7% with colchicine vs 17.8% with placebo), with no serious adverse events reported. A prespecified

on-treatment analysis of patients who tolerated colchicine revealed a significant reduction in the secondary endpoint of POAF in colchicine-treated patients (27% vs 41.2%; 95% CI, 3.3-24.7). Notably, perioperative beta-blocker (57.2% vs 56.1%) and amiodarone (7.2% vs 10%) use were similar in colchicine- and placebo-treated patients, respectively.

Although limited in sample size and scope, these studies make a compelling argument for the use of perioperative colchicine to reduce the incidence of PPS following cardiac surgery. The role of colchicine in the prevention of POAF remains less clear; a potential benefit may have been confounded by the high rate of adverse effects observed in COPPS-2. Additional study into timing of initiation and treatment duration may be warranted to optimize this treatment strategy. Both studies utilized a colchicine dose of 0.5 mg twice daily for 1 month; however, it is possible that a shorter duration or lower initiation dose might produce similar benefit with a more favorable side-effect profile. This may be particularly relevant for POAF, given its typical early and short-lived presentation following cardiac surgery (peak incidence on POD 2, with 94% of cases occurring before the end of POD 6).³

ACUTE PERICARDITIS

Pericarditis, or inflammation of the pericardial sac, is the most common disorder involving the pericardium. The etiology is often idiopathic, with the most common causes presumed to be viral or autoimmune. Other causes include neoplasm, trauma, or cardiac injury.¹³ The most common complication of pericarditis is disease recurrence, which occurs at a rate of 15% to 50%.¹⁴ The mainstay of therapy for acute pericarditis is NSAIDs, with corticosteroids as second-line alternatives due to their association with increased rates of recurrent pericarditis.¹³ Colchicine was originally investigated for the treatment of acute pericarditis due to its ability to decrease leukocyte motility and inflammatory processes.

The COPE (Colchicine for Acute Pericarditis) trial was the first randomized trial to evaluate the use of colchicine in an initial episode of acute pericarditis.¹⁴ This single-center, prospective, open-label, randomized trial assessed colchicine use in conjunction with conventional aspirin therapy. Patients in the colchicine group received 1 to 2 mg on day 1, followed by 0.5 to 1 mg daily for 3 months. The dose was reduced to a 1 mg initial dose and 0.5 mg daily maintenance dose for patients weighing less than 70 kg and those

intolerant to the usual dose. All patients received aspirin 800 mg every 6 to 8 hours for 7 to 10 days, with a gradual taper over 3 to 4 weeks. Use of corticosteroids was restricted to those with aspirin contraindications. Idiopathic pericarditis was the most common etiology in over 80% of patients. The primary endpoint, pericarditis recurrence rate, occurred in 11.7% in the colchicine arm versus 33.3% in those receiving aspirin monotherapy ($P = .009$) during the 2,873 patient-months of follow-up. Symptom persistence at 72 hours was lower in the colchicine group as well (11.7% vs 36.7%; $P = .003$). At 18 months, recurrence rates were 10.7% versus 32.3%, respectively ($P = .04$). There were few adverse effects related to colchicine in the trial, which the authors attributed to the use of the lowest effective dose and weight-based dosing. There were 5 cases of diarrhea (8.3%), which resolved with study drug discontinuation. Minor side effects such as dyspepsia and abdominal pain were reported in 6.7% of patients receiving aspirin monotherapy, which did not require drug withdrawal. Limitations of this trial include its open-label design and subjective symptom interpretation by patients and physicians. The authors concluded that colchicine is an effective adjunctive agent for the treatment of acute pericarditis due to improved symptom control at 72 hours and an approximately 3-fold decrease in pericarditis recurrence rates.

Following this study, Imazio and colleagues¹⁵ published the larger ICAP (Investigation on Colchicine for Acute Pericarditis) trial. This was a placebo-controlled, randomized, multicenter trial of 240 patients assessing the use of colchicine to treat the first attack of acute pericarditis and prevent recurrences. Patients were randomized to receive colchicine 0.5 to 1 mg daily (0.5 mg daily in those <70 kg or intolerant to the higher dose) or placebo. All patients received conventional therapy with aspirin 800 mg or ibuprofen 600 mg every 8 hours for 7 to 10 days, followed by a 3- to 4-week taper. Corticosteroid therapy was again restricted to those with aspirin contraindications. The primary endpoint was incessant or recurrent pericarditis. Secondary endpoints included symptom persistence at 72 hours, remission within 1 week, time to first recurrence, number of recurrences, disease-related hospitalization, cardiac tamponade, and constrictive pericarditis. The primary endpoint occurred in 16.7% of the colchicine group and 37.5% of the placebo group ($P < .001$). Recurrent pericarditis occurred in 9.2% versus 20.8%, respectively ($P = .02$). The colchicine group also had

significantly fewer pericarditis recurrences, fewer disease-related hospitalizations, and a delayed time to first recurrence compared to the placebo group. The overall rate of adverse events was similar between the groups at 11.7% versus 10% in the colchicine and placebo groups, respectively ($P = .84$). Rates of gastrointestinal disturbance (9.2% vs 8.3%; $P = .67$) and study drug discontinuation (11.7% vs 8.3%; $P = .52$) were also similar between groups.

Based on the above data, randomized studies with larger sample sizes and longer follow-up may be indicated to determine colchicine's role in the treatment of acute pericarditis and the impact of prolonged therapy on patient safety and tolerability. Currently, colchicine is a guideline-recommended second-line therapy for the treatment of acute pericarditis.¹⁶ However, the low incidence of study drug discontinuation and adverse effects observed in clinical trials and the substantial decrease in recurrence rates with colchicine make it an attractive potential first-line therapy for acute pericarditis in conjunction with conventional anti-inflammatory agents.

RECURRENT PERICARDITIS

Despite appropriate management of acute pericarditis, recurrence remains a common complication in as many as 30% of patients.¹⁷ Recurrent pericarditis may manifest as either intermittent (>6 weeks from initial episode) or incessant (<6 weeks from initial episode) attacks, though first recurrences generally develop within 18 months of the initial episode.¹⁸ In most cases, relapses are presumed to be either idiopathic or resulting from viral or immunologic stimuli.^{17,19} Clinical symptoms during recurrent attacks are generally mild and limited to pleuritic chest pain. Life-threatening complications of acute pericarditis, such as cardiac tamponade, rarely develop during subsequent episodes; however, quality of life may be significantly impacted based on the severity and frequency of recurrences.¹⁸ NSAIDs are the established standard of care for treatment of recurrent pericarditis, although colchicine has been utilized as adjunctive therapy in clinical practice for many years.²⁰ Data supporting its use for this indication have previously been limited to results of observational studies and expert opinion. A series of randomized clinical trials was recently conducted to assess the outcomes of colchicine therapy in the contemporary management of recurrent pericarditis.

The CORE (COLchicine for REcurrent pericarditis) trial randomized 84 patients with a first recurrence of pericarditis to receive open-label

conventional therapy, with or without adjunctive colchicine therapy.²¹ Conventional therapy consisted of aspirin 800 mg 3 to 4 times daily for 7 to 10 days, followed by a taper over 3 to 4 weeks. Patients with a contraindication to aspirin were eligible to receive a corticosteroid-based regimen. Colchicine was administered at a dose of 2 mg on day 1, followed by a daily maintenance dose of 1 mg for 6 months. A 50% dose reduction was provided for patients weighing less than 70 kg and patients intolerant to full-dose colchicine. To lessen medication adverse effects, gastrointestinal prophylaxis with omeprazole was provided to all patients. The primary efficacy endpoint, the rate of recurrent pericarditis, developed in 24% of patients receiving colchicine and 50.6% of patients receiving conventional therapy at 18 months ($P = .02$). Colchicine use was also associated with a reduction in symptom persistence at 72 hours from onset (10% vs 31%; $P = .03$). Therapy was well tolerated in the majority of patients in both groups, with overall adverse events occurring at rates of 7.1% and 14.3%, respectively, in the colchicine and placebo groups. No serious adverse events were reported during the study, although 3 patients (7%) discontinued colchicine therapy secondary to diarrhea. Symptom resolution occurred shortly after discontinuation.

To confirm the safety and efficacy of colchicine in the management of recurrent pericarditis, Imazio and colleagues²² subsequently conducted the CORP (Colchicine for Recurrent Pericarditis) trial. This was the first multicenter, randomized, double-blind, placebo-controlled assessment of colchicine in this population. All patients received conventional therapy with aspirin 800 to 1,000 mg or ibuprofen 600 mg 3 times daily for 7 to 10 days, followed by a taper over 3 to 4 weeks. Again, use of a corticosteroid regimen served as conventional therapy for patients with a contraindication or intolerance to aspirin. Patients were randomized to receive either placebo or colchicine 2 mg on day 1, followed by a daily maintenance dose of 1 mg for 6 months. Colchicine doses were reduced by 50% in patients weighing less than 70 kg and in patients experiencing gastrointestinal intolerance. Gastrointestinal prophylaxis with a proton-pump inhibitor (PPI) was prescribed to all patients receiving an NSAID. The primary efficacy endpoint, the rate of recurrent pericarditis at 18 months, occurred in 24% of patients receiving colchicine versus 55% of placebo-treated patients ($P < .001$). Colchicine therapy was also associated with significant improvements in several secondary endpoints, including symptom persistence at 72 hours (23% vs 53%; $P = .001$), 1-week remission rates

(82% vs 48%; $P < .001$), time to first recurrence (2.5 vs 1.0 months; $P < .001$), and number of recurrences (0.1 vs 1.0; $P < .001$). Adverse effects and therapy discontinuations occurred at a rate of 6.7% in both groups, with gastrointestinal intolerance contributing to all events in the colchicine arm. No serious adverse events were identified during the study, although therapy discontinuation occurred at a rate of 8% in the colchicine group and 7% in the placebo group.

Imazio and colleagues²³ performed the CORP-2 (Colchicine for Recurrent Pericarditis 2) trial to examine the role of colchicine therapy in preventing recurrent pericarditis in patients with multiple prior episodes. In this multicenter, double-blind trial, adults with a history of at least 2 prior pericarditis episodes were randomized to treatment with colchicine 0.5 mg twice daily or placebo. Patients weighing less than 70 kg and patients intolerant to the usual dose received therapy with once-daily colchicine. All patients received conventional therapy consisting of aspirin, ibuprofen, or indomethacin dosed according to the treating physician, as well as gastrointestinal prophylaxis with a PPI. The primary efficacy endpoint of the study, the rate of recurrent pericarditis at 18 months, occurred in 21.6% of patients receiving colchicine versus 42.5% in the placebo group ($P = .0009$). Patients treated with colchicine were less likely to experience symptoms at 72 hours (19.2% vs 44.2%; $P = .0001$) and were more likely to achieve remission at 1 week (83.3% vs 59.2%; $P = .0001$). Although there was not a statistically significant difference in time to relapse between the colchicine and placebo groups, (8.1 vs 5.3 months; $P = .220$), average number of relapses per patient (0.28 vs 0.63; $P = .0004$) and disease-related hospitalizations (1.7% vs 10.0%; $P = .013$) occurred less often in patients receiving colchicine. Overall adverse effects (11.7% vs 8.3%; $P = .519$), gastrointestinal intolerance (7.5% vs 7.5%), and therapy discontinuation (6.7% vs 5.8%) occurred to a similar extent in the colchicine and placebo arms, respectively. Serious adverse events were not observed in either group. The study investigators concluded that colchicine is a safe and effective adjunctive therapy in the management of recurrent pericarditis. Furthermore, based on the results of CORP-2 and additional clinical trials, authors suggest that colchicine be considered a first-line treatment option for both acute and recurrent pericarditis.

Cumulative results of the CORE, CORP, and CORP-2 trials indicate that colchicine effectively reduces the incidence of recurrent pericarditis, while also lessening symptom duration, when used as

adjunctive therapy with conventional anti-inflammatory agents. Even though the majority of enrolled patients received prophylaxis with a PPI, gastrointestinal disturbance was consistently the most common adverse event reported in both arms of these studies. Overall, the low incidence of clinically significant adverse events and therapy discontinuation suggests that colchicine is well tolerated when administered in addition to conventional therapy. Despite these promising outcomes, the risks and benefits of prolonged colchicine therapy in the management of recurrent pericarditis remain unknown. Further assessments of larger scope and longer follow-up may be warranted to establish the optimal duration of colchicine therapy when used to prevent recurrent pericarditis.

IMPLICATIONS FOR CLINICAL PRACTICE

Results of the above studies exemplify the potential expanded role for colchicine in the management of a number of inflammatory-mediated cardiac conditions. Although the studies are relatively small in scale, colchicine has consistently and reproducibly demonstrated an ability to improve the clinical course of acute and recurrent pericarditis.^{14,15,21-23} Given the magnitude of improvement (>50% reduction in recurrence rates) provided by adjunctive colchicine therapy, with an acceptable safety profile, colchicine may be considered a first-line adjunctive therapy for the management of these conditions. Data supporting the use of colchicine for primary prevention of PPS are less robust but equally promising, stemming from 2 well-designed clinical trials.^{8,12} This is especially noteworthy, as virtually no treatment options currently exist for this indication. Based on the limited available data, colchicine therapy may be considered for susceptible individuals following cardiac surgery to attenuate the risk of PPS. Although data regarding timing of initiation is controversial, we recommend delaying initiation to the postoperative period to minimize the risk of adverse effects and maximize patient tolerability and benefit. Treatment duration also warrants further study; available data suggest that 1 month of therapy is sufficient for primary prevention of PPS, but it remains to be seen whether shorter durations provide similar benefit with less toxicity. Finally, colchicine's role in the prevention of POAF remains uncertain. Although a potential benefit may exist, we recommend that beta-blockers and amiodarone remain the mainstay of POAF prevention until further large-scale studies with a primary endpoint of POAF are conducted.

For all indications, consideration should be given to dose-limiting factors such as side effects and drug-drug interactions. Gastrointestinal side effects of colchicine are common, and some patients may not be willing to continue therapy should they occur. Furthermore, colchicine is a substrate of CYP3A4 and concentrations may be increased by drugs that are inhibitors, such as diltiazem, verapamil, azithromycin, and ketoconazole.

The biggest hindrance to expanding colchicine use relates to its cost. In 2006, the FDA launched the “Unapproved Drug Initiative,” which targeted old drugs that had never been formally approved through modern regulatory pathways. In 2007, URL Pharma conducted pharmacokinetic and clinical research trials in acute gout treatment, which led to the FDA approval and market exclusivity of *Colcrys* for 3 years. Additionally, *Colcrys* was granted 7 years of market exclusivity for the treatment of familial Mediterranean fever under the Orphan Drug Act. Because of these rulings, the manufacturer was able to market colchicine at an increased price, skyrocketing costs from approximately \$0.09 to about \$6 per tablet. This has created financial barriers for many patients who have been successfully treated with colchicine for years, while also directly affecting insurance programs.¹ The FDA recently granted approval of generic colchicine, however, the price is still inflated at an estimated \$4 per tablet. Costs are expected to decrease as generic drug distribution increases, but providers should still consider pharmacoeconomic implications when prescribing colchicine for off-label indications.

CONCLUSIONS

Cumulative evidence suggests that colchicine has potent anti-inflammatory actions. Its role in the treatment of acute pericarditis and in the prevention of recurrent pericarditis are the most well established to date. As such, we recommend colchicine be considered a first-line adjunctive treatment modality for the management of these indications. Even though published data describing perioperative colchicine therapy surrounding cardiac surgery are less robust, available evidence is compelling and suggests colchicine may effectively reduce the incidence of PPS. Current data for prevention of POAF in cardiac surgery are inconclusive; further large-scale studies with a primary endpoint of POAF are needed. Above all, it is clear that careful patient selection, consideration of disease-drug and drug-drug interactions, and cost analysis will be key to maximizing patient benefit while limiting potential harm.

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