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Colchicine and myocardial infarction: A review

Colchicine et infarctus du myocarde : revue

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KEYWORDS
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Summary The inflammatory response is frequent after acute myocardial infarction, and may worsen ischaemia-reperfusion injuries, leading to increased infarct size and poor prognosis. Therefore, inflammation may be a promising therapeutic target, and anti-inflammatory drugs appear to be potential additional treatments in this context. Among these treatments, colchicine — a well-known drug that has been used for centuries in clinical practice for rheumatism — may represent the ideal candidate. Indeed, colchicine exerts direct anti-inflammatory and pleiotropic effects, with potential anti-arrhythmic, anti-fibrotic and anti-atherosclerotic effects, which are particularly interesting in this population of patients. The effects of colchicine in the context of acute myocardial infarction were first studied in preclinical models, with a decrease in inflammation demonstrated in several in vitro and in vivo models. Moreover, a decrease in infarct size and positive effects on haemodynamic variables were also recently demonstrated in a mouse model. Regarding clinical studies, the positive effect of colchicine in stable coronary disease and atherosclerosis was assessed initially. More recently, the value of colchicine in acute myocardial infarction has been studied, showing a positive effect on inflammation and infarct size reduction. Finally, a randomised trial (the COLCOT study) has shown a reduction in outcomes in patients with acute coronary syndrome treated with colchicine.
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Abbreviations: AMI, acute myocardial infarction; CRP, C-reactive protein; MCP-1, monocyte chemoattractant protein-1.

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MOTS CLÉS
Infarctus du myocarde ;
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Inflammation ;
Cardioprotection

Résumé La réponse inflammatoire est fréquente après un infarctus du myocarde (IDM) et peut aggraver les lésions d'ischémie-reperfusion, entraînant une augmentation de la taille de l'infarctus, de mauvais pronostic. Par conséquent, l'inflammation peut représenter une cible thérapeutique prometteuse et les médicaments anti-inflammatoires apparaissent comme un traitement supplémentaire potentiel dans ce contexte. Parmi ces traitements, la colchicine, un médicament bien connu et utilisé depuis des siècles en pratique clinique dans le cadre des pathologies rhumatismales, pourrait représenter le candidat idéal. En effet, la colchicine exerce des effets anti-inflammatoires directs et des effets pléiotropes avec en particulier des effets anti-arythmiques, anti-fibrotiques et anti-athérosclérotiques potentiels, particulièrement intéressants dans cette population de patients. Les effets de la colchicine dans le contexte de l'IDM ont d'abord été étudiés dans des modèles précliniques, avec une diminution de l'inflammation démontrée dans plusieurs modèles in vitro et in vivo. De plus, une diminution de la taille de l'infarctus ainsi que des effets positifs sur les paramètres hémodynamiques ont également été récemment mis en évidence dans un modèle murin. En ce qui concerne les études cliniques, un effet bénéfique de la colchicine dans la maladie coronaire stable et l'athérosclérose a été démontré dans un premier temps. Plus récemment, l'intérêt de la colchicine dans l'IDM a été étudié, montrant un effet positif sur l'inflammation et la réduction de la taille de l'infarctus. Enfin, un essai randomisé, l'étude COLCOT, a montré une diminution des évènements chez les patients atteints de syndrome coronarien aigu traités par la colchicine.

Background

Inflammatory response is common after acute myocardial infarction (AMI). The massive and rapid loss of myocardial muscle through cellular necrosis, apoptosis and autophagy activates an intense inflammatory response [1], with inflammation developing as a result of recruitment of inflammatory cells and induction of expression of pro-inflammatory cytokines and chemokines [1,2]. The most common circulating biomarker used in clinics is C-reactive protein (CRP), with a peak frequently observed around day 3 after the AMI [1,3]. In the context of AMI, inflammation is deeply involved in the pathophysiology of ischaemia-reperfusion lesions and fibrosis. As previously described, inflammation exerts a deleterious effect at the onset of reperfusion. Inflammation contributes to infarct size and the cardiac remodelling process, leading to heart failure. Inflammation status is a major predictor of adverse events after AMI [2—4]. Therefore, inflammation appears to be a promising therapeutic target in patients with AMI. Several anti-inflammatory therapies seem to be potential candidates, but have been poorly studied in this context until now [5].

Among these appealing candidates, colchicine is an interesting therapeutic option in AMI. This molecule exerts various anti-inflammatory effects, through inhibition of neutrophil chemo-attraction, the inflammasome network and pro-inflammatory cytokines [6]. Indeed, colchicine, which has been used for centuries in the treatment of rheumatic disease, is one of the oldest drugs still available, and is well tolerated [6]. Furthermore, colchicine has been shown to exert anti-atherosclerotic actions, and has been proposed to reduce inflammation in patients with stable coronary disease [6—8].

This translational review offers an overview of the mechanisms of action of colchicine, the basic science underlying its effects on AMI and clinical evidence for its role as a therapeutic option in AMI.

Colchicine: Mechanisms of action

Colchicine, extracted from Colchicum plants, is one of the oldest drugs currently used — mainly in rheumatic disease [6,8,9]. The active chemical compound was isolated in 1820 [10]. The pleiotropic effect of this alkaloid is related to its capacity to bind to tubulins and disturb microtubule polymerisation. In fact, colchicine destabilises the cytoskeleton and all the cellular processes requiring dynamic $\alpha\beta$-tubulin heterodimer polymerisation [6,9,11—13], including cell division, migration and cell shape, intracellular protein trafficking and secretion, ionic homeostasis and organelle organisation. Colchicine binds to soluble tubulins and, according to the dose, may either prevent microtubule elongation or, at higher doses, induce microtubule depolymerisation. Among its pleiotropic effects, colchicine affects the immune system and has anti-inflammatory properties. Colchicine downregulates multiple inflammatory pathways, leading to a decrease in neutrophil function and migration through the vascular endothelium by tubulin disruption [13]. Moreover, colchicine inhibits the NLRP-3 inflammasome by reducing cleavage of prointerleukin-1β to active interleukin-1β [13,14]. Similarly, pro-inflammatory cytokines and expression of adhesion molecules are potential targets for colchicine, preventing both local chemo-attraction of inflammatory cells and systemic inflammation [11—14]. In a previous study, a systemic anti-inflammatory effect, characterised by a decrease in cytokines, such as interleukin-6

and monocyte chemoattractant protein-1 (MCP-1), was described as being implicated in the post-ischaemic inflammatory response [15]. Among these cytokines, MCP-1 plays a major role in leukocyte recruitment, angiogenesis, inflammation activation and resolution. An antibody against MCP-1 was shown to reduce infarct size in a rat model of myocardial infarction, through a decrease in adhesion molecule expression and myocardial infiltration by macrophages [16]. Similarly, gene therapy targeting MCP-1 showed a positive effect on left ventricular dilatation in a murine model of myocardial infarction, suggesting an important role for this cytokine in this context [17].

Colchicine therapy reduces the local production of coronary chemokines, such as MCP-1 [18], and the secretion of tumour necrosis factor-α by macrophages. In addition, its inhibitory action on the Ras homologue family member A (RhoA) signalling cascade has been shown to reduce the release of interleukin-1β by macrophages and myofibroblast differentiation [19,20]. In addition to inhibition of the transforming growth factor-β signalling pathway, colchicine may also exert some anti-fibrotic effects [21,22]. Inflammation pathways in atherosclerosis are presented in Fig. 1 and Fig. 2, and the potential effects of colchicine on these pathways are presented in the Central illustration. Taken altogether, these mechanisms of action and pleiotropic effects of colchicine have a positive effect at the cellular level that may be protective in the context of AMI.

Colchicine and AMI in preclinical models

Anti-atherosclerotic effect through inflammation

Since 1990, many experiments in vitro and in vivo have been designed to assess the potential anti-atherosclerotic effect of colchicine therapy. Colchicine was able to decrease the migratory and proliferative activities of smooth muscle cells in atherosclerotic plaques. These effects were associated with a decrease in L-selectin expression on neutrophils, and a reduction in CRP and lipoprotein-associated phospholipase A2 (Lp-PLA2) concentrations. In a high-fat diet rabbit model, the anti-inflammatory effect of colchicine led to a decrease in aortic plaque burden associated with lower concentrations of plasma fibrinogen [23]. In addition, in an atherogenic mouse model, colchicine treatment was associated with an increase in nitric oxide production [24].

Colchicine effects on the ischaemic myocardium

On the other hand, colchicine may exert pleiotropic non-inflammatory effects that are particularly interesting in AMI, and several animal studies have been designed to evaluate the cardioprotective effect of low doses of colchicine. Colchicine treatment has been found to inhibit cardiac apoptosis [25] and ventricular hypertrophy [26] and exert anti-fibrotic effects [27] via remodelling of the microtubule cytoskeleton and/or by a direct anti-inflammatory effect. Moreover, colchicine was shown to exert anti-arrhythmic effects at the cellular level by reducing fibrosis in the left atrium in a rabbit model of heart failure [28]. These results suggest that colchicine could be a potential therapeutic strategy to treat the acute and chronic consequences of myocardial infarction. More recently, in a rat model of ischaemia reperfusion, Bakhta et al. elegantly observed that a short colchicine pre-treatment course decreased reperfusion injuries by limiting interleukin-1β-induced inflammatory injury and local anti-fibrotic effects [29]. Furthermore, a single dose of intravenous colchicine (0.4 mg/kg) during ischaemia was able to reduce infarct size and the circulating T troponin concentration 24 hours after ischaemia-reperfusion, reflecting a reduction in myocardial injury. In addition to an acute cardioprotective effect, colchicine also exerts long-term potential positive effects on cardiac haemodynamics, with an increase in the aortic velocity time-integral (reflecting cardiac output) seen on echocardiography realized 8 weeks after an AMI [15]. Moreover, after permanent occlusion of the left anterior descending coronary artery, colchicine improved adverse cardiac remodelling, heart failure development and survival during the MI recovery phase by inhibiting acute inflammation and NLRP3 inflammasome activation [30]. Studies using colchicine treatment in large animal models of heart failure are sparse. In a dog model subjected to a 120-minute coronary artery occlusion followed by a 6-hour reperfusion [31], the intravenous injection of colchicine reduced post-ischaemic myocardial neutrophil accumulation, but no myocardial protection could be detected in terms of infarct size.

In summary, numerous studies in vitro and in vivo have described the beneficial effect of colchicine administration on atherosclerosis and after myocardial injury. Colchicine was mostly associated with a reduction in infarct size and better cardiac function in the acute and chronic phase after an AMI. These cardioprotective effects are probably linked to limitation of systemic inflammation via the inhibition of the inflammasome network that is implicated during the acute phase of MI. More importantly, colchicine improves long-term cardiac remodelling, with improved haemodynamic variables and reduced myocardial fibrosis. Thus, colchicine appears to be a promising new therapeutic strategy for chronic ischaemic heart failure in preclinical models.

Colchicine and AMI in clinical practice

Inflammation is deeply involved in each step of coronary artery disease, with a continuum between atherosclerosis and acute ischaemic events. Indeed, progression of atherosclerosis and acute thrombotic complications leading to AMI (plaque rupture) are driven by inflammation [32]. Thus, through common anti-inflammatory pathways, colchicine may have a positive effect on both atherosclerosis and the ischaemic myocardium.

Anti-atherosclerotic effect through inflammation

The potential effect of anti-inflammatory drugs in coronary artery disease has been advocated for decades. In 1992, Chaldakov first suggested conducting a study of

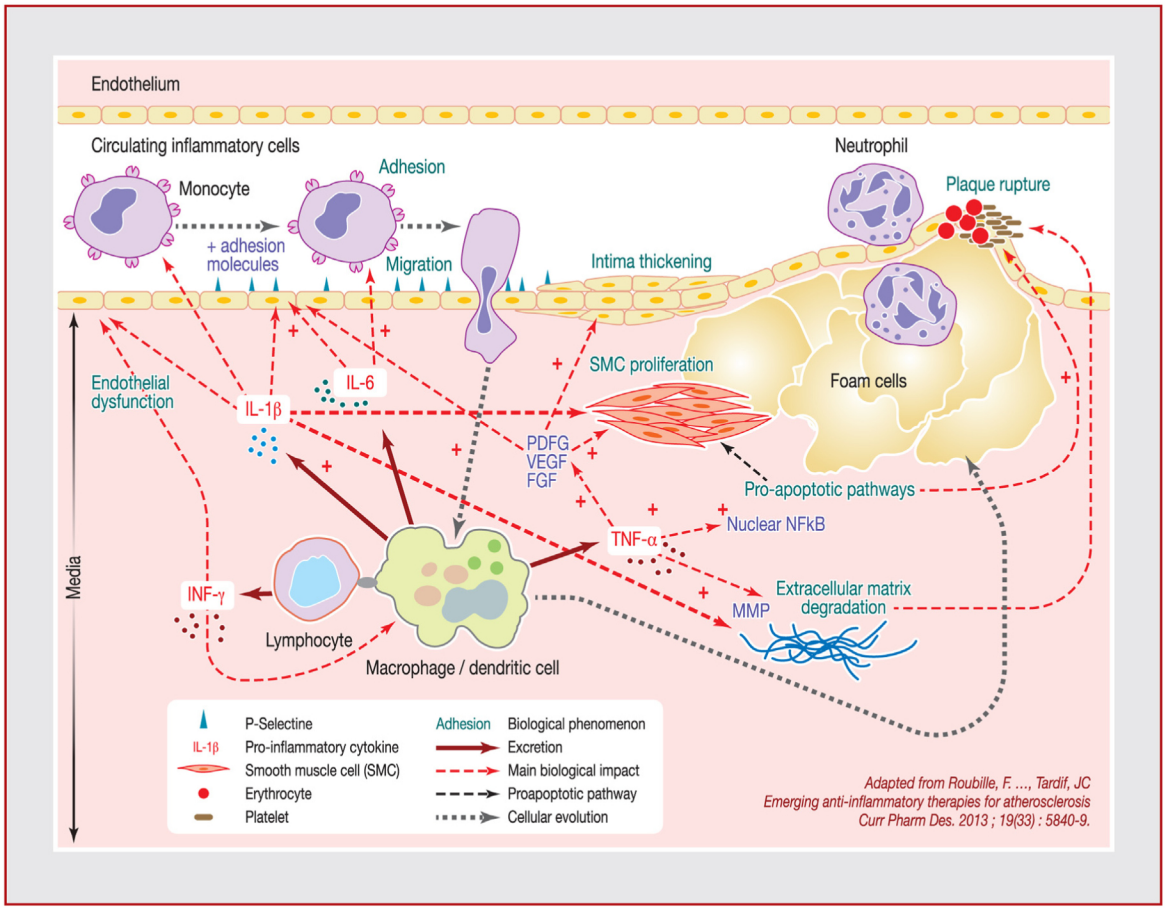

Figure 1. Potential pathways involved in atherosclerosis: inflammation, endothelial dysfunction and extracellular matrix remodelling. FGF: fibroblast growth factor; IL: interleukin; INF: interferon; MMP: matrix metalloproteinase; NF: nuclear factor; PDGF: platelet-derived growth factor; SMC: smooth muscle cells; TNF: tumour necrosis factor; VEGF: vascular endothelial growth factor. Adapted from [42].

anti-inflammatory drugs, including colchicine, in patients with angina and AMI [5]. First, colchicine showed efficiency in pericarditis and Dressler syndrome [33]. A positive effect on cardiovascular events in patients treated with colchicine for gout was suggested for the first time in 2007 [34], and has been supported by several meta-analyses and reviews [4,6,7]. The first randomised study of the effect of colchicine in stable coronary disease was the ''Low-Dose Colchicine for Secondary Prevention of Cardiovascular Disease'' (LoDoCo) study, which included 532 patients with stable coronary artery disease who received colchicine (0.5 mg twice daily) or placebo. This study showed the efficacy of colchicine in terms of incidence of acute coronary syndrome, out-of-hospital cardiac arrest and non-cardioembolic ischaemic stroke (hazard ratio 0.33, 95% confidence interval 0.18—0.59; $P < 0.001$) [35]. In this study, the mechanism that might explain the positive effect of colchicine was inhibition of neutrophil function, a well-known factor in plaque instability.

Colchicine effects on the ischaemic myocardium

Based on the promising results from the basic science [15,29,31], data from the literature on the effect of colchicine in patients with AMI are emerging. An observational study suggested a positive effect of colchicine on plaque stabilisation evaluated by coronary computed tomography angiography after acute coronary syndrome [36]. The first randomised study was conducted by Raju et al., and included 80 patients with acute coronary syndrome or stroke treated with colchicine or placebo for 30 days [37]. This pilot study failed to demonstrate a reduction in systemic inflammation assessed by CRP at 30 days. More recently, Deftereos et al. conducted a prospective randomised study that included 151 patients admitted for ST-segment elevation myocardial infarction, 77 of whom were treated with colchicine [38]. In this study, colchicine was administrated in the catheterisation laboratory just before the reperfusion (2 mg loading dose), and was continued for 5 days. The authors demonstrated that colchicine significantly reduced infarct size assessed by reduction in creatine kinase area under the curve and cardiac magnetic resonance imaging. This effect on infarct size was accompanied by a decrease in neutrophil count and CRP, which are indicators of inflammation. Therefore, this study demonstrated, for the first time, a reduction in infarct size via the anti-inflammatory effect of colchicine in AMI. The second study — the ''Interest of Colchicine in the Treatment of Patients with Acute Myocardial Infarction and with Inflammatory Response'' (COLIN) study — was conducted in

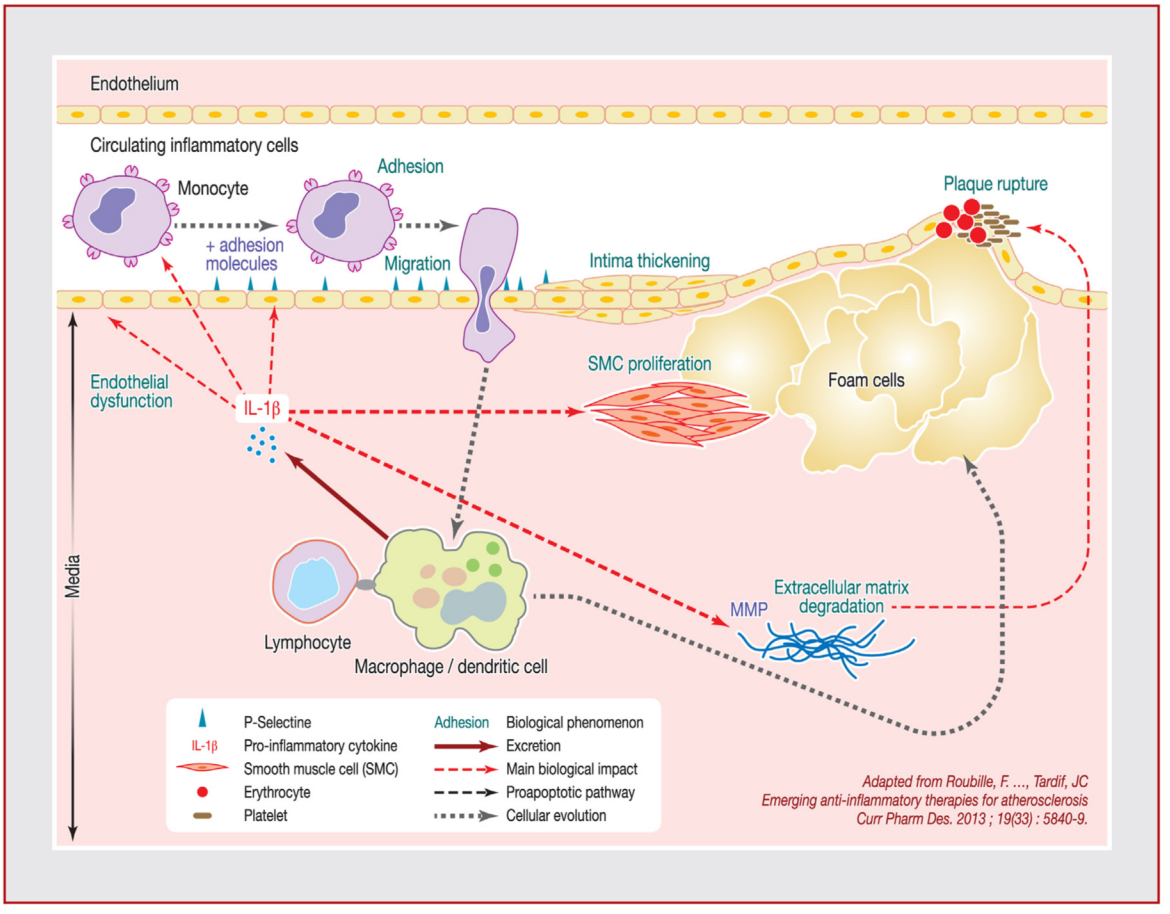

Figure 2. Potential pathways involved in atherosclerosis: inflammation, endothelial dysfunction and extracellular matrix remodelling, with a focus on interleukin-1β (IL-1β). MMP: matrix metalloproteinase; SMC: smooth muscle cells. Adapted from [42].

France, and included 44 patients referred for ST-segment elevation myocardial infarction and undergoing primary percutaneous intervention [39]. Patients were randomised to receive colchicine (1 mg) for 1 month plus optimal medical treatment or optimal medical treatment alone. The primary endpoint was CRP peak, reflecting the maximal inflammation. No difference in CRP peak was highlighted in this study. The lack of effect of colchicine in this study may be explained by the late administration of colchicine in the intensive care unit, after reperfusion and without a loading dose. More recently, the ''Low-Dose Colchicine after Myocardial Infarction'' (LoDoCo-MI) study evaluated the effect of 1 month of treatment with low-dose colchicine (0.5 mg daily) versus placebo on residual inflammation, assessed by CRP in 237 patients, 30 days after an AMI [40]. Despite a trend in favour of a lower CRP concentration in the colchicine group, CRP concentrations were not significantly different between the groups. These negative results may suggest that the treatment should be given at the onset of reperfusion, as soon as possible, to optimise its action and reduce reperfusion injuries associated with inflammation burden. More recently, the results of the ''Colchicine Cardiovascular Outcomes Trial'' (COLCOT), an international randomised trial that included 4745 patients who received colchicine (0.5 mg per day) or placebo after AMI, have been published. The primary endpoint was a composite criterion of cardiovascular death, resuscitated cardiac arrest, acute myocardial infarction, stroke or hospitalisation for angina requiring coronary revascularisation [41]. In this study, treatment with colchicine within the 30 days after an AMI decreased the risk of cardiovascular ischaemic events.

Several ongoing randomised trials are investigating the effect of colchicine in patients with AMI; the main characteristics of these trials are presented in Table 1. Likewise, the ''Colchicine for Left Ventricular Remodelling Treatment in Acute Myocardial Infarction'' (COVERT-MI) randomised trial is currently recruiting patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. The estimated enrolment is 194 patients, randomised to receive colchicine (loading dose of 2 mg at the time of revascularisation, followed by 0.5 mg daily for 5 days) versus placebo. The primary endpoint is left ventricular remodelling measured by magnetic resonance imaging.

Adverse events with colchicine

Colchicine, which has been used for centuries in clinical practice, is one of the oldest drugs still available, and is well tolerated. Gastrointestinal discomfort is the main adverse outcome. In the COLCOT trial, which included patients within 30 days after an AMI, diarrhoea was reported in

Table 1 Ongoing trials evaluating colchicine in acute myocardial infarction.

Study name (country)	Objective	Primary endpoint(s)	Patients	Primary completion date	NCT
COVERT-MI (France)	To evaluate adverse LV remodelling, infarct size and microvascular obstruction reduction with colchicine in patients with AMI undergoing PCI	Percentage increase in LVEDV measured by MRI	194	2022	NCT03156816
CLEAR SYNERGY (Canada)	To evaluate the effect of treatments (colchicine and spironolactone), after PCI for AMI, on the culprit artery (PCI with SYNERGY™ Stent) and non-culprit arteries	MACE for SYNERGY™ Stent (composite of death, recurrent target vessel MI, stroke or ischaemia-driven target vessel revascularisation); first occurrence of CV death, recurrent AMI or stroke in the colchicine comparison within 2 years; first occurrence of CV death or new or worsening HF in the spironolactone comparison within 2 years	4000	2021	NCT03048825
CLEAR SYNERGY Neutrophil Substudy (Canada)	To assess the effect of colchicine on neutrophil activation in AMI, and the clinical and genetic factors that determine heterogeneity of response to colchicine; and to explore a risk score, including markers of neutrophil activity associated with MACE, over 3 years after AMI	Change in soluble L-selectin between baseline and 3 months after AMI in the placebo versus colchicine groups	670	2021	NCT03874338

Three recruiting ongoing studies were registered on ''ClinicalTrials.gov'' on April 2020; studies were discarded if withdrawn ($n = 2$), not yet recruiting ($n = 2$), completed ($n = 2$) or if the status was unknown ($n = 2$). AMI: acute myocardial infarction; CV: cardiovascular; HF: heart failure; LV: left ventricular; LVEDV: left ventricular end-diastolic volume; MACE: major adverse cardiac events; MI: myocardial infarction; MRI: magnetic resonance imaging; PCI: percutaneous coronary intervention.

around 10% of patients in the colchicine group, without significant difference compared with the placebo group. A rare, but significantly higher incidence of pneumonia was reported as a serious adverse event in 0.9% of patients in the colchicine group [41]. In the literature, colchicine treatment discontinuation has been reported in 10% of individuals [32].

To summarise, few data are available in the literature on the effect of colchicine in the AMI context in clinical practice. This drug has demonstrated a positive effect on infarct size and inflammation, without clear data on clinical outcomes. Ongoing studies should add valuable information in this setting.

Conclusions

Colchicine is a well-known drug, which has been used for centuries in inflammatory disease, and has various anti-inflammatory effects. Colchicine has demonstrated efficacy in terms of cardioprotection at the cellular level and in several animal models. Recently, data from the literature have

suggested a positive effect of colchicine in clinical practice, reducing inflammation in the context of AMI as well as infarct size. However, the clinical impact of colchicine was unknown until now. Ongoing randomised studies should provide a concrete response to this unresolved question.

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None.

Disclosure of interest

The authors declare that they have no competing interest.

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