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VIEWPOINT

Antirheumatic drugs for cardiovascular disease prevention: the case for colchicine

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ABSTRACT

We summarised four pivotal Randomised Controlled Trials (RCTs) with antirheumatic drugs on the secondary prevention of cardiovascular events. The favourable effects of canakinumab and colchicine confirm (low-grade) inflammation as an independent risk factor for cardiovascular events. While colchicine might be the first drug in the clinic, we expect that this is only the first in a future series of anti-inflammatory drugs used in secondary prevention of cardiovascular events.

Chronic inflammation is a key driver in the development of atherosclerotic cardiovascular disease. Proinflammatory mediators such as TNFα and IL-1β are important in the development of dysfunctional endothelium, the first step of atherogenesis. The next step is subendothelial monocyte infiltration where accumulated LDL cholesterol is oxidised leading to atherosclerotic plaque formation.[1] Plaques rupture or develop superficial erosions, causing thrombosis and cardiovascular events.[2]

The important proinflammatory cytokine IL-1β is generated after proteolytic cleavage of pro-IL-1β by caspase-1 that in turn is activated by the nucleotide-binding oligomerisation domain-containing, leucine-rich repeat-containing and pyrin domain-containing protein 3 (NLRP3) inflammasome. Uric acid crystals as well as cholesterol crystals initiate inflammation by complement activation. C3b then activates macrophages to produce the NLRP3 inflammasome.

Methotrexate (MTX) significantly reduces the cardiovascular disease risk in rheumatoid arthritis (RA) by favourable effects on vascular function and blood pressure.[3] The precise underlying mechanisms are not known but are thought to be related with targeting specific inflammatory pathways, particularly the effects on 5′ adenosine

monophosphate-activated protein kinase seem to be pivotal.[4]

Recognition of the important role of inflammation in atherogenesis led to trials, in non-arthritis patients, with several anti-inflammatory drugs, that is, canakinumab, MTX and colchicine, to study their potential for secondary prevention of cardiovascular events in patients with established cardiovascular disease.

Two agents target the IL-1β pathway: Canakinumab, an expensive monoclonal antibody, directly inhibits this cytokine; in Europe, it is approved for patients with refractory gout, cryopyrin-associated periodic fever syndromes and Still's disease. Colchicine is a very old and cheap drug that decreases production of IL-1β and other pro-inflammatory cytokines through inhibition of the formation of the NLPR3 inflammasome. Recently, four pivotal RCT's with these two agents have been published.

The first study (from 2017) compared three different dosages of canakinumab (50 mg, 150 mg and 300 mg given subcutaneously) versus placebo in 10.061 patients with a history of myocardial infarction and a high-sensitive C reactive protein level of ≥2 mg/L.[5] The primary endpoint was a composite index of non-fatal myocardial infarction, non-fatal stroke and cardiovascular death: after a mean follow-up of 3.7 years, a statistically significant decrease was found in the 150 mg group (HR 0.85, with 95% CI:

0.74 to 0.98, p=0.021) and in the 300 mg group (HR 0.86, 95% CI: 0.75 to 0.99, p=0.031). Thus, this landmark study demonstrated for the first time that an anti-inflammatory drug could reduce the occurrence of cardiovascular events in patients with a previous myocardial infarction. However, the higher incidence of fatal infections and the (current) prohibitively high drug costs

disqualifies this drug for widespread use in secondary cardiovascular prevention.

Therefore, the Cardiovascular Inflammation Reduction Trial (CIRT) study from 2019 on the effects of MTX for the secondary prevention of atherosclerotic events in patients with previous myocardial infarction or multivessel coronary disease is of interest.[6] MTX is an inexpensive antirheumatic drug, widely recommended as first-line choice for RA.[7 8] Unfortunately, the result of the study in 4786 patients comparing MTX 15–20 mg/week or placebo over 2.3 years was negative: the HR for the primary endpoint was 1.01, 95% CI: 0.82 to 1.25. CRP levels did not decrease during the study, probably related to the low CRP levels at baseline, 1.5 mg/L. For comparison, the mean CRP level at baseline in the canakinumab study (ref) was 4.2 mg/L and decreased 40% during the study.

Remarkably, serum levels of IL-1β and IL-6 also did not decrease in CIRT, which suggests that MTX in this population did not target these critical cytokines.

However, in patients with inflammatory conditions, such as RA, the results can be different: Roubille *et al* showed a 28% reduction in cardiovascular events in MTX users.[9]

The Colchicine Cardiovascular Outcomes Trial study, published in 2019, randomised 4745 patients with a recent myocardial infarction to colchicine 0.5 mg/day or placebo, in addition to their cardiovascular medication.[10] The primary endpoint was a composite index of cardiovascular death, resuscitated cardiac arrest, myocardial infarction, stroke or urgent hospitalisation for angina leading to coronary revascularisation. This endpoint was met in 5.5% of colchicine-treated patients and in 7.7% of the placebo group (HR 0.77, 95% CI: 0.61 to 0.96, p=0.02). However, this difference was based on a 50% reduction in angina leading to revascularisation and 75% reduction in stroke, without significant reduction in the other three endpoints. Therefore, the results were criticised in that the benefit was modest and driven by the soft endpoint of angina for revascularisation and thus did not support routine use of colchicine without a better understanding on the absence of effect on myocardial infarct and death.[11]

What about the side effects? Diarrhoea was found in similar proportions, 9.7% (colchicine) versus 8.9% (placebo), p=0.35, probably related to the low dosage of colchicine. Somewhat unexpectedly, pneumonia occurred more often in colchicine users (0.9% vs 0.5%, p=0.03). Another remarkable point is that statins were used in 94% of patients, but myalgias, regarded as a common side effect, occurred only slightly more frequently in colchicine users: 21.2% versus 18.5%.

Recently, Nidorf *et al* published a study (low dose colchicine (LoDoCo2)) that randomised 5522 patients to colchicine 0.5 mg/day or placebo.[12] Only patients with chronic coronary disease were included, 84% had a previous acute coronary syndrome. After a median follow-up of 29 months, the primary endpoint (cardiovascular death,

myocardial infarction, ischaemic stroke or ischaemic-driven coronary revascularisation) was met in 6.8% of the colchicine group and in 9.6% of the placebo group: (HR 0.69, 95% CI: 0.57 to 0.83, p=0.001). In addition, favourable (non-significant) trends were seen for cardiovascular death (20 in colchicine-treated patients vs 25 in placebo) but not for non-cardiovascular death (53 vs 35, respectively).

Very recently, in an interesting but relatively small Australian randomised controlled study (COPS) in 795 patients with an acute coronary syndrome, 24 cardiovascular events were observed in the colchicine group and 38 in the placebo group (p=0.09), although that there was an increased risk in non-cardiovascular death in the colchicine group (5 vs 0, p=0.024).[13] It is possible that the imbalance in non-cardiovascular death was related to chance, in the COPS trial 3/5 non-cardiovascular deaths occurred in patients who ceased colchicine early (<30 days) and died months later. In the LoDoCo2 trial, a favourable trend was seen for cardiovascular death in the colchicine group: as a consequence, the risk of non-cardiovascular death was higher in the placebo group. In meta-analyses, no significant increase in non-cardiovascular death was found.[14 15] That is reassuring, but further research on this topic should be on the research agenda.

WHAT CAN WE LEARN FROM THESE TRIALS?

The favourable results for canakinumab and colchicine confirm (low-grade) inflammation as an independent risk factor for cardiovascular events and a new opportunity for treatment. The negative results in the MTX study do not detract from this, as the levels of CRP, IL-1β and IL-6 did not decrease during MTX treatment.

In addition, the large number of included patients yield important information on side effects: cancers, particularly non-basal cell skin cancers, occurred more often in the MTX group;[16] the sample size of this study exceeds previous RCTs within the field of rheumatology with MTX. Remarkably, the occurrence of myalgias did not differ significantly between colchicine and placebo users. Whether or not colchicine leads to an increased risk of non-cardiovascular death needs to be elucidated.

The data on the favourable cardiovascular effects and safety of colchicine are convincing, and the drug costs are low. Moreover, all rheumatologists have experience in the long-term use with this drug and side effects are usually mild and rare,[17] although colchicine must not be described in patients with advanced renal disease and might be limited by leucopenia and polyneuropathy. Perhaps the most burning question is: how to implement the findings of these studies? We have several recommendations:

First, we believe that cardiologists are not (yet) used to prescribe anti-inflammatory drugs for secondary prevention of cardiovascular events and may be somewhat reluctant to do that. Thus, our first-line action should be to

initiate contact between the rheumatologist and the cardiologist and to discuss whether the additional use of an anti-inflammatory drug such as colchicine is an option in patients at high risk for secondary cardiovascular events.

Second, we also feel that national organisations of rheumatology should start forging bridges with national organisations of cardiology to help to implement the use of anti-inflammatory drugs for the secondary prevention of cardiovascular events in patients with atherosclerosis. The same applies to our larger organisations, such as EULAR, ACR and ILAR.

Third, the recent convincingly positive results lead to many follow-up questions on the research agenda: is the benefit seen with colchicine and canakinumab in secondary prevention also applicable in primary prevention? As rheumatologists, we would be inclining this first and foremost in patients with inflammatory rheumatological diseases.

Fourth, for the academic rheumatologist, these findings point to many important avenues for future research. Studies of these mechanisms have been boosted by the availability of successful treatments, and we anticipate that the demonstrated clinical benefit of IL-1 blockade will refine our understanding of the role of this cytokine in atherogenesis and that of future successful treatments in this arena.

In summary, we are convinced that the use of anti-inflammatory and immunomodulatory medications is now becoming a reality for the secondary prevention of cardiovascular events, with colchicine as the first drug in the clinic, but with the expectation that hopefully this is only the first in a future series of anti-inflammatory drugs. As rheumatologists, being experts on the use of these medications, we should embrace a new role in extending their potential benefits to millions of individuals.

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REFERENCES

1. Kattoor AJ, Pothineni NVK, Palagiri D, *et al*. Oxidative stress in atherosclerosis. *Curr Atheroscler Rep* 2017;19:42.
2. Vergallo R, Crea F. Atherosclerotic plaque healing. *N Engl J Med Overseas Ed* 2020;383:846–57.
3. Hansildaar R, Vedder D, Baniaamam M, *et al*. Cardiovascular risk in inflammatory arthritis: rheumatoid arthritis and gout. *Lancet Rheumatol* 2021;3:e58–70.
4. Mangoni AA, Zinellu A, Sotgia S, *et al*. Protective effects of methotrexate against proatherosclerotic cytokines: a review of the evidence. *Mediators Inflamm* 2017;2017:1–11.
5. Ridker PM, Everett BM, Thuren T, *et al*. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *N Engl J Med* 2017;377:1119–31.
6. Ridker PM, Everett BM, Pradhan A, *et al*. Low-Dose methotrexate for the prevention of atherosclerotic events. *N Engl J Med* 2019;380:752–62.
7. Smolen JS, Landewé RBM, Bijlsma JWJ, *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis* 2020;79:685–99.
8. Singh JA, Saag KG, Bridges SL, *et al*. 2015 American College of rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol* 2016;68:1–26.
9. Roubille C, Richer V, Starnino T, *et al*. The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: a systematic review and meta-analysis. *Ann Rheum Dis* 2015;74:480–9.
10. Tardif J-C, Kouz S, Waters DD, *et al*. Efficacy and safety of low-dose colchicine after myocardial infarction. *N Engl J Med* 2019;381:2497–505.
11. Newby LK. Inflammation as a treatment target after acute myocardial infarction. *N Engl J Med* 2019;381:2562–3.
12. Nidorf SM, Fiolet ATL, Mosterd A, *et al*. Colchicine in patients with chronic coronary disease. *N Engl J Med* 2020;383:1838–47.
13. Tong DC, Quinn S, Nasis A, *et al*. Colchicine in patients with acute coronary syndrome: the Australian cops randomized clinical trial. *Circulation* 2020;142:1890–900.
14. Samuel M, Tardif J-C, Bouabdallaoui N, *et al*. Colchicine for secondary prevention of cardiovascular disease: a systematic review and meta-analysis of randomized controlled trials. *Can J Cardiol* 2020;S0828-282X:31053–9.
15. Xia M, Yang X, Qian C. Meta-Analysis evaluating the utility of colchicine in secondary prevention of coronary artery disease. *Am J Cardiol* 2021;140:33–8.
16. van Vollenhoven RF, Nurmohamed M. Methotrexate for prevention of cardiovascular events. *N Engl J Med* 2019;380:2276–76.
17. Stewart S, Yang KCK, Atkins K, *et al*. Adverse events during oral colchicine use: a systematic review and meta-analysis of randomised controlled trials. *Arthritis Res Ther* 2020;22:28.