Letter to the Editor

Canakinumab: can it untie the Gordian knot of cardiovascular disease in patients with familial Mediterranean fever?

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Familial Mediterranean fever (FMF) is a monogenic autoinflammatory disease, characterized by inflammatory attacks of fever and polyserositis [1]. Missense mutations in the MEFV gene triggering abnormal activation of the pyrin inflammasome and the subsequent excessive production of interleukin-1β (IL-1β) constitute the major underlying pathophysiological mechanism [2].

Patients with FMF are at high cardiovascular risk, which adds a significant burden to their quality of life, complicating at the same time their therapeutic management [3]. In their cross-sectional study with a prospective 3-year follow-up period, Yilmaz *et al.* observed that patients with FMF and secondary amyloidosis had increased risk of cardiovascular events, highly associated with elevated levels of asymmetric dimethyl arginine (ADMA), decreased flow-mediated dilatation (FMD) and an excessive inflammatory state [3].

Cakar *et al.* observed that patients with FMF during disease attacks had higher pulse wave velocity (PWV) and lower branchial and aortic augmentation indexes, both surrogate markers of arterial stiffness [4], when compared with asymptomatic patients and healthy controls [5]. Impaired arterial stiffness, as represented by PWV, correlated significantly with the main inflammatory markers, including serum C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cells count (WBC), fibrinogen and neutrophil/lymphocyte ratio. In another cross-sectional study, Acay *et al.* observed that atherogenic index (triglycerides/high-density lipoprotein-cholesterol) was significantly higher in patients with FMF compared to healthy controls [6]. The authors concluded that the atherogenic index may be an indicator of accelerated atherosclerosis in those patients, an observation that needs to be further elucidated in large-scale prospective studies.

A recently published study by Basar *et al.* shed light on the association between MEFV gene mutations and early coronary artery disease (CHD) [7]. More specifically, the researchers observed that MEFV gene mutations were significantly more frequent in patients with early CHD, when compared with those suffering from CHD in the presence of well-established risk factors or healthy controls. Interestingly, there were twice as many patients with early CHD and at least one MEFV gene mutation, compared with the two other study groups [7].

Puricel *et al.* conducted a retrospective clinical study, involving all patients admitted with acute coronary syndrome (ACS) aged less than

30 years in their department, during a 16-year period [8]. Acute coronary syndrome was of non-atherosclerotic (non-ATS) etiology in 37% of all patients, while FMF constituted a major underlying etiology in the latter group (7%). The 5-year mortality and major adverse cardiovascular event (MACE) rates were 19% and 7% in the non-ATS and the ATS groups, respectively. Despite the presence of certain risk factors in both groups, mainly smoking and dyslipidemia, it is undoubtable that FMF is a major risk factor for cardiovascular disease, implicating both ATS and non-ATS mechanisms. On the other hand, there is contradictory evidence supporting that FMF is associated with lower incidence rates of certain cardiovascular and metabolic risk factors compared to healthy controls [9]. However, the aforementioned study conducted by Twig *et al.* lacks stratification of the results by the degree and severity of disease activity and genetic variants, due to the fact that the researchers included only military participants with FMF, who can be considered as healthier than other FMF patients [9].

Colchicine is considered as the first line treatment option in patients with FMF, with potential preventive action against cardiovascular disease, partially due to improvement in endothelial function [10, 11]. However, it is ineffective or not tolerated in a significant proportion of those patients (5–10%). In such cases, canakinumab, a monoclonal antibody against IL-1β, offers an alternative treatment option in patients with colchicine-resistant disease [12].

It was recently reported in CLUSTER, a phase 3 clinical trial, that canakinumab led to a complete response at week 16 in 61% of all stratified FMF patients compared to 6% of those FMF patients assigned to placebo ($p < 0.0001$) [12]. In an explanatory analysis it was found that 71% of all colchicine-resistant FMF patients achieved a complete response with canakinumab ($p < 0.0001$), while, after week 16, an extended dosing interval of canakinumab bi-monthly led to disease control up to 46% in the same study group [12]. Despite the increased risk of infections associated with canakinumab administration, none was opportunistic, while all resolved without consequences.

Experimental data support that cholesterol crystals activate the NOD-like receptor pyrin domain containing protein inflammasome, which finally leads to the generation of IL-1β and the triggering of a systemic inflammatory response [13]. The CANTOS trial, conducted by Ridker *et al.*, investigated the potential role of canakinumab at three separate doses, 50, 150 or 300 mg, injected subcutaneously every three months, in cardiovascular disease [14]. The primary efficacy end point was nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death. After a median follow-up period of 3.7 years, the researchers observed that hazard ratios (HR) for the primary endpoint for the three separate doses of canakinumab compared to placebo, were as follows: in the 50-mg group, 0.93 (95% confidence interval (CI): 0.80–1.07; $p = 0.30$); in the 150-mg group, 0.85 (95% CI: 0.74–0.98; p = 0.021); and in the 300-mg group, 0.86 (95% CI: 0.75–0.99; $p = 0.031$). Regarding the secondary efficacy endpoint (primary endpoint plus hospitalization for unstable angina that required an urgent revascularization procedure), only canakinumab 150 mg led to a statistically significant result, in comparison with placebo (HR = 0.83; 95% CI: 0.73–0.95; $p = 0.005$). Canakinumab did not affect mortality rates among the different study groups [14].

However, a sub-analysis of the CANTOS trial showed that those patients who achieved hsCRP levels lower than 2 mg/l with canakinumab treatment had a 25% reduction in the incidence rate of major cardiovascular events (HRadj = 0.75; 95% CI: 0.66–0.85, $p < 0.0001$), and 31% reduction in both cardiovascular (HRadj = 0.69; 95% CI: 0.56–0.85, $p = 0.0004$) and all-cause mortality (HRadj = 0.69; 0.58–0.81, $p < 0.0001$), while those patients featuring greater inflammatory activity with hsCRP levels higher than 2 mg/l did not benefit from canakinumab treatment at a statistically significant level [15].

A closer look at the aforementioned data and a meticulous interpretation of the derived evidence leads to the conclusion that canakinumab might play a crucial role in terms of decrease in cardiovascular morbidity and mortality in FMF patients, constituting an attractive and promising treatment option. Another fact is that there is a distinct phenotype of patients, those with excessive inflammatory activity, who might benefit most from canakinumab administration. Randomized controlled trials with appropriate design and careful recruitment of FMF patients will elucidate whether canakinumab can untie the Gordian knot of cardiovascular disease in those patients.

Conflict of interest

The author declares no conflict of interest.

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