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Colchicine: protection of the brain beyond the heart?

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1. Introduction

A large body of evidence has demonstrated the crucial role of inflammation in atherosclerosis [1]. Many drugs failed to prove any effect on cardiovascular mortality, while low dose colchicine successfully reduced cardiovascular events in stable coronary disease [2,3]. The 2021 guidelines for cardiovascular prevention included low-dose colchicine as a potential tool for patients at high risk of recurrent events despite maximum tolerated conventional treatments [4]. This editorial highlights the impact of colchicine on stroke prevention in previous trials.

Colchicine is an alkaloid extracted from plants colchicum (Autumn Crocus). Its use has been well documented for gout, familial Mediterranean fever, and pericarditis. The primary mechanism of action of colchicine is tubulin disruption leading to the downregulation of multiple inflammatory pathways as the reduction in neutrophils functions and migration through vascular endothelium. Colchicine has a modest effect on NLRP-3 inflammasome. Attenuation of the NLRP3 inflammasome pathway is supported by a reduction of interleukin-18, interleukin-1 receptor antagonist, and interleukin-6 [5].

2. Colchicine and secondary risk prevention: what is known

The COLCOT (Colchicine Cardiovascular Outcome Trial) and LoDoCo2 (Low-Dose Colchicine 2) trials showed a benefit of low-dose colchicine (0.5 mg per day) started respectively in the month following myocardial infarction or in patients with chronic coronary disease after at least 6 months of a clinically stable condition [2,3]. In the COLCOT trial [3], the primary end point was composite including resuscitated cardiac arrest, myocardial infarction (MI), stroke, or urgent hospitalization for angina requiring coronary revascularization. By far, the most important risk reduction was for stroke (HR 0.26 (95% confidence interval [CI], 0.10–0.70)), whereas MI was not significantly reduced by colchicine (HR = 0.91 (95% CI, 0.68–1.21)). Consistently, the LoDoCo2 trial [2] demonstrated a hazard reduction of stroke of 0.66 (0.35–1.25) $p = 0.20$, but without statistically significant difference.

Such a suspected large reduction in stroke was unexpected, but underlying mechanisms remain unclear.

3. Colchicine and stroke: what could be the link?

Colchicine has been shown to reduce the risk of atherothrombosis of large vessel (including intra or extracranial vessels). As well, colchicine has been shown to reduce the risk of atrial fibrillation (AF) in several conditions.

First, in preclinical studies, colchicine has been shown to reduce the NLRP3 inflammasome, while NLRP3 has been shown to play a role in the pathogenesis of AF [6]. In clinical studies, the postoperative period was mainly investigated in cardiac surgery. Shortly a/ post-operative period is

associated with high levels of inflammatory cytokines (IL-1 β , IL-6, CRP), b/ inflammation is statistically associated with the onset of AF in cardiac surgery [7], c/ higher the rate of inflammatory markers was, higher the risk of AF [8]. In a sub-study of the COPPS trial, colchicine reduced the incidence of postoperative AF at 30 days compared to placebo (12% vs. 22%, P = 0.021) [7].

There, after an acute MI, AF (whether it is a recent or preexisting AF) is associated with a worse prognosis and increased mortality [9]. Post AMI AF is frequent (up to 11%) after ACS [10]. Importantly, recent onset AF (even in case of transient AF) was associated with ischemic stroke [11]. To explain the mechanisms of recent onset AF after an AMI is challenging because of multifactorial etiologies. Acute ischemia, atrial volume overload, mitral valve leakage, acute inflammation are overlapping and deeply involved in AF settings [12]. Consistently, the most severe patients with the most altered LVEF, and higher rates of CRP because of large infarction, are the most concerned by AF after AMI. Taken all these observations together, we hypothesize that colchicine could decrease inflammatory process, reduce atrial remodeling, and prevent post AMI AF in these patients, then reducing the embolic risk.

In addition, colchicine could also interfere with the coagulation processes. With supratherapeutic concentrations, colchicine has been shown to turn normal discoid platelets to rounded, inhibiting their activation, reduction in vitro platelet aggregation [13]. In therapeutic concentrations, while colchicine was not associated to reduce platelet to platelet aggregation, it inhibits NETOSIS after AMI [14], reducing the neutrophil to platelet aggregation. Inhibiting the NET formation, colchicine reduces microvascular obstruction via pro-inflammatory and prothrombotic pathways.

Altogether, this paves the way for colchicine in preventing stroke in high-risk patients.

Until now, there are only few studies registered. There are only three studies registered on the clinicaltrials.gov website with the terms 'colchicine and stroke' (2 September 2021). Among them, two are preliminary investigations and the third one is the colchicine for Prevention of Vascular Inflammation in Non-cardio Embolic Stroke CONVINCENCE trial (NCT02898610). This trial will evaluate the use of colchicine in adults over 40 years of age who have suffered an ischemic stroke not caused by cardiac embolism and compare low dose colchicine to placebo.

One other hypothesis was a possible prevention of large thrombus burdens by reducing the size of MI infarction and improving LVEF, not observed in the very recent COVERT-MI trial [15].

4. Colchicine in acute phase after AMI: the first fail of colchicine?

Indeed, the COVERT-MI trial failed to demonstrated any effect of colchicine in the acute phase of AMI, based on MRI measurements. The protocol was a short-term high-dose oral colchicine treatment given as soon as possible after reperfusion in STEMI patients. This suggests that the mechanisms to prevent infarcts may be completely different to modifying them after they have occurred, not obviously explained by the colchicine dose.

5. Colchicine and cardiac denervation prevention: next step to cross?

This is the golden age of anti-inflammatory therapies in myocardial infarction and atherosclerosis. Despite recent failure, the full potential of colchicine may not have been considered. We recently performed a pre-clinical study of acute myocardial infarction in mice treated with colchicine or Saline injection. ECG monitoring, immunofluorescence histology, and NGF sanguine measuring were performed. Here was demonstrated that colchicine improved heart rate variability, reduces cardiac denervation [16]. Based on this novel paradigm, the COLD-MI trial will evaluate cardiac innervation in patients after AMI using the well-known myocardial 123I-MIBG SPECT. According to the present proof of concept study, COLD-MI may thus open important understanding in the cardioprotective effects of

colchicine.

6. Conclusion

Protecting the heart is the first step to keep our patients alive. Protecting the brain is the ultimate step in leading them to recovery. Interestingly, colchicine appears as a promising tool for both targets and the previous large trials suggested that. The ultimate step would be to demonstrate the impact of colchicine in a high-risk population before any cardiovascular event.

Conflict of interest

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