ONLINE EXCLUSIVE

Colchicine may decrease cardiovascular events in patients with coronary artery disease

This oral anti-inflammatory agent may offer a low-cost option for prevention of cardiovascular events in this patient population.

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PRACTICE CHANGER

Consider prescribing colchicine 0.5 mg daily as an addition to current standard-of-care therapies for patients with coronary artery disease (CAD) to prevent further cardiovascular events (CVEs).

STRENGTH OF RECOMMENDATION

B: Based on a single randomized controlled trial (RCT).[1]

Nidorf SM, Fiolet ATL, Mosterd A, et al; LoDoCo2 Trial Investigators. Colchicine in patients with chronic coronary disease. *N Engl J Med*. 2020;383:1838-1847.

ILLUSTRATIVE CASE

A 62-year-old woman with a past medical history of type 2 diabetes, hyperlipidemia, hypertension, and remote myocardial infarction (MI) presents to her primary care office for a preventive visit. She is a nonsmoker and has been taking her daily medications as prescribed, including an angiotensin-converting enzyme inhibitor, high-intensity statin, and aspirin. Her diabetes is well controlled. What else would you consider recommending to decrease this patient's risk for future CVEs?

Cardiovascular disease (CVD) is a major contributor to morbidity and mortality, affecting more than 50% of patients older than 60.[2] Despite control of risk factors with standard treatment modalities, patients with established CVD remain at high risk for future events, which makes elucidating and targeting other causative pathways essential.[3]

Inflammation has been identified as a key player in the development and progression of atherosclerosis and its downstream effects, with increased inflammatory markers correlating with increased risk for CVEs.[4] Due to these findings, anti-inflammatory treatments have been under investigation as agents to further reduce risk for CVEs. In 1 such trial, the Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS), patients with MI and elevated C-reactive protein levels treated with the interleukin-1 beta inhibitor canakinumab showed reduced risk for future CVEs compared to those receiving placebo.[5] However, due to canakinumab's high cost, inconvenient subcutaneous administration, and increased incidence of fatal infections, other agents are under investigation.

Colchicine is a potent anti-inflammatory agent, with approval in the United States for treatment of gout and familial Mediterranean fever. It works broadly to reduce inflammation by disrupting tubulin polymerization.[6,7] Colchicine decreases interleukin-1 beta production through inactivation of the NLRP3 inflammasome pathway, which has been associated with the inflammatory component driving atherosclerotic plaque progression and instability.[5,8] Colchicine's oral adminis-

tration, relative cost-effectiveness, and safety profile make it an attractive option for potential use in secondary prevention of CVEs.

The Low-Dose Colchicine (LoDoCo) trial, published in 2013, demonstrated a reduction in CVEs in those with CVD taking guideline-directed medical therapy (GDMT) plus colchicine 0.5 mg/d, compared with those taking GDMT alone.[9] However, the LoDoCo study enrolled only 532 patients and was not placebo controlled. The Colchicine Cardiovascular Outcomes Trial (COLCOT), published in 2019, was a randomized, double-blind, placebo-controlled trial that aimed to further evaluate the effects of colchicine on CVEs on a larger scale and to assess its longer-term safety.[10] In this study, the colchicine group had a significantly lower risk of CVEs vs placebo, with a comparable safety profile.[10]

STUDY SUMMARY

Fewer CVEs occurred when colchicine was added to the regimen

The randomized, multicenter, double-blind Low Dose Colchicine 2 (LoDoCo2) trial evaluated whether colchicine 0.5 mg daily reduces CV death, spontaneous (nonprocedural) MI, ischemic stroke, or ischemia-driven coronary revascularization in patients with chronic CAD (composite primary endpoint). This trial included 5522 patients, ages 35 to 82, in Australia and the Netherlands. Patients were eligible to participate if they had evidence of CAD by invasive coronary angiography, coronary calcium score, or computed tomography angiography, as well as evidence of clinical stability for 6 months. Exclusion criteria included moderate-to-severe renal impairment, severe heart failure, severe valvular disease, or intolerance to colchicine.

Patients (N = 6528) took colchicine 0.5 mg daily as part of a 1-month, open-label run-in phase; 1006 patients stopped taking colchicine during this time. Perceived adverse effects were observed in 611 of these patients, the most common being gastrointestinal (GI) upset (437 patients). After the run-in phase, the remaining 5522 patients were randomized to either the colchicine or placebo group. Both groups continued to receive GDMT for CVD, including antiplatelet therapy, anticoagulants, and hypertensive therapy as indicated. Lipid-lowering therapies were continued in 96.7% of the colchicine group and 96.6% of the placebo group. These patients were then followed for a minimum of 1 year (median duration, 28.6 months).

The primary endpoint occurred less frequently in the colchicine group than in the placebo group (6.8% vs 9.6%; $P < .001$; number needed to treat = 36). The incidence rates for 2 of the individual outcomes in the composite, MI (hazard ratio [HR] = 0.7; 95% CI, 0.53-0.93) and ischemia-driven coronary revascularization (HR = 0.75; 95% CI, 0.60-0.94), were significantly lower in the colchicine group. The other outcomes were no different from placebo.[1]

There was a similar incidence of serious adverse events, such as noncardiovascular death, cancer diagnosis, and hospitalization for infection, pneumonia, or GI issues. High-dose statins were used by 3413 patients (61.8%). Myalgia (data collected only from the Netherlands cohort) was reported more commonly in the colchicine group than the placebo group (21.2% vs 18.5%; cumulative incidence ratio = 1.15; 95% CI, 1.01-1.31). Myotoxic effects were rare in both groups.[1]

WHAT'S NEW

RCT supports potential for anti-inflammatory therapy in CAD

This large RCT demonstrated that the addition of daily colchicine reduces CVE risk in patients with known CAD while maintaining a good safety profile.[1]

CAVEATS

Watch for potential drug interactions in patients with renal dysfunction

Prescribers should be aware of potential drug interactions, especially in those with renal or hepatic dysfunction, when prescribing colchicine, as it is metabolized through cytochrome P450 3A4 (CYP3A4) and excreted via the P-glycoprotein transport system, by which many statins are also metabolized and act as a competitive substrate.[7] In addition, simvastatin, and to a lesser degree atorvastatin, are CYP3A4 inhibitors.

Also of note, the 0.5-mg colchicine tablet

is not available in some countries—including the United States, where only 0.6-mg tablets are available. The 0.6-mg dose would likely have the same benefit and similar adverse effect profile but was not included in the study.

CHALLENGES TO IMPLEMENTATION

GI tolerability may be an issue

Colchicine is widely available and relatively low in cost, at approximately $32 per month for the 0.6-mg daily tablets. A major limitation is lack of tolerability, as adverse effects such as nausea, vomiting, diarrhea, and abdominal pain are frequently reported. JFP

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