Old drug, new trick: colchicine for cardiovascular diseases

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Title: Efficacy and safety of low-dose colchicine after myocardial infarction

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Summary

In the Colchicine Cardiovascular Outcomes Trial (COLCOT), Tardif and colleagues evaluated the effects of colchicine on cardiovascular outcomes as well as its long-term safety profile in patients who recently had a myocardial infarction.[1] Colchicine is an inexpensive, oral anti-inflammatory medication that acts by inhibiting tubulin polymerisation and microtubule generation and, possibly, has effects on cellular adhesion molecules, inflammatory chemokines and the inflammasome. It is very commonly used for treating gout, familial Mediterranean fever and pericarditis. It has a distinct advantage of having a very well understood safety profile.

COLCOT was a randomised, double-blind, placebo-controlled, investigator-initiated trial, where patients were assigned in a 1:1 ratio to receive either colchicine (at a dose of 0.5 mg once daily) or placebo. This multicentre trial had 167 sites from 12 different countries. Patients who had a myocardial infarction within 30 days and underwent treatment according to standard guidelines were enrolled. Patients with severe heart failure, stroke within the previous 3 months, coronary-bypass surgery either within the previous 3 years or planned, inflammatory bowel disease or chronic diarrhoea, neuromuscular disease or a persistent creatine kinase level elevation with greater than three times the upper limit of the normal range, haematologic abnormalities, severe renal disease, severe hepatic disease, drug or alcohol abuse, current or planned long-term glucocorticoid usage and those with history of known colchicine hypersensitivity were excluded.

The primary efficacy endpoint was a composite of death from cardiovascular causes, resuscitated cardiac arrest, myocardial infarction, stroke or urgent hospitalisation for angina leading to coronary revascularisation. The secondary endpoints consisted of the components of the primary efficacy endpoints.

A total of 4,745 patients underwent randomisation (with 2,366 being assigned to the colchicine group and 2,379 to the placebo group) and were followed for a median of 22.6 months. In the colchicine group 2,226 completed the trial and in the placebo group, 2,232. The mean duration of enrollment was 13.5 days after myocardial infarction. The mean age was 60.6 years, 19.2% were women. Most patients (93.0%) underwent percutaneous coronary intervention for their index myocardial infarction. Aspirin was being used by 98.8%, 97.9% were on a different antiplatelet agent and 99% were using a statin.

A primary endpoint event occurred in 5.5% of the patients in the colchicine group, as compared with 7.1% of those in the placebo group [hazard ratio 0.77; 95% confidence interval (CI) 0.61–0.96; p = 0.02 by the log-rank test). Among components of primary endpoints, death from cardiovascular causes (hazard ratio 0.84; 95% CI 0.46–1.52), resuscitated cardiac arrest (hazard ratio 0.83; 95% CI 0.25–2.73), myocardial infarction (hazard ratio 0.91; 95% CI 0.68–1.21), stroke (hazard ratio 0.26; 95% CI 0.10–0.70) and urgent hospitalisation for angina leading to coronary revascularisation (hazard ratio 0.50; 95% CI 0.31–0.81) all had shown better response in colchicine group. The total number of primary endpoint events (first and recurrent) was 154 in the colchicine group and 223 in the placebo group.

The incidence of adverse events that were related to the active drug or placebo was 16.0% vs 15.8%. Gastrointestinal adverse events, such as like diarrhoea (9.7% vs 8.9%) and nausea (1.8% vs 1.0%), were more common in colchicine group. Pneumonia was reported as a serious adverse event in 0.9% of the patients in the colchicine group, compared with 0.4% in the placebo group (p = 0.03).

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In COLCOT the risk of the primary composite efficacy endpoints was significantly lower among the patients who were randomly assigned to receive 0.5 mg of colchicine once daily than among those who received placebo. In the colchicine group significantly lower incidence of strokes (0.2% vs 0.8%) and urgent hospitalisations for angina leading to coronary revascularisation (1.1% vs 2.1%) were observed. Limitations of COLCOT were short duration of follow up of 23 months, and enrollment of patients with early myocardial infarction.

Opinion

Inflammation appears to play an important role in atherosclerosis. Hence constant attempts have been made by researchers to identify a suitable anti-inflammatory drug that can reduce cardiovascular morbidity and mortality without causing major adverse events. In recent times, two major trials looked at this aspect. In Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) 15% fewer cardiovascular events were observed in patients who received canakinumab, which is an anti-interleukin-1β monoclonal antibody, in comparison with placebo group; however, this group also had slightly higher incidence of fatal infections.[2,3] In Cardiovascular Inflammation Reduction Trial (CIRT), methotrexate, a very widely used disease-modifying antirheumatic drug, did not affect cardiovascular outcomes or markers of inflammation when compared with placebo.[4,5]

Colchicine has been a potent anti-inflammatory drug for acute gout flares for many years. Colchicine was administered in higher doses previously but owing to its gastrointestinal side effects in recent times it is more frequently used at low doses. Role of colchicine in cardiovascular disease until recently was limited to pericarditis. It has also shown a preventive role in treating postoperative and postcatheter ablation atrial fibrillation.[6] For the first time, in Low-Dose Colchicine (LoDoCo) trial, colchicine was studied in patients with stable coronary disease at a dose of 0.5 mg once daily, the patients had fewer cardiovascular events.[7] This study, however, included only 532 patients and was not placebo controlled.

In atherosclerosis innate immune system activation plays a crucial role in plaque initiation, progression and rupture. Recently NLRP3 (nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3) inflammasome was identified as a key player in orchestrating lipid-driven vascular inflammation.[8] The NLRP3 inflammasome leads to IL-1β production and this, in turn, promotes atherosclerotic plaque development and destabilisation. Colchicine can inhibit NLRP3 inflammasome and thus IL-1β production.[9]

Colchicine had shown encouraging results in LoDoCo trial for patients with stable coronary heart disease.[7] A larger trial, LoDoCo2 trial, is assessing its benefits involving over 5,000 patients.[10]

COLCOT looked at potential for colchicine to limit the inflammatory processes that occur immediately post acute coronary syndrome. In this trial, colchicine was associated with a 1.6% absolute reduction in the primary composite endpoints. However, short duration of follow up and only few patients had biomarker testing at baseline and follow up, which could not confirm the proposed mechanism of reduction of inflammatory parameters, are limitations of this study. Also, it is worth noting that the pathophysiologic mechanisms of acute coronary syndrome are likely to differ from stable coronary heart disease.

Overall, these studies of colchicine are encouraging and underscore its utility in and repurposing for cardiovascular diseases. With current knowledge of inflammatory atherosclerotic mechanisms there is a strong rationale to use colchicine to reduce the risk of atherosclerotic vascular disease along with statins and antiplatelet therapy. Presently we are at an exciting phase with sufficient short-term evidence of benefits on colchicine and we are looking at the future for long-term data.[11]

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