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Expanded indications

Colchicine revival?

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Background

Colchicine is an alkaloid extracted from Colchicum plants (*Colchicum autumnale,* Herbstzeitlose). It was first used about 3500 years ago in ancient Egypt and since the 6th century in Europe for the treatment of gout [1]. The pure substance was isolated in the early 19th century and since then has been available for medical use. Today, colchicine plays a role in the treatment of gout, familial Mediterranean fever, pericarditis, Behçet disease and others (table 1). Increasing evidence exists for a potential benefit of colchicine in atherosclerotic coronary disease. Since June 2021 colchicine is officially available in Switzerland (Colctab®) with therapeutic indications for gout, familial Mediterranean fever and pericarditis.

Mechanisms of action

Although different mechanisms of action have been identified, not all pharmacotherapeutic mechanisms of colchicine in divers medical conditions are fully understood. Well investigated mechanisms include tubuline polymerisation and anti-mitotic effects, which directly impact on cells involved in the development and progression of atherosclerosis. These include macrophages, platelets, neutrophils, vascular smooth muscle cells, T cells and endothelial cells.

Colchicine exerts its anti-inflammatory properties by inhibiting secretion of several cytokines and chemokines. An important role involves the caspase-1-mediated modulation of the NLRP3 inflammasome, which has been suggested to be centrally involved in atherosclerotic inflammation [2]. NLRP3 is part of the innate immune system and is present in neutrophils, eosinophils and monocytes. Upon detection of harmful signals it is activated and allows interleukin (IL)-1β and IL18 to mature. In brief, colchicine exerts potential beneficial effects on macrophages and the NLPR3 inflammasome, reduces IL-1β, IL-18, tumour necrosis factor (TNF)-α, IL-6 and selectin expression, impairs platelet-leucocyte interactions and decreases T-cell activation, vascular smooth muscle cell proliferation and circulating pro-inflammatory microRNAs [3]. In addition to or as a sum of all these effects, treatment with colchicine might result in improved endothelial function in patients with stable coronary artery disease [4].

Safety aspects

Typical side effects of colchicine are gastrointestinal effects such as nausea, vomiting or diarrhoea. These symptoms often resolve upon dose reduction or discontinuation of administration. It is of note that the symptoms mostly occur within 24 hours after first administration, dose increase or upon drug interaction. An important issue is the risk of drug-drug interactions with the potential risk of colchicine toxicity. Typical drug interactions occur when P-glycoprotein inhibitors or strong cYP3a4 inhibitors are given.

Commonly used drugs that can increase bioavailability of colchicine are amiodarone, macrolide antibiotics, antimycotics, calcium-channel blockers, ranitidine, human immunodeficiency virus protease inhibitors or ciclosporin. The risk of drug interactions is increased in patients with renal or hepatic impairment.

Colchicine and pericarditis

Colchicine is increasingly used for the treatment of acute and recurrent pericarditis [5]. Pericarditis is an inflammatory pericardial syndrome with or without pericardial effusion. For a clinical diagnosis two of the following four criteria must be present: (1) pericarditic chest pain, (2) pericardial rubs, (3) new widespread STelevation or PR depression, (4) pericardial effusion (new or worsening).

Anti-inflammatory treatment should be initiated with aspirin or a nonsteroidal anti-inflammatory drug (NSAID); colchicine can be added as an adjunct to aspirin/NSAID therapy (class 1, level A). The choice of drug depends on patients‘ comorbidities (e.g., renal impairment, history of gastrointestinal bleeding) and physician expertise.

Several randomised clinical trials over the last two decades have been shown that colchicine treatment in pericarditis is effective and safe and reduces recurrence rates [6–9].

Recommendations for colchicine therapy in acute and recurrent pericarditis is recommended for 3 months at a dose of 2 × 0.5 mg daily (1 × 0.5 mg for patients <70 kg). Treatment duration in recurrent pericarditis can be extended up to 6 months (table 2).

Colchicine and atherosclerotic cardiovascular disease

Chronic inflammation plays a key role in the development and progression of atherosclerosis. However, the use of anti-inflammatory drugs in large randomised trials provided mixed results. The IL-1beta inhibitor Canakinumab led to a significantly lower rate of re-

Table 1: Overview of indications, adverse reactions and contraindications for colchicine use.

	Medical condition
Indication	Gout, familial Mediterranean fever
Off-label indication	acute or recurrent pericarditis, stable ischaemic heart disease, secondary prevention of atherosclerotic cardiovascular events, prevention of postpericardiotomy syndrome, Behçet disease, calcium pyrophosphate crystal arthritis (“pseudogout”), Sweet syndrome (acute febrile neutrophilic dermatosis), vasculitis, cutaneous small-vessel
Adverse reactions	diarrhoea, nausea, vomiting (5–10%); pharingeal/laryngeal pain; leucopenia (<0.1%)
Contraindications	concomitant use of strong cYP3a4 inhibitors, pregnancy, renal or hepatic impairment, no combination with drugs that inhibit P-glycoprotein

current cardiovascular events at the cost of fatal infections, whereas treatment with low-dose methotrexate was not effective [10, 11].

Over recent years, more and more evidence has emerged, that low-dose colchicine (0.5 mg daily) might have beneficial effects in patients with established atherosclerotic cardiovascular disease. There are major trials including more than 10,000 patients with either acute myocardial infarction (COLCOT trial) or chronic coronary disease (LoDoCo, LoDoCo2 trials [12–14]).

COLCOT included 4745 patients who were recruited within 30 days after acute myocardial infarction and investigated the impact of low-dose colchicine at a daily dose of 0.5 mg on a combined endpoint of cardiovascular death, resuscitated cardiac arrest, myocardial infarction, stroke, or urgent hospitalisation for angina leading to coronary revascularisation. Compared with placebo, low-dose colchicine led to significantly less ischaemic cardiovascular events. These events were mainly driven by reduction of stroke and unstable angina. Most common adverse events were diarrhoea and nausea with comparable event rates for colchicine and placebo. However, there were more infections in the colchicine group.

LoDoCo and LoDoCo2 included patients with stable coronary artery disease. Endpoints were a composite of death from cardiovascular causes, resuscitated cardiac arrest, myocardial infarction, stroke, or urgent hospitalisation for angina leading to coronary revascularisation in LoDoCo and a composite of cardiovascular death, spontaneous myocardial infarction, or ischaemic stroke in LoDoCo2. Again, low-dose colchicine at a dose of 0.5 mg daily reduced the risk for cardiovascular events significantly. The efficacy of colchicine in patients with chronic coronary disease enrolled in the LoDoCo2 trial was independent of history and timing of prior acute coronary syndrome. However, this study observed a trend towards increased non-cardiovascular mortality, which requires further attention. Interestingly, reduction of cardiovascular events with colchicine might be independent of reduction of high-sensitivity C-reactive protein (CRP) levels. Therefore, systematic monitoring of inflammation parameters is not required during treatment with colchicine, whereas renal function should be assessed at least in patients with decreased renal function.

Overall, these are impressive data with a 23% and 31% cardiovascular risk reduction in patients with acute and stable coronary artery disease and established secondary prevention therapies. The magnitude of benefit of low-dose colchicine in COLCOT and LoDoCo2 is consistent with data from previous trials of secondary prevention therapies, such as lipid-lowering, blood pressure-lowering, and antithrombotic therapies [15– 17]. Based on the results of COLCOT and LoDoCo2, the most recent 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice state that "the encouraging results justify consideration of low-dose colchicine in selected, high-risk patients" with a class IIb recommendation [18] (table 3)

Table 2: Treatment of acute and recurrent pericarditis.

Drug	Acute pericarditis	Recurrent pericarditis
aspirin	750–1000 mg every 8 hours (1–2 weeks)	500–1000 mg every 6–8 hours (weeks – months)
ibuprofen	600 mg every 8 hours(1–2 weeks)	600 mg every 8 hours (weeks – months)
indomethacin	–	25–50 mg every 8 hours (weeks– months)
colchicine	0.5 mg twice daily (0.5 mg daily in patients <70 kg or intolerant of higher dose) (3 months)	0.5 mg twice daily (0.5 mg daily in patients <70 kg or intolerant of higher dose) (3–6 months)

Table 3: Recommendation for anti-inflammatory therapy [18].

Recommendation	Class	Level
low-dose colchicine (0.5 mg o.d.) may be considered in secondary prevention of cvd, particularly if other risk factors are insufficiently controlled or if recurrent cvd events occur under optimal therapy	iib	a

Colchicine and COVID-19

Inflammation plays a central role in severe COVID-19 [19]. Higher levels of inflammation markers, such as CRP, ferritin and IL-6 are associated with poor outcome in patients with severe COVID-19. In particular, activity of the inflammasome NLPR3 correlates with the severity of COVID-19 [20]. Since anti-inflammatory treatment with corticosteroids or IL-6 inhibitors showed clinical benefits [21, 22], the role of colchicine for the treatment of COVID-19 has been proposed and investigated in two large-scale randomised trials. The RECOVERY trial recruited 19,423 patients hospitalised for COVID-19 [23]. Patients were treated with 0.5 mg colchicine twice daily for 10 days or until discharge. However, during the 28-day follow up no reductions in mortality, duration of hospital stay, or risk of progressing to invasive mechanical ventilation or death was observed for patients treated with colchicine. The COLCORONA trial enrolled 4488 community-treated COVID-19 patients not being hospitalised [24]. In this trial, in patients with polymerase chain-reaction (PCR)-confirmed COVID-19 colchicine reduced the primary endpoint of death or hospital admission due to COVID-19 infection significantly, which was not the case in the whole population. This discrepancy could be explained by the lower event rate of patients included without PCR test.

In view of these mixed results, colchicine is not recommended for the treatment of patients with severe COVID-19.

Colchicine outlook

There are multiple ongoing trials to investigate the role of colchicine in acute coronary syndromes, in particular in patients undergoing coronary angiography and stenting (CLEAR SYNERGY; COLCARDIO-ACS) as well as in patients with transient ischaemic attack / stroke (CONVINCE; CASPER). All trials will use colchicine at a daily dose of 0.5 mg. Since the role of reduction of inflammation markers in the beneficial effects of colchicine remains unclear, CASPER and COLCARDIO-ACS will include patients with elevated high-sensitivity CRP >2 mg/l with a treatment duration of 1 year and 3 years, respectively. The goal of further research should be to elucidate mechanisms and identify subgroups of patients who might have the largest benefit from colchicine treatment.

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References

The full list of references is included in the online version of the article at https://cardiovascmed.ch/article/doi/CVM.2023.02220.