



Colchicine—regeneration of an old drug

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Abstract

Immunomodulation by colchicine is a well-established therapy for targeting inflammatory pathways in gout, pericarditis and Behcet's disease. In more recent times, evidence has emerged demonstrating a potential role for colchicine in several cardiac conditions. This article aims to summarise the evidence behind the established guidelines for use of low-dose colchicine in pericarditis and examine the evolving evidence for its use in cardiovascular disease and most recently COVID-19.

Keywords Atherosclerosis · Cardiovascular disease · Colchicine · COVID-19 · Pericarditis

An ancient drug

The plant source of colchicine, the autumn crocus (*Colchicum autumnale*), was first described for management of rheumatism and swelling in an Egyptian medical papyrus. Circa 1500 BC [1]. *Colchicum* corms were later used by the Persian physician Avicenna and were recommended by Ambroise Paré in the sixteenth century and appeared in the *London Pharmacopoeia* of 1618 [2, 3]. *Colchicum* use waned over time, likely due to the severe gastrointestinal side effect preparations caused. Colchicine was first isolated as the active alkaloid of *Colchicum* in 1820 and was later purified by P. L. Geiger to an active ingredient, which he named colchicine. It quickly became a popular remedy for gout [3].

Pharmacology of colchicine

The anti-inflammatory effect of colchicine differs from conventional non-steroidal anti-inflammatory drugs (NSAIDs) and steroids in that it does not act on the arachidonic acid

pathway [4]. Rather, it targets white blood cells (WBCs) and causes microtubule depolymerisation which in turn inhibits motility, phagocytosis and degranulation of the WBCs [5]. It also inhibits interleukin-1beta (IL-1 β) and interleukin-18 (IL-18) by attenuating NLRP3 inflammasome protein complex formation, which has an increasingly recognised role in mediating crystal-induced gout, recurrent idiopathic pericarditis and more recently atherosclerotic coronary artery disease [4–7]. Colchicine is lipid-soluble and absorbed in the jejunum and ileum. It has 44% bioavailability, and it is metabolised by CYP3A4 [4]. It is predominantly excreted by the liver with 10–20% excreted by the kidneys. Colchicine is contraindicated in patients with severe renal or hepatic impairment, pregnancy or breastfeeding and patients with blood dyscrasias.

Early studies of colchicine in pericardial disease

Over the past three decades, the journey of colchicine for the treatment of pericardial diseases has been long and successful, achieving top indications in clinical guidelines and real world use in day to day clinical practice. The first indication of colchicine in cardiac disorders was reported for recurrent pericarditis in 1987 in Barcelona [8]. Nevertheless, it was not until the beginning of the twenty-first century that the value of colchicine in acute and recurrent pericarditis was fully demonstrated in a series of well-designed, randomised clinical trials (RCTs) [9–12]. The use of colchicine for acute pericarditis was first proposed by Rodriguez de la

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Serna et al. in Barcelona in 1987, based on its efficacy in preventing polyserositis in patients with familial Mediterranean fever [8]. During the 1990s, a number of small studies across France and Israel were published to validate the use of colchicine to treat recurrent pericarditis [13–16]. In 2005, a pan-Mediterranean study addressed the hypothesis that pretreatment with corticosteroids may attenuate the beneficial effect of colchicine. The authors found that only 18% of patients had relapses under colchicine therapy and 30% after its discontinuation. They concluded that treatment with colchicine was highly effective in preventing recurrent pericarditis, whereas pretreatment with corticosteroids exacerbated and extended the course of recurrent pericarditis [15]. These early studies paved the way for the large contemporary smaller RCTs on which current guidelines and practice is based.

Acute and recurrent pericarditis—data supporting current practice

In 2005, the COPE (COlchicine for acute PEricarditis) prospective, randomised, open-label trial, which included patients ($n = 120$) with a first episode of acute pericarditis, showed that colchicine with dose of 0.5 mg bid, in addition to conventional anti-inflammatory therapy, significantly reduced symptoms at 72 h (11.7% vs. 36.7%; colchicine vs placebo respectively, $p = 0.003$). In addition, the recurrences of pericarditis at 18 months were significantly less frequent in patients treated with colchicine when compared to placebo (10.7% vs. 32.3%, colchicine vs placebo respectively; $p = 0.004$) and the number needed to treat (NNT) to prevent one recurrence was 5 patients [17].

Recurrent pericarditis is one of the most common and troublesome complications of acute pericarditis, occurring in 10–50% of patients with pericarditis. The CORE (COlchicine for REcurrent pericarditis) trial in 2005 [9], the CORP (COlchicine for Recurrent Pericarditis) trial in 2011 [18], and the CORP-2 (efficacy and safety of colchicine for treatment of multiple recurrences of pericarditis) trial in 2014 [10] investigated the safety and efficacy of colchicine as an adjunct to conventional therapy for recurrent pericarditis. The CORE study, an open-label prospective trial in which patients ($n = 84$) with a first recurrence of acute pericarditis were randomised to receive either aspirin alone or aspirin plus colchicine (1 mg per day) for 6 months, showed that the association of aspirin plus colchicine demonstrated a significant reduction in the rate of recurrent events at 18 months compared with aspirin alone (24.0% vs. 50.6%, respectively, $p = 0.02$) after a mean follow-up of 20 months [9].

Following on from CORE and COPE, the CORP study was a multi-centre controlled randomised trial involving 120

patients with recurrent pericarditis, in which the association of colchicine plus aspirin/non-steroidal anti-inflammatory drugs (NSAIDs) showed a significant reduction in recurrent events at 18 months in comparison with aspirin/NSAIDs alone (relative risk reduction, 0.56 (95% CI, 0.27 to 0.73); NNT = 3) [18]. In addition, colchicine reduced the persistence of symptoms at 72 h (relative risk reduction, 0.56 (CI, 0.27 to 0.74), increased the remission rate at 1 week, and prolonged the time to subsequent recurrence. A total of 120 patients were randomised, 60 to colchicine and 60 to placebo. Baseline characteristics were similar between the two arms. The majority of patients (82%) had idiopathic pericarditis; about 18% had a possible autoimmune cause. Six percent had undergone prior cardiac surgery, 11% prior myocardial infarction, and 9% had been treated with corticosteroids before. Overall adverse effects were similar (7% overall adverse events in both groups), including gastrointestinal (7% vs 5%, colchicine vs placebo, respectively) and hepatotoxicity (0% vs 2%, colchicine vs placebo, respectively). Drug withdrawal rates were similar (8% vs 7%, colchicine vs placebo, respectively) [10, 18].

The results of CORP indicate that low-dose colchicine, in addition to empiric anti-inflammatory therapy, may be safe and efficacious in reducing rates of recurrent pericarditis in patients with mostly idiopathic recurrent pericarditis [10, 18]. It also improves remission rates and hastens symptom resolution. These findings expanded on earlier findings by Imazio in the CORE and COPE trials. Although infrequent, recurrent pericarditis can be quite troublesome and sometimes debilitating. Prior to these trials, treatment options had been limited either by efficacy or side effects. These studies provided robust and consistent results, indicating that colchicine added to conventional anti-inflammatory treatment significantly reduced the rate of subsequent recurrences of pericarditis in patients with the first but also subsequent recurrences. However, further studies were needed to outline whether it could be used as a solitary agent.

In the CORE and CORP trials, the colchicine dose was 1.0–2.0 mg on the 1st day followed by a maintenance dose of 0.5–1.0 mg/day, for 6 months; in the CORP-2 trial, the authors removed the loading dose and introduced the weight-adjusted dose of 0.5 mg twice daily for 6 months for patients weighing > 70 kg or 0.5 mg once daily for patients weighing ≤ 70 kg to improve patient compliance. The authors further concluded that corticosteroid therapy given in the index attack can favour recurrences [9, 10, 18]. Taken together, the findings of these studies suggested that colchicine should be regarded as a first-line treatment for recurrent pericarditis in the absence of contraindications even in patients with multiple recurrences.

The largest and most recent ICAP (Investigation on Colchicine for Acute Pericarditis) trial, published in 2013 was a randomised, double-blind trial comparing the effects of

colchicine versus placebo in patients with a first episode of acute pericarditis [12]. In the ICAP trial, colchicine reduced the risk of recurrent pericarditis at 18 months compared to placebo (16.7% vs. 37.5%, $p < 0.001$ with relative risk reduction of 0.56; and 95% confidence interval (CI), 0.30 to 0.72), NNT of 4. Colchicine also reduced the rate of symptom persistence at 72 h (19.2% vs. 40.0%, $p = 0.001$), the number of recurrences per patient (0.21 vs. 0.52, $p = 0.001$), and the number of hospitalisations (5.0% vs. 14.2%, $p = 0.02$) versus placebo. In the ICAP trial, a loading dose was not given, and dosing was adjusted according to weight (0.5 mg twice daily for 3 months for patients weighing > 70 kg or 0.5 mg once daily for patients weighing ≤ 70 kg) in order to improve patient compliance. The authors found that patients had similar side effects in the colchicine and placebo groups, thus supporting the use of a weight-adjusted maintenance dose without any loading dose [12].

Inflammatory pathobiological pathways in coronary artery disease—the evolving therapeutic role of colchicine

Despite lifestyle changes and risk-factor reduction, patients with chronic coronary disease remain at high risk for acute cardiovascular events [19]. A large body of evidence has demonstrated the role of inflammation in atherosclerosis with recent large trials providing evidence suggesting that interventions to mitigate inflammation may reduce the risk of cardiovascular events [21, 22]. Contemporary use of colchicine is evolving to recognise this central role of inflammation in coronary disease and suggesting promising new indications for the use of colchicine to target the inflammatory mediators of coronary artery disease [20].

Intriguing work with studies from Russell Ross, P Libby and others [21, 22] which showed histopathological and biochemical evidence demonstrating the central role of pro-inflammatory cellular and signalling pathways, not only in development of atherosclerosis but also in the pathophysiology of plaque rupture leading to ACS. Atherosclerosis shares many characteristics of a chronic inflammatory process with this data suggesting that lipoproteins or their derivatives (e.g. oxidised lipoproteins) contribute to smouldering inflammation in atherosclerotic plaques. Moreover, the large clinical data of successful intervention trials with statins demonstrated, in addition to a mortality benefit and marked reduction in LDL cholesterol, a pleiotropic anti-inflammatory effect with these agents. In addition, Ridker and colleagues conducted prospective clinical trials using hsCRP as a biomarker of inflammation and demonstrated significant reductions in hsCRP with statins [23, 24].

The next chapter of this clinical story examines canakinumab, a monoclonal antibody selective for interleukin-1 β .

The Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS trial) demonstrated evidence suggesting that inflammation plays a causal role in the pathogenesis of cardiovascular disease and related complications and, furthermore, that mitigation of inflammatory cytokines by canakinumab may reduce the risk of cardiovascular events [25]. In this study, the investigators randomised 10,061 patients with previous MI and hsCRP ≥ 2 mg/L in a 1:1:1:1.5 ratio to one of three doses of canakinumab or placebo. At a median follow-up of 3.7 years, the 150-mg dose was associated with a 0.6% absolute reduction in the primary end point (composite of MI, stroke or cardiovascular death), which was driven largely by the reduction in the incidence of myocardial infarction [25]. A comparable modest treatment benefit in a secondary end point that additionally included hospitalisation for unstable angina requiring urgent revascularisation was also observed in the 150-mg dose [25]. Treatment with canakinumab resulted in a 15% lower risk of cardiovascular events when compared to placebo in individuals with established atherosclerotic heart disease [25]. In addition, canakinumab reduced hsCRP level from baseline in a dose-dependent manner through 48 months, without reduction in the LDL-C level [25]. However, in a pooled analysis, canakinumab groups were observed to have a 0.13% absolute increase in fatal infection, presumably related to potent immunosuppression [25].

Given the modest effect size, no significant difference in all-cause mortality, increased risk of fatal infection and the high cost associated with biologic treatments, is not surprising that canakinumab never progressed to widespread use for this indication. However, the true benefit of the CANTOS trial is that it was the first of 4 important trials looking at the role of anti-inflammatory therapy in cardiovascular disease and paved the way for further studies looking at the role of colchicine.

In contrast to canakinumab, colchicine is a low-cost, widely available anti-inflammatory medication. With a long track record of safe use among patients with gout and pericarditis, colchicine represents a possible alternative method of achieving modulation of inflammation to reduce cardiovascular events in patients with established atherosclerotic heart disease which is more readily translatable to the clinical practice [7, 19].

Colchicine in acute myocardial infarction

In late 2019, there came fresh interest in colchicine with the publication of the COLchicine Cardiovascular Outcomes Trial (COLCOT) trial in which Tardif and colleagues evaluated the effects of colchicine on cardiovascular outcomes in addition to its long-term safety profile in patients who recently had a myocardial infarction [26]. COLCOT randomised 4745 patients presenting with myocardial infarction

(within 30 days) to colchicine or placebo [26]. Among patients who suffered a recent myocardial infarction, low-dose colchicine 0.5 mg OD was shown to be effective at preventing major adverse cardiovascular events compared with placebo (5.5% in the colchicine group vs 7.1% in the placebo group, hazard ratio, 0.77; 95% confidence interval [CI], 0.61 to 0.96; $P=0.02$) [26]. Benefit was primarily due to a reduction in the incidence of stroke and urgent hospitalisation for unstable angina leading to revascularisation [26]. Furthermore, colchicine appeared to be beneficial among patients with diabetes. The study drug was well tolerated and associated with a similar incidence of infection and diarrhoea compared with placebo [26].

COLCOT looked at the potential for colchicine to limit the inflammatory processes that occur immediately post-acute coronary syndrome [26]. In this trial, colchicine was associated with a 1.6% absolute reduction in the primary composite endpoints [26]. However, short duration of follow-up and only few patients had biomarker testing were limitations of this study. Also, it is worth noting that the pathophysiologic mechanisms of acute coronary syndrome are likely to differ from stable coronary heart disease. However, despite this, the results of COLCOT were encouraging and underscores the evolving data suggesting benefit for colchicine therapy coronary artery disease.

Colchicine in stable coronary artery disease

In 2020, the LoDoCo2 trial was published, which was an investigator-initiated, randomised, controlled, double-blind, event-driven trial of low-dose colchicine (LoDoCo2) to determine whether 0.5 mg of colchicine once daily, as compared with placebo, prevents cardiovascular events in patients with chronic coronary disease [27]. In LoDoCo2, 5522 patients were randomised, 2972 assigned to the colchicine arm and 2740 to the placebo arm. This trial focused on chronic coronary disease as opposed to acute coronary syndromes. This trial was an extension of an earlier trial of low-dose colchicine (the original LoDoCo trial in 532 patients) in 2013 which also showed the risk of acute cardiovascular events was lower among those who received colchicine in patients with chronic coronary disease on optimal medical therapy [28].

LoDoCo2 was an overall positive trial which showed that patients taking colchicine had a decreased risk of the composite endpoint of cardiovascular death, MI, stroke and coronary revascularisation [27]. The primary outcome occurred in 6.8% of the patients in the colchicine arm vs 9.6% of patients in the placebo arm, with a hazard ratio 0.69 and relative risk reduction of 31% [27]. These results with colchicine are consistent with those obtained in the first LoDoCo trial [28] and the COLCOT trial [26] and provide further support for the

potential benefits of anti-inflammatory therapy in patients with coronary disease. The data is summarised in Table 1.

Limitations

Inflammatory biomarker testing

Other relevant prior research includes the 2018 CIRT study, which failed to show a similar benefit with methotrexate and was subsequently stopped early due to lack of efficacy [29, 30]. Specifically, in that trial, methotrexate did not reduce inflammatory biomarkers [29]. At median 2.3 years (after termination of the study early for lack of efficacy), there was no difference in the primary endpoint of nonfatal myocardial infarction, nonfatal stroke, hospitalisation for unstable angina leading to revascularisation, or cardiovascular death [29]. At 8 months, there was no noticeable reduction from baseline in inflammatory markers including C-reactive protein, interleukin-1B or interleukin 6 with methotrexate therapy [29]. There was a modest increase in the incidence of cytopenias, elevated liver function tests and non-basal cell skin cancers in patients randomised to methotrexate [29].

In contrast to CANTOS, enrollment in CIRT did not require a residually elevated C-reactive protein level, and the median level at enrollment was relatively low at 1.6 mg/L [29]; thus, lack of benefit may have been related to enrollment of patients with limited inflammatory activity to target. This led leading authors of CANTOS to conclude that ‘when you reduced inflammation, you had benefit. When you did not, there was no benefit’.

No significant numbers of individuals had inflammatory biomarker testing at baseline and follow-up in either the COLCOT [26] or LoDoCo2 trials [27]. As a result, confirmation of the proposed mechanism of benefit of colchicine (reduction in inflammatory mediators) was not achieved by these studies.

Applicability to clinical practice

The generalisability of the study is another point of concern. In the LoDoCo2 trial, eligible patients entered an open-label run-in phase for 1 month, during which time they received colchicine once daily. At the end of the run-in phase, the patients who were stable, with no side effects and had good adherence were randomly assigned in a 1:1 ratio to receive 0.5 mg of colchicine once daily or matching placebo [27]. The use of a run-in period is not a negative aspect to the study as it increases follow-up and enriches the study for the population cohort who are likely to benefit. But an important point to recognise is that, in the translation of the results to the general population, we are likely to see that there is an

Table 1 A summary of data

	CANTOS	COLCOT	LOCODO1	LOCODO2
Year	2017	2019	2013	2020
Sample size and indication	<i>N</i> = 10,061 1. Canakinumab (<i>n</i> = 6717) 50 mg (<i>n</i> = 2170) 150 mg (<i>n</i> = 2284) 300 mg (<i>n</i> = 2263) 2. Placebo (<i>n</i> = 3,344)	<i>N</i> = 4745 Colchicine 0.5 mg daily (<i>n</i> = 2366) Placebo (<i>n</i> = 2379)	<i>N</i> = 532 Colchicine 0.5MG (<i>n</i> = 282) Control (<i>n</i> = 250)	<i>N</i> = 5522 Randomised in a 1:1 fashion to either colchicine 0.5 mg daily or matching placebo Colchicine 0.5 mg 2762 Placebo 2760
Intervention	Randomised–canakinumab vs placebo Randomised in a 1:1:1:1.5 ratio	Randomised 1:1 to colchicine 0.5 mg daily or placebo	Randomised 1:1 to colchicine 0.5 mg daily or placebo	Open-label run-in phase for 1 month, then randomisation 1:1 ratio
Primary end points	A composite of myocardial infarction, stroke or cardiovascular death	A composite of death from cardiovascular causes, resuscitated cardiac arrest, MI, stroke, or urgent hospitalisation for angina leading to revascularisation	A composite of acute coronary syndrome, non-cardioembolic CVA, or out-of-hospital cardiac arrest	A composite of cardiovascular death, spontaneous (nonprocedural) myocardial infarction, ischemic stroke, or ischemia-driven coronary revascularisation
Results	1. Placebo: 4.50 per 100 person-year 2. Canakinumab 50 mg: 4.11 per 100 person-year, <i>p</i> = 0.30 [<i>></i> threshold <i>p</i> = 0.02115] 3. Canakinumab 150 mg: 3.86 per 100 person-year, <i>p</i> = 0.02075 [<i><</i> threshold <i>p</i> = 0.02115] 4. Canakinumab 300 mg: 3.90 per 100 person-year, <i>p</i> = 0.0314 [<i>></i> threshold <i>p</i> = 0.01058])	131 (5.5%) vs 170 (7.1%), <i>p</i> = 0.02	5.5% vs 16%, <i>p</i> < 0.001	CV death, MI, stroke, ischemia-driven revascularisation, for colchicine vs. placebo, was 9.6% vs 6.8%, <i>p</i> < 0.001

Comparisons are colchicine vs control

underestimation of the prevalence of adverse reactions when compared to the general population.

‘The percentage of women in the trial was lower than would be expected’, the investigators note, ‘given the percentage of women with chronic coronary artery disease in the general population’. The authors have failed to address how this sex imbalance came about and how it should affect the study’s interpretation. The authors agreed this was a concern but did not elaborate on how it affects LoDoCo2’s generalisability. ‘We should go further and dedicate further research towards [women] because it’s an understudied population. So it’s an important question’.

There is a hesitancy to begin acting upon the results of these recent trials which likely comes from the limitations to the above studies. LoCoDo2 did not record blood pressure measurements or lipid levels at baseline or during the trial [27]. The authors note, at baseline, the patients were well treated with respect to chronic coronary disease, with 99.7% taking an antiplatelet agent or an anticoagulant, 96.6% a lipid-lowering agent, 62.1% a beta-blocker and 71.7% an inhibitor of the renin–angiotensin system [27]. However, in the absence of objective lipid levels or blood pressure recordings, we can only infer good risk factor control. There is no provided data on medication compliance prior to enrollment vs increased compliance due to increased engagement with healthcare.

Dosing and biological plausibility

The safety and tolerability of colchicine has been demonstrated in multiple large randomised cardiovascular trials. This evidence is further reflected in the most recent guidelines from the European Society of Cardiology on the management of acute pericarditis which recommends the use of colchicine as first-line therapy to improve the response to medical treatment and prevent recurrences. Colchicine (0.5 mg once daily in patients < 70 kg or 0.5 mg BID in those ≥ 70 kg) is recommended for 3 months as an adjunct to aspirin/NDSAID therapy (class I recommendation–level of evidence A). These dosing recommendations are based on evidence from the ICAP trial [12]. In the ICAP trial, a loading dose was not given, in contrast to the CORE and CORP trials, and dosing was adjusted according to weight (0.5 mg twice daily for 3 months for patients weighing > 70 kg or 0.5 mg once daily for patients weighing ≤ 70 kg) in order to improve patient compliance [9, 10, 12]. The authors found that patients had similar side effects in the colchicine and placebo groups, thus supporting the use of a weight-adjusted maintenance dose without any loading dose. Notably, no study provided data on the burden of adverse events and side effects according to dosing regimen. Adverse events were not further subdivided between the weight adjusted dosing regimens in ICAP [12].

COLCOT and LoCoDo differ from the pericardial disease trials completely by deciding not to use loading doses or weight adjusted dosing, but instead a low dose, once daily maintenance dose of colchicine 0.5 mg [26–28]. This new maintenance dose of colchicine was similarly tolerated and had similar side effect profile and adverse events to the older trials which used loading doses of 1.0–2.0 mg on the 1st day followed by a maintenance dose of 0.5–1.0 mg/day and weight-adjusted dosing (0.5 mg twice daily for 3 months for patients weighing > 70 kg or 0.5 mg once daily for patients weighing ≤ 70 kg). Further evidence is needed to provide clarity of the dosing of colchicine for maximum benefit in secondary prevention, while achieving minimal side effects.

Colchicine is a substrate for both CYP3A4 and the transport protein P-gp. This is of particular importance in the post-MI cohort of patients, for which high-dose statins will be prescribed routinely. Co-administration of colchicine and statins consists of a potentially concerning drug–drug interaction since it provokes myotoxicity, myopathy and various degrees of rhabdomyolysis. Lipophilic statins and colchicine are biotransformed in the liver, primarily via CYP3A4 enzyme system leading to elevated blood levels of both agents and resulting in increased potential for combined myotoxicity. Because of unique physiochemical properties, not all statins have the same drug interaction potential. Statins that undergo phase I metabolism by the CYP3A4 isoenzyme are referred to as statin 3A4 substrates (atorvastatin and simvastatin). Statins that do not use the CYP3A4 isoenzyme metabolic pathway are referred to as statin non-3A4 substrates (pravastatin, fluvastatin, and rosuvastatin). The LoDoCo2 authors note that 94% of patients enrolled were taking a statin. However, this is not subdivided further by metabolic pathway. Dosages, patient compliance and CV-related biomarkers such as lipids were not recorded. Hence, going forward, it would be of great clinical importance not only to increase awareness of this potential complication but also the more advantageous type of statin that we should choose in combination with colchicine.

Colchicine in COVID-19

The evolving evidence on the role of colchicine is not limited to its use in coronary artery disease. The emergence of the COVID-19 pandemic has led to a rapid search by researchers for anti-inflammatory therapy which may help to mitigate the associated ‘cytokine storm’ associated with COVID-19 ARDS. The benefit of dexamethasone in patients with COVID-19 requiring respiratory support [31] shows the importance of inflammation in this patient group. Colchicine has been proposed as a treatment for COVID-19 based on its anti-inflammatory actions [32]. In COVID-19, the degree of inflammasome activation, particularly the nucleotide binding

domain (NOD)-like pyrin domain 3 (NLRP3) inflammasome, correlates with disease severity [33]. Notably, colchicine can block the activation of NACHT-LRRPYD-containing protein 3 (NLRP3) inflammasome, which was demonstrated to be directly induced by the viroporin-E of SARS-CoV [33].

Three small trials that compared colchicine with usual care or placebo in patients hospitalised with COVID-19, emerged early in the pandemic and suggested a potential favourable effect of colchicine on outcome measures of clinical improvement or duration of hospitalisation. A 2-day shorter duration of hospitalisation was reported in a trial of 100 patients with laboratory confirmed SARS-CoV-2 infection and pulmonary involvement who were randomly assigned to receive either hydroxychloroquine plus colchicine or hydroxychloroquine plus placebo [34].

A second trial reported a reduced duration of hospitalisation and oxygen therapy in 36 patients hospitalised with COVID-19 allocated colchicine compared with 36 patients allocated usual care, which included hydroxychloroquine, azithromycin, and methylprednisolone [35].

Finally, the GRECCO-19 trial reported a lower rate of clinical deterioration in 55 patients randomly assigned to receive colchicine compared with 50 patients randomly assigned to receive usual care, which did not include corticosteroids [32]. The total number of patients in all three of these trials combined was 285, with seven deaths during the follow-up period, meaning that these three studies are not able to reliably assess the effects of colchicine on mortality.

In the colchicine in patients admitted to hospital with COVID-19 (RECOVERY) trial, published in 2021, the use of colchicine was not associated with a reduction in mortality, duration of hospitalisation, or the risk of being ventilated or dying for those not on ventilation at baseline [31]. These results were consistent across the prespecified subgroups of age, sex, ethnicity, duration of symptoms before randomisation, level of respiratory support at randomisation, and use of corticosteroids [31]. The RECOVERY trial found no evidence of benefit from colchicine, which suggests that the anti-inflammatory properties of colchicine are either insufficient to produce a meaningful reduction in mortality risk or are not affecting the relevant inflammatory pathways in moderate-to-severe COVID-19. Although most patients in this study received concomitant corticosteroid therapy, there was no evidence that colchicine was beneficial in those patients not receiving a corticosteroid [31]. Recovery had similar limitations to LoDoCo2. Detailed information on laboratory markers of inflammation and immune response and information on radiological features was not collected; therefore, it is not

possible to assess if the effect of treatment varied between such subgroups of patients.

In contrast to earlier small trials, the RECOVERY trial, with more than 11,000 participants and more than 2000 deaths, had sufficient power to detect modest treatment benefits, which were not observed. The RECOVERY trial only studied patients who had been hospitalised with COVID-19; therefore, it was unable to provide any evidence on the safety and efficacy of colchicine used in other patient groups.

Prevention of COVID-19 complications in an outpatient setting ideally requires an orally administered and inexpensive medication targeting the inflammasome with a known favourable safety and tolerability profile. The COLCORONA trial looked at the efficacy of colchicine in non-hospitalised patients with COVID-19 [36]. The authors performed a randomised, double-blind trial involving non-hospitalised patients with COVID-19 diagnosed by polymerase chain reaction (PCR) testing or clinical criteria. The patients were randomly assigned to receive colchicine (0.5 mg twice daily for 3 days and once daily thereafter) or placebo for 27 days. The primary efficacy endpoint was the composite of death or hospitalisation for COVID-19 [36].

The authors included 4488 patients, of the 6000 they had planned to enroll. They conclude that the risk of death or hospitalisation due to COVID-19 infection in the 30 days following randomisation, was lower among the patients who were randomly assigned to receive colchicine than among those who received placebo. However, the primary endpoint was negative, occurring in 4.7% of the colchicine group and 5.8% of the placebo group (OR 0.79; 95.1% CI 0.61 to 1.03; $p=0.08$). Individually, neither mortality (0.2% vs 0.4%; OR 0.56; 95% CI 0.19 to 1.67) nor hospitalisation due to COVID-19 (4.5% vs 5.7%; OR 0.79; 95% CI 0.60 to 1.03) were statistically significant.

The benefits of colchicine appeared to be more marked in patients with diabetes and men [36]. Diabetes is pro-inflammatory state, which might explain the greater risk of complications of COVID-19 in patients afflicted by that disease. Because the event rates were higher in patients with these characteristics, the effect of colchicine might have been more readily detectable.

Finally, the study was stopped early when 75% of the planned patients were recruited and had completed the 30-day follow-up [36]. The authors provide explanation for this, citing the logistical issues of the pandemic and the need to disseminate results quickly in view of the current state of the pandemic. However, this suggests a degree of optimism which could result in an increased likelihood of bias (Table 2).

Table 2 A summary of data pericarditis trials

Year	Setting	Clinical question	Intervention	Colchicine dosing	Favourable results	
COPE	2005	Acute pericarditis	Colchicine Rx the first episode of acute pericarditis?	ASA vs. ASA + colchicine	Loading, then maintenance $\times 3/12$	Colchicine reduced: 1. The recurrence rate compared to aspirin alone (10.7% vs. 32.3% at 18 months; $p=0.004$) 2. Symptom persistence at 72 h (11.7% vs 36.7%; $p=0.003$)
CORE	2005	First recurrence	Colchicine Rx first recurrence of pericarditis?	ASA alone vs. conventional treatment + colchicine**	Loading, then maintenance $\times 6/12$	Colchicine reduced: 1. The recurrence rate at 18 months (24.0% vs 50.6%; $p=0.02$) 2. Symptom persistence at 72 h (10% vs 31%; $p=0.03$)
ICAP	2013	Acute pericarditis	First episode of acute pericarditis, colchicine reduce recurrent pericarditis vs placebo?	Colchicine or placebo + conventional	Weight adjusted	Colchicine reduced: 1. The risk of recurrence at 18 months (16.7% vs 37.5%, $p<0.001$) 2. Symptom persistence at 72 h (19.2% vs. 40.0%, $p=0.001$)
CORP	2011	First recurrence	Colchicine in prevention of recurrent pericarditis	Usual care + placebo or colchicine	Loading, then maintenance $\times 6/12$	Colchicine reduced the recurrence rate at 18 months (24% vs 55%)

Conclusions

Colchicine is clearly efficacious for the treatment and prevention of acute and recurrent pericarditis and represents the cornerstone of therapy of these pericardial diseases. Overall, the studies of colchicine in cardiovascular disease are encouraging and underscore its utility in and repurposing for inflammatory conditions which includes cardiovascular diseases. With current knowledge of inflammatory atherosclerotic mechanisms, there is a rationale to use colchicine to reduce the risk of atherosclerotic vascular disease in select patient groups, along with statins and antiplatelet therapy. However, clarity on who should receive the drug, how, and to what end are all important questions. Writing committees for guidelines will want to select a very particular patient population with evidence base. There is strong evidence supporting the benefit of mitigating the inflammatory axis in coronary artery disease. There are studies for colchicine in recent post-MI patients and now studies in patients with chronic coronary disease, but it is still not clear for which patients colchicine will be beneficial and the timing of initiating treatment. These questions will need to be answered if colchicine were to become part of routine secondary prevention guidelines.

Prior to RECOVERY, no trial had been able to reliably assess the effects of colchicine on COVID-19 mortality. RECOVERY—a large, randomised trial, did not support the

use of colchicine in adults hospitalised with COVID-19 [31], and COLCORONA was stopped before the scheduled sample size had been fully enrolled due to logistical reasons, and the result was not statistically significant [36]. Thus, the role of colchicine in treatment of COVID-19 in patients not requiring hospitalisation remains uncertain. Future trials in this setting are ongoing.

The use of colchicine for cardiovascular disease prevention in selected high-risk patients was briefly discussed in the recent 2021 ESC guidelines on cardiovascular disease prevention in clinical practice [37]. The task force remarked that the results of COLCOT and LoDoCo2 in particular were encouraging, and the results may justify consideration of low-dose colchicine in selected high-risk patients. However, ESC also concluded that further clinical study data and experience in daily practice were needed to establish the use of colchicine in daily practice [37].

Presently, we are at an exciting phase with sufficient short-term evidence of benefits on colchicine and we are looking at the future for long-term data together with associated safety and tolerability information.

Availability of data and material Not applicable.

Code availability Not applicable.

Declarations

Conflict of interest The authors declare no competing interests.

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