SHORT COMMUNICATION

Use of colchicine in atherosclerotic heart disease

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Lin B, Pillinger M, Shah B, et al. Use of colchicine in atherosclerotic heart disease. Curr Res Integr Med 2018; 3(S1):2-4.

Despite many recent advances in prevention and treatment, cardiovascular disease remains the leading cause of death worldwide (1). The traditional paradigm of lipid accumulation and the formation of atherosclerotic plaque is increasingly recognized as incomplete, and inadequate to fully explain the underlying mechanisms of cardiovascular risk. Inflammation is now appreciated as a major contributing factor to the progression of atherosclerotic heart disease (ASHD); however, traditional anti-inflammatory treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids has not only failed to show benefit but appears deleterious (2). The deleterious effects of these medications may not be related to their anti-inflammatory actions, but to other unrelated physiological effects that these drugs possess (e.g., hypertension and renal disease for NSAIDs, hypertension and lipid abnormalities for glucocorticoids). Alternatively, the adverse side effect profile of some of these agents may relate to their anti-inflammatory potency in specific settings, such as post-acute myocardial infarction (MI), where some degree of an inflammatory response may be needed for the healing process. Therefore, it may be necessary to focus on anti-inflammatory agents with a more focused target of action and limited or no adverse side effects. The possibility that the benefits of statin therapy on cardiovascular risk may be due, in part, to an anti-inflammatory mechanism supports such a paradigm (3,4). Furthermore, the recently reported Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) trial showed a reduction in major adverse cardiovascular events with anti-inflammatory therapy targeting IL-1β in patients post-MI. Unlike with statin therapy, the cardiovascular benefit observed with anti- IL-1β therapy was independent of lipid-lowering therapy and underlines the importance of anti-inflammatory strategies for cardiovascular prevention. Unfortunately, not everyone achieved a significant anti-inflammatory response with canakinumab, and in patients without a significant decrease in high sensitive C-reactive protein (hsCRP) concentration there was no observed cardiovascular benefit (5). Moreover, canakinumab resulted in an increased rate of fatal infections, and the cost of canakinumab is several hundred thousand dollars a year, making this approach impractical for a large population (6).

Colchicine is an ancient medication, currently FDA approved for the treatment of gout and familial Mediterranean fever (7). Although its uses in other rheumatic diseases (e.g., calcium pyrophosphate crystal disease, small vessel vasculitis, Behcet's syndrome) are fairly well established, the potential of colchicine use in ASHD has only recently begun to be studied (8).

Colchicine has multiple mechanisms of action that reduce inflammation, but the mechanisms of benefit that may lead to a decrease in major adverse cardiovascular events in patients with ASHD remain incompletely elucidated. Incorporation of colchicine-bound free tubulin dimers into microtubules blocks subsequent polymerization, which then inhibits leukocyte functions such as superoxide and cytokine release and cell adhesion and migration (9-11). Colchicine can further reduce leukocyte recruitment to inflamed or injured vascular endothelium by modulation of adhesion molecules on the surface of leukocytes and endothelial cells, chemoattractant secretion, and leukocyte deformability (12-14). Colchicine also inhibits the NLRP3 inflammasome and subsequent formation of IL-1β, thus suggesting that at least some effects of colchicine may mimic those of canakinumab (15,16). Our group has also shown colchicine to decrease the aggregation between leukocytes and platelets, but not platelet-to-platelet aggregation, suggesting that colchicine may exert an anti-thrombotic mechanism at the site of inflammation without potentially increasing the risk of bleeding (17). In vivo, colchicine has been shown to reduce hsCRP concentration, in patients with ASHD already on statin and anti-platelet therapy (18). Colchicine has also been shown to reduce low attenuation plaque volume on coronary computed tomography angiography, a measure of plaque instability (19). Any or all of these functions are potential mechanisms by which colchicine may reduce cardiovascular events, making it a medication worthy of consideration (20).

The extent of colchicine's effects on clinical cardiovascular outcomes is under study. Our group conducted a retrospective cross-sectional study of 1288 patients with gout, a cohort at high cardiovascular risk, and first reported that treatment with colchicine was associated with a 54% relative risk reduction in MI (1.2% vs 2.6%; RR 0.46; p=0.03) (21). A subsequent retrospective cohort study by an independent group examined 501 gout patients and observed a similar protective effect with colchicine, including a 49% relative risk reduction in a composite outcome of MI, stroke, and transient ischemic attack (22.7 *vs.* 43.4 events per 1000 patient years; HR 0.5, 95% CI 0.30-0.88; p=0.016), and a 73% relative risk reduction in all-cause mortality (52.6 *vs.* 95.1 events per 1000 patient years; HR 0.55, 95% CI 0.35-0.85; p=0.007) (22). A single-center, open-label study randomized 532 patients with stable coronary artery disease already on statin and anti-platelet therapy to either colchicine 0.5 mg/day or no colchicine. Low-dose colchicine use resulted in a decrease in cardiovascular events defined as a composite of acute coronary syndromes, out-of-hospital cardiac arrests, and non-cardioembolic ischemic strokes over a median follow-up period of 3 years (5.3% *vs.* 16.0%; HR 0.33, 95% CI 0.18-0.59; p<0.001) (23). A Cochrane systematic review of 4992 patients in 39 randomized controlled trials of any clinical setting involving long-term colchicine versus any control demonstrated a significant decrease in MI (1.2% *vs.* 5.8%; RR 0.2, 95% CI 0.07-0.57; p=0.003), but no significant reduction in all-cause mortality (17.8% *vs.* 19.3%; RR 0.94, 95% CI 0.82-1.09; p=0.43) (24).

The potential of colchicine to reduce angioplasty and stent-related recurrent events has also been evaluated. A randomized, double-blinded study of 196 patients with diabetes mellitus who underwent percutaneous coronary intervention with a bare metal stent demonstrated a reduction in in-stent restenosis as assessed by follow-up angiography (16% *vs.* 33%, p=0.007) and intravascular ultrasound (24% *vs.* 43%, p=0.006) with 6 months of twice daily colchicine (0.5 mg) versus placebo (25). However, another double-blinded, placebo-controlled study of 145 patients undergoing elective coronary angioplasty of 393 lesions without stent placement demonstrated no improvement in the rate of angiographic restenosis with up to 6 months of twice daily colchicine (0.5 mg) (26).

Finally, several studies have assessed the potential role of colchicine specifically in the acute setting. One such study randomized 151 patients ST-segment elevation MI (STEMI) to receive either colchicine (2 mg load followed by 0.5 mg twice a day for five days) or placebo and demonstrated a significantly lower infarct size, as measured by CK-MB concentrations, with colchicine use (3144 *vs.* 6184 ng/hr/mL, p<0.001). A subset of these patients (n=60) also underwent cardiac magnetic resonance imaging, which confirmed that

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Received: January 4, 2018, Accepted: January 21, 2018, Published: February 05, 2018

colchicine administration resulted in a reduction in infarct size proportional to left ventricular myocardial volume (13% *vs.* 19.8%, p=0.034) (27). Our group is currently conducting a single-center, double-blind study in which 400 patients undergoing percutaneous coronary intervention are randomized to either a pre-procedural load of colchicine (1.2 mg followed by 0.6 mg one hour later) or placebo, and assessed for peri-procedural myocardial necrosis (primary outcomes) and rate of 30-day major adverse cardiovascular events (secondary outcome) (28). A substudy of patients also have a concomitant analysis of inflammatory profiles (co-primary endpoints include neutrophil surface expression of L-selectin and soluble IL-6 concentration) (29). The multicenter, randomized, double-blind Colchicine Cardiovasclar Outcomes Trial (COLCOT) is investigating the effect of long-term administration of colchicine 0.5 mg daily in 4500 patients with a documented MI in the prior 30 days. The primary endpoint is a composite of cardiovascular death, resuscitated cardiac arrest, acute MI, stroke, or hospitalization for angina requiring coronary revascularization (30). The multicenter, international, randomized, double-blind Colchicine and Spironolactone in Patients With STEMI/SYNERGY Stent Registry (CLEAR-SYNERGY) trial is investigating the effects of colchicine 0.5 mg twice a day and/or spironolactone 25 mg once a day following primary percutaneous coronary intervention in the setting of STEMI. The primary outcome measure in the colchicine comparison is a composite of cardiovascular death, recurrent MI, or stroke (31).

Is it time for colchicine to be considered an accepted therapy for cardiovascular treatment and prevention? Probably not quite. First, studies to date have been relatively small, and the data accrued would not likely meet the standard of proof if colchicine were a new drug coming up for first approval. However, there is sufficient mechanistic and pilot clinical data to encourage the careful evaluation of data from the large ongoing trials. Second, while colchicine is generally safe and well-tolerated when prescribed by experienced practitioners, colchicine toxicity is a well-recognized phenomenon and physician education would be needed to ensure that the drug is used safely. Caution with dose-adjustment in patients with renal disease and management of potential drug-drug interactions (particularly with P-glycoprotein and inhibitors, including some statins) requires attentiveness on the part of caregivers (7). Colchicine has a low median lethal dose (LD50), and, therefore, overdose needs to be guarded against carefully. Finally, the appropriate dose and duration of colchicine for cardiovascular indications has yet to be determined: is colchicine's potential benefit likely to come from long-term use or will it be most beneficial during acute events?

Nonetheless, colchicine has a number of advantages that might make it desirable as an add-on therapy to current treatment. First, when used properly, colchicine's kinetics make it relatively easy to comply with once or twice daily dosing. Second, the fact that colchicine has minimal or no independent impact on platelets at the recommended doses makes it a potentially desirable partner to current cardiovascular regiments that typically include multiple drugs that raise the risk of bleeding. Third, while colchicine in the United States is now much more expensive than it was previously, it is still much cheaper than newer agents and biologics—and even cheaper in many other parts of the world. In sum, we seem to be approaching the day when colchicine may be added to the armamentarium for the prevention of cardiovascular disease. Whether and when that day comes will depend on the results of the next round or two of clinical investigation.

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