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Modulating inflammation to reduce atherosclerotic cardiovascular events: should colchicine be part of the therapeutic regimen?

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In a previous editorial in this journal we reviewed the large Canakinumab Anti-Inflammatory Thrombosis Outcome Study (CANTOS) and concluded based on the results from CANTOS that Koch's postulates were fulfilled with respect to the pivotal role of inflammation in atherosclerosis.[1] Briefly this study included 10,061 patients with atherosclerotic cardiovascular disease (ASCVD) with a high sensitivity C-reactive protein (hsCRP) level ⩾2 mg/l. Canakinumab, a monoclonal antibody to interleukin (IL) 1-beta, reduced both hsCRP levels and ASCVD events without altering lipoproteins such as low-density lipoprotein cholesterol (LDL-C). A major concern was the increase in deaths due to infections that prevented us from recommending it as part of the mainstay armamentarium against ASCVD, a recommendation supported by the general consensus.

This was a very important advance since studies targeting other inflammatory pathways with Salsalate, a p38-MAPKinase inhibition (losmapimod) and lipoprotein-associated phospholipase A2 inhibition (darapladib) have all yielded null effects as reviewed previously.[2,3]

In this regard it is worth mentioning the Cardiovascular Inflammation Reduction Trial (CIRT) with methotrexate published after CANTOS.[4] This trial compared low-dose (15–20 mg weekly) methotrexate with placebo in reducing inflammation and prevention of atherosclerotic events. The participants constituted 4786 patients who had previous myocardial infarction or multivessel coronary disease along with either type 2 diabetes or the metabolic syndrome. The initial primary end point included a composite of non-fatal myocardial infarction, non-fatal stroke or cardiovascular death. However, towards the conclusion of the trial, hospitalization for unstable angina leading to urgent revascularization was also added as part of the composite primary end point. The median level of hsCRP at randomization was 1.6 mg/L. The trial was terminated early (median follow-up of 2.3 years) as it had crossed a pre-specified boundary for futility for the primary end point. After a median follow-up of 2.3 years (maximum 5 years), the occurrence of the primary end point was similar in methotrexate-treated and placebo groups; hazard ratio (HR) 0.96 with 95% confidence interval (CI) of 0.79–1.16, $p = 0.67$. There was no significant change in the levels of IL-1β, IL-6, hsCRP or LDL-C levels between the two groups. Cardiovascular death and death from any cause were similar in both groups, with no effect of diabetes and the metabolic syndrome. It is noteworthy that development of cancers (non-basal-cell skin cancer) was significantly higher in the methotrexate group (rate ratio: 1.72, $p = 0.02$).

Recently, much attention has focused on colchicine, an alkaloid derived from the autumn crocus, since it possesses anti-inflammatory effects and lowers IL-6 and hsCRP levels.[5–7] The anti-inflammatory effects that have been advanced to date appear to be due to binding to tubulin and preventing its polymerization into microtubules. This results in an inhibition of leukocyte migration and activation and inhibition of neutrophil–platelet interaction. It also inhibits the pivotal Nod-like receptor pyrin domain containing 3

(NLRP3) inflammasome, which produces IL-1 and IL-18. Colchicine should be used with extreme caution in patients with severe renal and hepatic impairment, especially in combination with cytochrome P3A4 (CYP3A4) or P-glycoprotein (P-gp) inhibitors. In addition to the common gastro-intestinal side effects it can cause bone marrow suppression, myopathy and rhabdomyolysis. Hence it should be used at doses <1.0 mg with drugs metabolized by these pathways such as macrolide antibiotics, cyclosporine, verapamil, amiodarone, diltiazem; however, at doses of 0.5 mg daily, diltiazem and amiodarone are safe, and only clarithromycin, anti-rejection and antifungal therapy should be avoided.[5–7]

For the purpose of this editorial we will focus on the four largest studies with colchicine as defined by a sample size of at least 500 patients and a duration of at least 1 year as we want to ascertain the risk–benefit ratio given the signal for a potential increase in non-cardiovascular death.

The first study to report a benefit of colchicine was the low dose colchicine trial (LoDoCo) undertaken in Australia on 532 patients with stable ASCVD for at least 6 months.[8] This trial was a prospective randomized observer-blinded endpoint (PROBE) design in which 282 patients received colchicine 0.5 mg/day or no colchicine ($n=250$) and the follow-up was for a median duration of 3 years. The primary outcome was the composite of acute coronary syndromes (ACS), out of hospital cardiac arrest and non-cardio-embolic ischemic stroke. The primary outcome occurred in 5.3% of those who received colchicine and 16% who did not receive colchicine: HR 0.33 with 95% CI of 0.18–0.59, $p<0.001$. The major driver of the reduction in the primary end point was non-stent related ACS. The primary cause of patient withdrawal from the trial was gastro-intestinal side effects (11%). They did not appear to report on any biomarkers of inflammation such as hsCRP. Also, the PROBE design introduces outcome ascertainment and reporting bias. There was no increase in cardiovascular or total mortality. The authors do point out that this hypothesis generating study needs to be confirmed in larger studies.

Tardiff *et al.*[9] reported on their study in 4745 patients recruited within 30 days of a myocardial infarction, that is, with ACS. In this colchicine cardiovascular outcome trial (COLCOT) patients were assigned to colchicine 0.5 mg/day ($n=2366$) or placebo ($n=2379$) and followed up for a median period of 22.6 months. The primary end point was a composite of death from cardiovascular causes, resuscitated cardiac arrest, myocardial infarction, stroke or urgent hospitalization for angina leading to coronary revascularization. The primary end point occurred in 5.5% of patients who received colchicine and 7.1% of those on placebo: HR of 0.77 with 95% CI of 0.61–0.96, $p=0.02$. This benefit appears to be explained predominantly by a reduction in stroke and urgent coronary revascularizations for angina. There was a significant increase in pneumonia in the colchicine group *versus* placebo: 0.9% *versus* 0.4%, $p=0.03$. There was no significant effect on cardiovascular or total mortality. In this study two biomarkers of inflammation were reported: hsCRP and white cell count. Compared with placebo the decreases in both were not significant. There was a significant increase in gastro-intestinal adverse events in the colchicine group.

The Colchicine in Patients with Acute Coronary Syndromes (COPS) study investigated the usefulness of colchicine in patients with ACS.[10] This was a placebo-controlled trial of patients with ACS who had evidence of ASCVD. A total of 795 patients were recruited. Patients received colchicine 0.5 mg twice a day for 1 month and then 0.5 mg/day for 11 months ($n=396$) or placebo ($n=399$). The primary outcome was a composite of death from any cause, ACS, ischemia driven urgent revascularizations and non-cardio-embolic stroke. Over the 12 month follow-up there was no significant difference in the primary end point between colchicine (6.1%) and placebo (9.5%): HR of 0.65 with 95% CI between 0.38 and 1.09, $p=0.10$. There was a higher rate of total death (8 *versus* 1 in the colchicine group, $p=0.047$) and especially non-cardiovascular death mainly related to sepsis (5 *versus* 0, $p=0.023$). Due to gastro-intestinal side effects and personal choice 15% of patients in the colchicine group discontinued medication. In a *post-hoc* analysis of the composite primary end point using the more appropriate end point of cardiovascular death rather than total death there appeared to be a significant reduction in the primary end point in favor of colchicine: HR 0.51 with 95% CI between 0.29 and 0.89, $p=0.019$. They did not report on any biomarkers of inflammation.

The final trial we discuss is a follow-up of LoDoCo termed the LoDoCo2 trial.[11] This was also a trial in patients with chronic ASCVD who were stable for at least 6 months but it was a randomized placebo-controlled trial including 5522 patients in whom 2762 were assigned to colchicine (0.5 mg/day) and 2760 to placebo. The primary end point was a composite of cardiovascular death, spontaneous myocardial infarction, ischemic stroke and ischemia driven coronary revascularization. The median duration of follow-up was 28.6 months. There was a significant decrease in the primary end point in the colchicine group (6.8%) compared with the placebo group (9.6%): HR of 0.69 with 95% CI between 0.57 and 0.83, $p < 0.001$. There appeared to be more deaths from non-cardiovascular causes in the colchicine group that were not significant: HR of 1.51 with CI of 0.99–2.31. Hospitalizations for infections including pneumonia did not differ between the two groups. Whilst gastro-intestinal side effects were common as in the other trials, in the Dutch cohort myalgia was more common with colchicine *versus* placebo: 21.2 *versus* 18.5, HR of 1.15 with CI between 1.01 and 1.31. In the main study, they did not report on biomarkers but in a sub-study of 174 patients, Opstal *et al.*[12] showed over 30 days that there was a significant reduction in hsCRP, NLRP3 inflammasone pathway biomediators as evidenced by decreases in 1L-18, IL-6 and IL-1 receptor antagonist and biomarkers of neutrophil degranulation such as myeloperoxidase. Whilst this is very good data on biomarkers of inflammation a weakness was the lack of a control group.

Based on these four trials what conclusions can we draw about the potential benefit of colchicine in patients with ASCVD? From the above studies it is evident that colchicine reduces the primary endpoint in three of the four studies. In the COPS study, when the appropriate endpoint of cardiovascular mortality instead of total mortality is used, colchicine had a significant benefit on the modified composite primary end point. In a recent meta-analysis and review by Fiolet *et al.*[13] including 11,816 patients (which includes these four studies) they show that low-dose colchicine reduces the risk of major adverse cardiovascular events in a broad spectrum of patients with coronary disease ranging from stable ASCVD to those with ACS by 25%, $p = 0.005$. Except for the Dutch subgroup there does not appear to be a substantial risk for myopathy and rhabdomyolysis in these studies despite statin use in over 94% of patients. Furthermore mortality and admission for sepsis does not appear to be an issue from their meta-analyses. Also in their meta-analysis they did not show an increase in total mortality but a trend to an increase in non-cardiovascular mortality ($p = 0.06$) not explained by cancer or infections. In their pooled analyses Galli *et al.*[14] showed an increase in non-cardiovascular death with colchicine therapy: odds ratio 1.55, 95% CI 1.10–2.17, $p = 0.001$. They were careful to caution in their conclusion that based on limited studies with a paucity of events the data are not conclusive. This contrasting result stems from the different definition of non-cardiovascular death used to allocate events in these analyses, which reflects the unclear definition used among trials with respect to this outcome.[15]

Whilst the increase in non-cardiovascular mortality, largely a nebulous and poorly defined entity thus far in these trials, is of concern, ongoing and future trials with larger sample sizes and, hopefully, follow-up of longer duration will settle this issue.[13,16] However, this concern does not seem to be borne out with the wide use of colchicine in patients with gout, familial Mediterranean fever and pericarditis for several decades.

In conclusion, the totality of evidence will support the addition of colchicine, a cost effective therapy, as part of our excellent regimen in patients with ASCVD provided the caveats detailed above with respect to severe renal function, severe liver disease and concomitant use of drugs that strongly inhibit CYP3A4 and P-gp are followed.

Conflict of interest statement

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References

1. Jialal I and Vikram VK. Inflammation and atherosclerosis: fulfilling Koch's postulates. *Ther Adv Cardiovasc Dis* 2018; 12: 5–6.
2. Jialal I and Chaudhuri A. Targeting inflammation to reduce ASCVD in type 2 diabetes. *J Diabetes Complications* 2019; 33: 1–3.
3. Libby P and Everett BM. Novel anti-atherosclerotic therapies. *Arterioscler Thromb Vasc Biol* 2019; 39: 538–545.
4. Ridker PM, Everett BM, Pradhan A, *et al.* Low-dose methotrexate for the prevention of atherosclerotic events. *N Engl J Med* 2019; 380: 752–762.
5. Shagroni T, Cazares AR, Kim JA, *et al.* Chapter 36: Nonsteroidal anti-inflammatory drugs, disease-modifying anti-rheumatic drugs, non-opioid analgesics, & drugs used in gout. In: Katzung BG (ed.) *Basic & clinical pharmacology*. 15th ed. New York, NY: McGraw Hill, 2021.
6. Fiolet ATL, Silvis MJM, Opstal TSJ, *et al.* Short-term effect of low-dose colchicine on inflammatory biomarkers, lipids, blood count and renal function in chronic coronary artery disease and elevated high-sensitivity C-reactive protein. *PLoS One* 2020; 15: e0237665.
7. D'Amario D, Cappetta D, Cappannoli L, *et al.* Colchicine in ischemic heart disease: the good, the bad and the ugly. *Clin Res Cardiol.* Epub ahead of print 13 March 2021. DOI: 10.1007/s00392-021-01828-9.
8. Nidorf SM, Eikelboom JW, Budgeon CA, *et al.* Low-dose colchicine for secondary prevention of cardiovascular disease. *J Am Coll Cardiol* 2013; 61: 404–410.
9. Tardif JC, Kouz S, Waters DD, *et al.* Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med* 2019; 381: 2497–2505.
10. Tong DC and Layland J. Colchicine in patients with acute coronary syndrome. The Australian COPS randomized clinical trial. *Circulation* 2020; 142: 1890–1900.
11. Nidorf SM, Fiolet ATL, Mosterd A, *et al.* Colchicine in patients with chronic coronary disease. *N Engl J Med* 2020; 383: 1838–1847.
12. Opstal TSJ, Hoogeveen RM, Fiolet ATL, *et al.* Colchicine attenuates inflammation beyond the Inflammasome in chronic coronary artery disease: a LoDoCo2 proteomic substudy. *Circulation* 2020; 142: 1996–1998.
13. Fiolet ATL, Opstal TSJ, Mosterd A, *et al.* Efficacy and safety of low-dose colchicine in patients with coronary disease: a systematic review and meta-analysis of randomized trials. *Eur Heart J.* Epub ahead of print 26 March 2021. DOI: 10.1093/eurheartj/ehab115.
14. Galli M, Princi G, Crea F, *et al.* Colchicine and risk of non-cardiovascular death in patients with coronary artery disease: a pooled analysis underlying possible safety concerns. *Eur Heart J Cardiovasc Pharmacother* 2021; 7: e18–e19.
15. Galli M, Princi G, Crea F, *et al.* Response-Letter to the editor: colchicine and risk for non-cardiovascular death in patients with coronary artery disease: a pooled analysis underlying possible safety concerns. *Eur Heart J Cardiovasc Pharmacother* 2021; 7: e72–e73.
16. Roubille F and Tardif JC. Colchicine for secondary cardiovascular prevention in coronary disease. *Circulation* 2020; 142: 1901–1904.