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EDITORIAL

Therapeutic role of colchicine in reducing cardiovascular risk associated with inflammation

Papel terapéutico de la colchicina en la reducción del riesgo cardiovascular asociado a la inflamación

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Atherosclerotic cardiovascular disease (CVD) is the leading cause of death in developed countries. In recent decades, highly significant advances have been made in preventing this disease by addressing the main cardiovascular risk factors (CVRFs), which include dyslipidaemia, hypertension and smoking, and treating diseases that also carry an increased risk such as diabetes mellitus (DM). However, patients with established CVD are still at high risk of recurrence of CV events despite suitable implementation of lifestyle changes and optimal drug treatment. The factors responsible for this residual risk include inflammation.

In recent years a great deal of knowledge has been accumulated pointing to inflammation as a determining factor in the development of arteriosclerosis.[1] Notably, the presence of inflammatory cells, along with deposition of low-density lipoprotein cholesterol (LDL-C) particles, has been found to be a common element in the onset and progression of arteriosclerotic lesions, and these inflammatory cells have been found to be more abundant in unstable plaques. This suggests that inflammation plays a major role in the final phase of plaque rupture. In addition, many studies have shown that high-sensitivity C-reactive protein (hs-CRP), an inflammatory biomarker synthesised in the liver in response to interleukin 6 (IL-6), enables identification of individuals with unstable arteriosclerotic disease at increased risk of acute cardiovascular events.[2]

However, despite this evidence, translation from knowledge of pathophysiology to verification that pharmacological intervention in the mechanisms of inflammation causes a significant reduction in cardiovascular risk in patients has been more elusive. Just some clinical trials have suggested that those statins that achieve greater reductions in hs-CRP levels yield a greater reduction in cardiovascular risk.[3] However, since at the same time these statins achieve the greatest reductions in LDL-C, the benefits achieved are difficult to interpret.[2] The soundest answers came with the CANTOS study. This was a clinical trial that assessed the effects on CVD of canakinumab, a monoclonal antibody for injection specifically intended to inhibit interleukin 1β (IL-1β), which is an essential cytokine in the IL-6, tumour necrosis factor alpha (TNF-α) and hs-CRP precursor inflammation cascade.[4] In the CANTOS study, administration of three doses of canakinumab every three months in 10,061 patients with a history of acute coronary syndrome and hs-CRP >2 mg/l, after a mean follow-up of 3.7 years, yielded a significant reduction in the primary endpoint, defined as a non-fatal acute myocardial infarction (AMI), non-fatal stroke or cardiovascular death, regardless of lipid levels. No reduction

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in overall mortality was found, and canakinumab was associated with a slight but statistically significant increase in the risk of fatal infection (0.31 versus 0.18 events per 100 person-years; p = 0.02). By contrast, administration of methotrexate in patients with established arteriosclerotic disease showed no cardiovascular benefits, though some observational studies in patients with rheumatoid arthritis treated with methotrexate suggested this.[5]

Colchicine is an anti-inflammatory drug originally derived from a herbaceous plant, *Colchicum autumnale*, also called autumn crocus or wild saffron. It is known to have been used for medicinal purposes since ancient times in Greece and Egypt. Traditionally, it has been used to treat gout, familial Mediterranean fever and pericarditis. The anti-inflammatory properties of colchicine have some unique characteristics. Although its exact mechanism of action is unknown, its main function is based on inhibition of tubulin polymerisation. The anti-inflammatory effects thereof are due to a combination of several mechanisms, but three in particular. First, alteration of tubulin results in modification of the structure of the NLRP3 inflammasome, thus reducing the release of IL-1β and other interleukins such as IL-6. It also alters neutrophil chemotaxis, thus impeding activation, degranulation and migration of neutrophils. Finally, in endothelial cells, colchicine inhibits production of IL-1β and expression of E-selectin, which are required for neutrophil adhesion.[6]

Research in recent years has revealed how the cellular effects of colchicine would translate to cardiovascular benefits for patients with established arteriosclerotic disease. In 2007, Nidorf et al. found that adding low-dose colchicine in patients with known coronary artery disease and optimal medical treatment with statins and antiplatelet drugs would cause significant reductions in hs-CRP levels.[7] Since then, various publications have demonstrated the beneficial effects of colchicine in terms of arteriosclerotic plaque morphology,[8] reduction of the risk of intra-stent stenosis[9] and reduction of the risk of cardiovascular events in patients with stable ischaemic heart disease.[10] The COLCOT clinical trial analysed the preventive effects of colchicine (0.5 mg/day) on a composite endpoint of AMI, stroke, emergency hospitalisation for angina with a need for coronary revascularisation or death due to a cardiovascular cause in 4,500 patients with a recent history of AMI (within the past 30 days). Colchicine yielded a 23% reduction in the primary endpoint (HR 0.77, 95% CI 0.67–0.96; p = 0.02) during a mean follow-up of 22.6 months.[11] While this study examined the effects of colchicine in patients having had a recent coronary event, a subsequent study focused on the risk reduction that colchicine can achieve in patients with chronic ischaemic cardiomyopathy. The LoDoCo2 study assessed cardiovascular risk reduction with the addition of colchicine (0.5 mg/day) versus placebo in 5,522 patients with chronic coronary disease with a follow-up of 29 months. The group treated with colchicine showed a reduction in the primary endpoint (consisting of cardiovascular death, AMI, ischaemic stroke or emergency coronary revascularisation) by 31% (HR 0.69, 95% CI 0.57—0.83; p < 0.001), as well as a reduction in the composite secondary endpoint of cardiovascular death and AMI, among other secondary endpoints. However, a higher incidence of non-cardiovascular death was detected in the group treated with colchicine; this was modest in absolute numbers and did not attain statistical significance.[12]

A systematic review and meta-analysis summarising the information available in clinical trials with colchicine in subjects with coronary heart disease was recently published by the Colchicine Cardiovascular Trialists Collaboration.[13] It concluded that colchicine (0.5 mg/day) added to conventional treatment in patients with a recent AMI or chronic coronary disease offers significant reductions in the risk of AMI, stroke and coronary revascularisation (22%, 46% and 23%, respectively) with no significant reduction in cardiovascular death. This meta-analysis again detected a slightly increased, non-significant number of non-cardiovascular deaths; in the analysis performed, this could not be attributed to infectious complications or cancer.

This evidence was reflected in the 2021 guidelines on cardiovascular prevention in clinical practice of the European Society of Cardiology which include, with a IIb level of evidence, a grade A recommendation to consider low-dose colchicine (0.5 mg/day) in secondary prevention in patients with CVD, especially if other risk factors are not sufficiently managed or if recurring events occur despite optimised treatment.[14]

Ultimately, colchicine, which is usually a well-tolerated drug at low doses, has been postulated as an additional therapeutic tool to reduce cardiovascular risk in patients in secondary prevention. The available evidence describes highly significant risk reductions that are especially difficult to achieve in patients already on optimised treatment. The inflammatory pathway is presented as a clear therapeutic target to reduce the residual risk of patients with arteriosclerotic CVD and colchicine as an effective alternative for our patients.

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Conflicts of interest

None in relation to this manuscript.

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