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Colchicine in Acute Myocardial Infarction: "Teaching New Tricks to an Old Dog"

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Editorial

Drug development is often not as linear as one would think. Repurposing of drugs for new uses is now common [1]. This is certainly the case of colchicine. Colchicine is one of the oldest anti-inflammatory drugs [2]. Colchicine was historically used as an unapproved drug to treat Mediterranean fever. In 2009, following compelling evidence *in vitro* and *in vitro* of the ability of colchicine to inhibit the assembly and activation of the NACHT-LRRPYD-containing protein 3 (NALP3 or NLRP3 [Nod-like receptor 3]) inflammasome in response to monosodium urate crystals, the United States Food and Drug Administration approved Colcrys™ for the treatment of Mediterranean fever and acute gouty arthritis [3].

The novel understanding of the mechanism of action of colchicine has opened the way to new investigation in the field of rheumatology and cardiology. Colchicine is now considered standard of care for the treatment of acute idiopathic or viral pericarditis [4]. More recently, colchicine has been studied in acute myocardial infarction (AMI) and heart failure. The NALP3/NRLP3 inflammasome is the major source of Interleukin-1β (IL-1β) in atherosclerosis and acute myocardial infarction [5,6]. IL-1β mediates progression of atherosclerosis, adverse cardiac remodeling after AMI, and worsening heart failure (HF) [6]. Considering the inhibitory effects of colchicine on the NALP3/NLRP3 inflammasome it was conceived that colchicine would prevent or improve cardiovascular disease. In the Low-Dose Colchicine for Secondary Prevention of Cardiovascular Disease [7], colchicine 0.5 mg daily for 3 years significantly reduced cardiovascular events in patients with stable coronary artery disease (5.3% *vs.* 16.0%, P<0.001, Table 1).

In an elegant study [8], patients with acute coronary syndrome showed enhanced myocardial production of IL-1β, consistent with active inflammation within the myocardium [9,10] and colchicine 1.5 mg given 6-24 hours prior to cardiac catheterization significantly reduced the myocardial production of IL-1β and the myocardial and systemic levels of Interleukin-6 (IL-6) (Table 1).

Consistent with a central role of the NALP3/NLRP3 in the inflammatory injury during ischemia-reperfusion [11,12], colchicine 1.5 mg followed by 0.5 mg 1 hour later and 0.5 mg twice daily for 5 days significantly reduced the size of the myocardial infarction in patients with ST-elevation AMI undergoing primary percutaneous coronary intervention [13] (Figures 1 and 2).

The exciting results of the pilot studies with colchicine require validation in appropriately powered clinical trials. The pilot studies are however informative on the tolerability of colchicine in patients with AMI or at risk for it. The gastrointestinal side effects appear to be the limiting factor, which however are dose dependent (ranging from 5% in the low dose study in stable patients [7] to 26% in the higher dose study in patients with AMI [13]. Therefore, it remains to be determined the optimal dose and duration of colchicine therapy, and whether other inflammasome inhibitors or IL-1 blocker would provide similar or better results [5,6].

	Year	Colchicine regimen	Comparison	Indication	Patients	Summary of results
Nidorf et al	2013	0.5 mg/day	Placebo	Established CAD, presenting for routine follow-up	n=532 (Active=282)	Treatment arm had significant reduction in ACS, out-of-hospital cardiac arrest, or ischemic stroke.
Martinez et al	2015	1 mg colchicine followed by 0.5mg 1 hour later, given 6-24 hours pre-catheterization	No colchicine	ACS or stable CAD, pre-cath	n=83	Treatment arm had significant reduction in transcoronary gradients of IL-1β, IL-18, and IL-6.
Deftereos et al	2015	2 mg loading dose followed by 0.5 mg twice daily, for a 5-day regimen	Placebo	STEMI <12hrs from pain onset	n=151 (Active=77)	Treatment arm had significant reduction in infarct size measured as area-under-the-curve of CK-MB and of MRI-determined infarct size.

Table 1: Colchicine in atherosclerosis and acute myocardial infarction.

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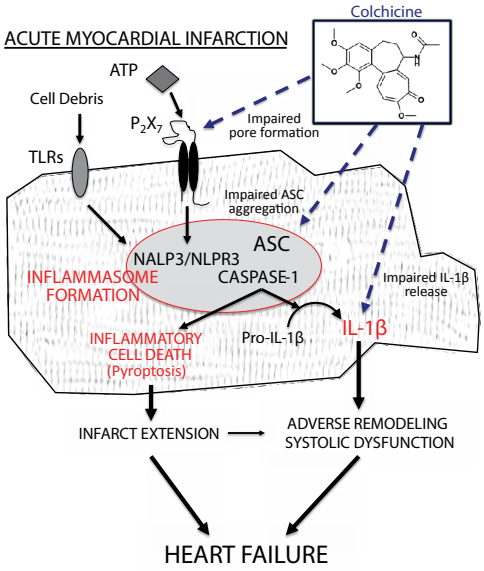

FIGURE 1. Effects of colchicine on the NLRP3 inflammasome. Colchicine (structure shown in the right upper hand insert) has been shown to inhibit of the formation of the purinergic receptor P2X7 (receptor for extracellular adenosine triphosphate [ATP]), to inhibit the aggregation of the ASC (apoptosis-associated speck-like protein containing a carboxy-terminal caspase-recruiting domain) within the NLRP3 (nucleotide-binding oligomerization domain-like receptor protein 3), and to inhibit the release of mature IL-1β (Interleukin-1) after processing by caspase-1.

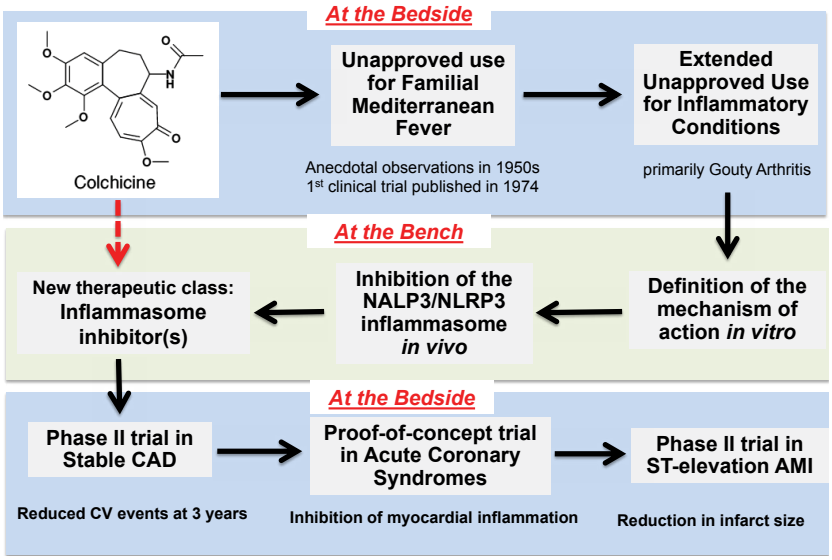

FIGURE 2. Translational research with colchicine.The diagram shows the historical process leading to the initial use of colchicine for Mediterranean Fever, followed by extended unapproved use for inflammatory conditions, and now being explored for treatment of acute coronary syndromes.

The story of colchicine should serve us a reminder that Translational Medicine can be bidirectional: not only from *bench-to-bedside* but also *bedside-to-bench*. The clinical observation of the power anti-inflammatory effects of colchicine has driven further research leading to the discovery of the NALP3/NLRP3 inflammasome inhibitory activity *in vitro* which in turn lead to new clinical trials.

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