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Seeking and treating inflammation in ischaemic heart disease: are we ready?

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Systemic inflammation, which contributes to atherosclerosis development and progression, plays a significant role in addressing the residual cardiovascular risk. Several studies have highlighted a linear correlation between high levels of the inflammation marker high-sensitivity C-reactive protein (hsCRP) and cardiovascular events. However, its use as a risk modifier remains debated, primarily due to its low specificity. The search for alternative systemic markers, such as interleukin-6 (IL-6), and signs of local inflammation, such as pericardial fat tissue, may provide improved prognostic tools. Computed tomography (CT)-positron emission tomography (PET) using 68Ga-DOTATATE, which binds to macrophage receptors, appears promising for identifying high-risk coronary lesions. Among invasive methods, optical coherence tomography is the only modality with sufficient resolution to study macrophages. Recent studies have shown how the regulation of inflammation may represent a new therapeutic strategy to safely reduce residual cardiovascular risk, particularly through molecules that inhibit microtubule formation and modulate IL-1α-1β signalling, IL-6, by lowering hsCRP values. The latest European Society of Cardiology guidelines recommended using colchicine in ischaemic heart disease with class IIA indication. However, the evidence of colchicine's efficacy in this context remains conflicting and inconclusive. In addition, using new systemic markers (IL-6) and modern non-invasive CT or CT-PET imaging techniques will lead to better accuracy in the diagnosis of inflammation, not only systemic but also organ- and lesion-specific.

The role of blood markers

If reducing LDL (low-density lipoprotein) cholesterol is a primary and secondary prevention goal, the treatment of inflammation residual risk has a more uncertain clinical location. Despite therapeutic doubts, the measurement of inflammation, routinely expressed by the high-sensitivity C-reactive protein (hsCRP) value, can stratify the residual risk of cardiac events[1] in patients with acute or chronic coronary syndrome.[2] According to a recent meta-analysis of 31 245 patients with atherosclerosis and on statin treatment, the hsCRP value better identified those at risk of cardiovascular events (including cardiac death and myocardial infarction) than the residual LDL cholesterol value. Furthermore, in subjects with hsCRP >2 mg/L, the risk of cardiovascular death remained elevated regardless of low-density lipoprotein cholesterol (LDL-C) level.[3] Data from a Swedish registry performed on 17 464 patients with previous myocardial infarction reached similar conclusions. A linear correlation was present between hs-CRP level and the risk of cardiovascular events for hs-CRP values between 2 and 5 mg/L. In contrast, the

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association was absent for values <1 mg/L.[4] Conversely, using hsCRP to stratify the risk of cardiovascular events in primary prevention is still a debated issue. A significant limitation of marker titration lies in its low specificity for coronary artery disease, being increased in many inflammatory diseases. Despite these limitations, a recent observation by Ridker *et al.*[5] highlights the prognostic role of hs-CRP even in primary prevention. The authors measured its level along with LDL cholesterol and lipoprotein(a) in 27 939 women without ischaemic heart disease. They then evaluated the clinical impact of the markers 30 years after enrollment, employing the composite of myocardial infarction, coronary revascularization, stroke, or death from cardiovascular causes as the primary endpoint. Each biomarker (including hsCRP) represented an independent variable of overall risk.

The role of hsCRP in the genesis of atherosclerosis and the occurrence of acute events is still unclear. While some *in vitro* and animal studies suggest a pro-atherogenic role of hsCRP,[2] many argue that hsCRP should instead be considered a systemic marker of disease, reflecting possible widespread generalized inflammation due to atherosclerosis. Indeed, it can be ruled out that the increase in the systemic marker is generated by a single plaque responsible for an acute coronary syndrome (ACS) or with features of vulnerability. Studies *in vitro*[6] or conducted with optical coherence tomography (OCT)[7] show a higher macrophage content at the level of plaques responsible for acute coronary events compared with non-culprit coronary lesions. Recently, much interest has developed among the scientific community in measuring inflammation with interleukin-6 (IL-6). This hypothesis has gained considerable support from Mendelian randomization studies suggesting that genetic variants implicated in IL-6 synthesis (resulting in a reduced inflammatory response) are associated with reduced coronary risk.[8] Its extensive use in cardiology, replacing hs-CRP, is possible in the future.

Role of 'imaging in the study of coronary inflammation'

Searching for signs of local (cardiac) inflammation instead of systemic blood markers can be an effective prognostic tool. The detection of epicardial adipose tissue is also emerging as a practical solution because of the ease with which it can be detected and quantified by echocardiography, computed tomography (CT), and magnetic resonance imaging. Perivascular adipose tissue is involved in local stimulation of atherosclerotic plaque formation. It also correlates with metabolic syndrome parameters, including increased waist circumference, hypertriglyceridaemia, hyperglycaemia, and finally coronary atherosclerosis.[9] Indeed, it is capable of secreting pro-inflammatory cytokines and adipokines, which are found to be more highly expressed in patients with coronary artery disease by promoting the formation of atherosclerosis. Interestingly, segments of the coronary artery that are covered by myocardium and are not exposed to perivascular adipose tissue do not exhibit atherosclerosis.

The CRISP study[9] enrolled 2040 patients undergoing coronary CT. At a median follow-up (FU) of 72 months, a correlation was appreciated between high perivascular fat attenuation index (FAI) values around the proximal right coronary artery and left anterior descending artery. A high perivascular FAI (cutoff ≥ 70-1 HU) measured around the right coronary artery (employed as a biomarker of global coronary inflammation) predicted cardiac mortality, [HR] 2.15, 95% CI 1.33–3.48; $P = 0.0017$.

CT–positron emission tomography (PET) with 68Ga-DOTATATE is proposed as an exciting solution that can discriminate high-risk coronary lesions. It is a novel marker of atherosclerotic inflammation that binds explicitly to macrophage receptors (somatostatin receptor subtype-2). Tarkin *et al.*[10] demonstrated that 8Ga-DOTATATE correctly identified culprit lesions of patients with ACS and was able to predict the presence of high-risk lesions according to CT assessment.

Among the invasive methods, OCT is the only one with sufficient resolution to study macrophages. In the CLIMA study,[11] the presence of macrophages identified subjects with an increased risk of challenging cardiac events (cardiac death or infarction) at FU. According to a recent study, the quantification of macrophages[12] assessed in the cross-section with more inflammation and expressed in circumferential arc had a more accurate prognostic impact than the simple qualitative evaluation (presence vs. absence). In addition, a poor correlation was present between focal inflammation identified by macrophage arc and systemic inflammation calculated by hsCRP value. Using artificial intelligence techniques to measure the mean value of macrophage arc in a given lesion may more accurately express the inflammatory component of plaques in the future.

Trials on the use of anti-inflammatory drugs

Multiple studies have evaluated the use of colchicine in subjects with ischaemic cardiopathy. The drug prevents microtubule polymerization by interfering with leukocyte function.[13]

The LODOCO II trial compared the use of colchicine 0.5 mg in subjects with chronic coronary syndrome for the first time in a large, randomized trial of 5522 patients.[14] The primary endpoint of the study, assessed at 2 years, was a composite of cardiovascular death, spontaneous infarction, ischaemic stroke, or coronary revascularization. The primary endpoint occurred in 6.8% of patients in the colchicine group and 9.6% of patients in the placebo group [hazard ratio (HR) 0.69, CI 0.57–0.83; $P < 0.001$]. Further confirming the efficacy of colchicine, the incidence of the hard end-point represented by cardiovascular death or myocardial infarction was also significantly reduced with the drug (1.3% vs. 1.8%, respectively, HR 0.71, $P = 0.001$). Finally, no differences were noted regarding hospitalizations for infection, including pneumonia or gastrointestinal affections.

The findings of the randomized COLCOT trial[15] also proceeded in the same direction as LODOCO. Colchicine was being tested in 4745 patients with recent prior myocardial infarction (within 30 days). The primary end point (composite of cardiovascular death, myocardial

infarction, resuscitated cardiac arrest, stroke, and hospitalization for angina) occurred in 5.5% of patients treated with Colchicine compared with 7.1% of subjects in the placebo group (HR 0.77; confidence interval 0.61–0.96, $P = 0.02$). The HR was 0.84 for cardiovascular death and 0.91 for myocardial infarction. The incidence of diarrhoea was non-significantly increased in the Colchicine-treated group but there was an increase in the incidence of pneumonia (0.9% vs. 0.4%, $P = 0.03$). Interestingly, no significant differences in the change of hsCRP were observed in the two groups. However, the significance of this observation is limited by the number of subjects in whom the inflammatory index was assessed (about 10% of the study population).

Against this background and in a climate undoubtedly favourable to the use of colchicine, as evidenced by the recent European Society of Cardiology guidelines that suggested the use of the drug in ischaemic heart disease[1] with upgrades from class II B to II A, came the CLEAR[16] trial testing colchicine in the setting of ACS.

CLEAR[16] was the first clinical end-point trial to test the superiority of colchicine vs. placebo in subjects with ACS, after the publication of small studies using surrogate end-points.[1] This was a multicenter, randomized, double-blind study of 795 patients with 12-month FU. Colchicine was used at a dose of 0.5 mg twice daily for the first month and then at 0.5 mg/day thereafter. The primary endpoint of the study, a composite of cardiovascular death, recurrence of myocardial infarction, stroke or revascularization, assessed at three years after enrollment occurred in 9.1% of subjects in the colchicine group and 9.3% of patients in the placebo group (HR 0.99 confidence interval 0.85–1.16 $P = 0.93$). Diarrhoea was more frequently observed in the colchicine-treated group (6.6% VS 0.2% $P < 0.001$).

Note how there was a downward trend at FU for no individual endpoints. The HR was 1.03 for cardiac death, 0.88 for infarct recurrence, 1.15 for stroke, and 1.01 for revascularization. The data, certainly not expected, are challenging to interpret because they differ markedly from other studies. There is no doubt that the CLEAR trial represents a setback in the use of colchicine in ischaemic heart disease. The different selection of patients included in the CLEAR trial [acute ST-elevation myocardial infarction (STEMI)] compared with the COLCOT and LODOCO trials do not seem a plausible justification. In a more severe clinical setting, even greater efficacy should have been expected from the use of a drug with anti-inflammatory action. In defense of the use of colchicine, it could be objected that in 25% of the subjects, the therapy was discontinued. Finally, the side effects of the drug should not be forgotten and in particular, the not inconsiderable incidence of diarrhoea.

Interleukin and chemokine inhibitors

The CANTOS study[17] evaluated for the first time in a clinical trial of patients with ischaemic heart disease the impact of a human anti-IL-1β monoclonal antibody. The study randomized 10 061 patients with previous myocardial infarction to three doses of canakinumab (50, 150, and 300 mg) vs. placebo. There was a significant reduction in hs-CRP values in the three canakinumab treatment groups compared with the baseline and placebo groups. In addition, in the canakinumab 150 and 300 mg groups there was a significant reduction in the primary endpoint (2-year composite of non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death) compared with the placebo group. Combining the two groups (150 and 300 mg) canakinumab was accompanied by a 15% reduction in the relative risk of meeting the primary endpoint. However, the significant decrease in cardiovascular events came at the expense of an increase in fatal infections.

The Virginia Commonwealth University Anakinra Remodelling Trial 3[8] was a randomized clinical trial that tested a new IL-1 receptor inhibitor. The trial included only 99 patients with STEMI myocardial infarction. Anakinra significantly reduced the level of hs-CRP and, with it, the incidence of death or new-onset heart failure compared with placebo (9.4% vs. 25.7%; $P = 0.046$ and 0% vs. 11.4%; $P = 0.011$). The Authors did not observe an increased incidence of serious infections in the Anakinra arm.

The RESCUE study[18] evaluated the efficacy of Ziltivekimab, a novel human antibody directed against the IL-6 ligand, in reducing inflammation in patients with advanced chronic kidney disease.

The randomized trial was conducted in 264 subjects with moderate to severe chronic kidney disease and increased HSCRP-HS levels (>2 mg/L). At 12 weeks, median hs-CRP levels were reduced by 77% for the 7.5 mg group, 88% for the 15 mg group, and 92% for the 30 mg group, compared with 4% for the placebo group. The drug was also well tolerated in the absence of serious side effects.

Preliminary studies on anakinra and Ziltivekimab, and other monoclonal antibodies against IL-6 receptors (Tocilizumab and Sarilumab) are certainly encouraging. Still, the small size of the study population calls for further documentation of efficacy.

Drugs with predominantly non-inflammatory action

Statins have emerged as drugs with marked anti-inflammatory and hypolipidaemic action. The anti-inflammatory action goes hand in hand with the LDL-C-lowering action and may be a consequence of it. The class of drugs, however, has a pleiotropic action that consists of attenuating T-cell activation and inhibiting pro-inflammatory cytokine secretion.

Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9) inhibitors also exert an anti-inflammatory action that does not seem to be attributable to a reduction in hs-CRP. Indeed, regression studies show that the drugs reduce the inflammatory component expressed by macrophage content at OCT.[19,20]

Glucagon-like peptide 1 agonists also exert a crucial anti-inflammatory function, limiting monocyte adhesion and macrophage accumulation within the plaque. The great efficacy of semaglutide shown in the SELECT study[21] in obese patients seems largely attributable to the drug's anti-inflammatory action, as documented by the lowering of hsCRP. The latter could be a consequence of the marked reduction in visceral fat as well as due to the drug's pleiotropic action.

Other molecules acting on different pathways such as ox-LDL antibodies, 5-Lipoxygenase inhibitors, and

Phospholipase A2 Inhibitors have also been tested. The drugs, however, have not provided encouraging results at present.[13]

Final considerations

Measuring inflammation with a systemic index (hsCRP) is a reasonable solution.[22] Shortly, however, other blood parameters, such as IL-6, may improve the accuracy in the diagnosis of inflammation. Non-invasive CT or CT-PET imaging methods will likely be able to identify coronary inflammation better, moving from the concept of systemic inflammation to that of organ inflammation. Regarding the therapy of inflammation in a secondary prevention pathway, the great utility of statins and PCSK9 inhibitors in silencing inflammation and lowering cholesterolaemia should be noted. There are, in my view, no drugs with anti-inflammatory action that we can rely on with certainty. Unfortunately, the results obtained with colchicine do not go in one direction in the face of side effects to be considered. New molecules that can inhibit IL-6 are certainly of interest. They could further improve the prognosis of subjects who are optimally treated with hypolipidaemic therapy but have residual inflammation. There remain, of course, issues of an economic nature to be addressed. For example, employing dual therapy with subcutaneous anti-PCSK9 and anti-IL-6 drugs represents a costly solution. It might be particularly advantageous to use small interfering RNA therapeutic solutions[8] that can silence the inflammatory component and lower cholesterolaemia.

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