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Will Colchicine Soon Be Part of Primary and Secondary Cardiovascular Prevention?

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Things change. Guidelines currently recommend that following an acute coronary syndrome (ACS) patients should take several drugs to reduce the risk of a recurrence. Most of the drugs on this list have been there for decades, based upon convincing results from high-quality clinical trials. As the underlying ACS disease substrate has changed, the need to retain some drugs on the list, for example beta-blockers, has been challenged.[1] The list of drugs recommended for high-risk primary prevention is much shorter, perhaps just aspirin and a statin.

In this editorial we would like to raise the possibility that a new drug, colchicine, will soon be added to these lists. This assertion is based upon a wealth of evidence demonstrating that inflammation plays an important role in atherogenesis, and that anti-inflammatory treatment reduces cardiovascular (CV) events. Colchicine is inexpensive, safe, and has been shown in clinical trials and observational datasets to reduce CV events. More clinical trial data is forthcoming.

Mechanism of Action

The anti-inflammatory activities of colchicine are complex and incompletely understood. Colchicine inhibits cytoskeletal microtubules and thus limits microtubule-dependent functions such as neutrophil chemotaxis, phagocytosis and protein excretion.[2] In relatively high concentrations colchicine suppresses activation of the nucleotide-binding and oligomerization domain-like receptor family pyrin domain-containing protein

3 (NLRP3) inflammasome by inhibiting its assembly.[3] Diverse stimuli such as hypoxia, disturbed blood flow, cholesterol crystals and microbial particles can activate the NLRP3 inflammasome, leading to the release of caspace-1.[3,4] Caspace-1 in turn activates the inactive precursors of the pro-inflammatory cytokines interleukin-1β (IL-1β) and interleukin-18 (IL-18).[3]

Coronary sinus levels of IL-1β, IL-18, and IL-6 have been reported to be higher than arterial and venous levels in patients with ACS.[5] Furthermore, colchicine administration significantly reduced the transcoronary gradients of all 3 cytokines in ACS patients by 40% to 88%. The same investigators subsequently showed that colchicine reduced caspase-1 mRNA levels in ACS patients.[6]

These data provide an explanation for how colchicine might prevent the occurrence of acute coronary events in persons with underlying atherosclerosis.

Colchicine for Secondary Prevention

Description of the secondary prevention studies in the table (COLCOT and LoDoCo).

Issues Related to Primary Prevention

Although a myriad of medications for secondary prevention have been developed, approved, and incorporated into clinical guidelines due to high-quality evidence from randomized trials, few have bridged the gap to high-

risk primary prevention. Recent updates to clinical guidelines also recommend earlier initiation of primary prevention therapies, such as statins, however, a substantial residual risk for a first ACS event remains.

Colchicine for Primary Coronary Prevention

In this issue of the *Canadian Journal of Cardiology*, results from a study by Shah and colleagues suggests that the anti-inflammatory properties of colchicine to reduce CV events post-ACS may extend to primary prevention.[11] Observational data from the New York Health Care System of the US Department of Veterans Affairs (2000-2009) was used to evaluate the effectiveness of colchicine to reduce the risk of coronary artery disease (CAD) among gout patients. In this relatively low-CV risk population (N=722 patients), current use of colchicine (median 23 months) was protective against incident CAD; however, statistical significance was not achieved [HR 0.49 (95% CI 0.23-1.05)]. In comparison, current use of colchicine was associated with a statistically significant reduction in CAD including myocardial infarction (MI) [HR 0.37 (95% CI 0.16-0.83)]. It should be noted that the inclusion of MIs to the CAD outcome added only 1 additional event (in the non-user group) compared to the primary analysis without MIs, which translated to statistically significant effect estimate.

Despite the limited power (N=722) and relatively short follow-up (median 23 months on colchicine and 96 months of follow-up) for a primary prevention study on a low CV-risk population, the trend towards a

statistically significant protective effect against incident CAD is promising for the application of colchicine in primary prevention. Although authors investigated potential effect measure modification by CV risk factors, the limited sample size prevented conclusive results, except for chronic kidney disease. In addition, the present study investigated colchicine for the prevention of CAD-related events and not the development of CAD. All components of the primary endpoint were determined from an event (percutaneous coronary intervention, coronary artery bypass graft surgery, or MI) or symptoms that would indicate testing (positive ischemic stress test or evidence of coronary artery disease on invasive angiography). Therefore, hypotheses about a potential role for colchicine in CAD development would require a prospective study that tests all patients for incident CAD.

Other observational data…

Ongoing Colchicine Trials

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Table 1. Characteristics of colchicine studies

Study	Sample Size	Study Type	Primary / Secondary Prevention	Study population	Primary Outcome	Median Follow-up	Effect estimate
Shah et al. (2020)	722	Observational	Primary	Gout patients	Stable CAD (excluding MIs)	96 months	HR 0.49 (95% CI 0.23-1.05)
Tardif et al. [COLCOT] (2020)	7,745	Randomized Controlled Trial	Secondary	Post-MI patients	Composite: CV death, resuscitated cardiac arrest, MI, stroke, urgent hospitalization for angina requiring revascularization	22.6 months	HR 0.77 (95% CI 0.61-0.96)
Solomon et al. (2016)	1,002	Observational	Primary	Gout patients	Composite: MI, stroke, TIA	15.7 months	HR 0.51 (95% CI 0.30-0.88)
Nidorf et al. [LoDoCo] (2013)	532	Randomized Controlled Trial	Secondary	Stable CAD	Composite: ACS, out-of-hospital cardiac arrest, noncardioembolic ischemic stroke	36 months	HR 0.33 (95% CI 0.18-0.59)
Crittenden et al. (2012)	1,288	Observational	Primary	Gout patients	MI	Not reported	RR=0.96, p=0.03

*CAD, coronary artery disease; MI, myocardial infarction; CV, cardiovascular; TIA, tr