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EDITORIAL

Inflammatory residual risk: An emerging target to reduce cardiovascular disease?

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For a long time, the most considered cause of atherosclerosis has been related to a cholesterol storage disorder, characterized by the deposition of cholesterol in the arterial wall. More recent data focused the attention on the proliferation and migration of smooth-muscle cells as well as on blood cells. Over the most recents years, however, the concept that inflammation may play a key role in the atherogenesis has been progressively raised, along with the discovery of the immune basis of allograft arteriosclerosis, which demonstrated that inflammation per se can drive arterial hyperplasia even in the absence of traditional risk factors. The understanding of the participation of inflammation in atherosclerosis cannot reduce the importance of traditional risk factors as causal pathogenic drivers of cardiovascular disease, but the validation of these concepts in humans could have an important impact on medical clinical practice both in prevention and in treatment.[1]

To reduce the burden of atherosclerotic diseases, several pharmacological interventions have been proposed and tested in different clinical conditions, including those involving high and very high cardiovascular-risk patients. Although the incidence of major cardiovascular events and their severity has been reduced as a result of the progress in the therapeutic management of the acute conditions, the occurrence of events and lethality persist in spite of optimal medical therapy. In particular, scientific and clinical identification of the so-called residual cardiovascular risk in statin-treated populations has substantially encouraged further exploration of the key pathophysiological mechanisms of life-threatening vascular events.

Following these studies, atherosclerosis and its complications are no longer viewed as mere consequences of high levels of cholesterol, blood pressure, plasma glucose, or cigarette smoking. They are now considered complex, multifactorial, and progressive disorders, in which proinflammatory biological pathways are not only involved but seem to play a major role. These proinflammatory factors may promote endothelial dysfunction and local inflammation, favoring vascular wall damage and development of atherosclerotic plaque, which may significantly contribute to several clinical manifestations.

Since the 1990s, the scientific community identified in elevated serum high-sensitivity C-reactive protein (hsCRP) levels, a marker of the vascular inflammatory process that predicts the progression of atherosclerotic plaque, its recurrent instability, and a worse outcome.[2] It was clear that independently or beside low-density lipoprotein (LDL) levels, or the concomitant presence of the other risk factors, hsCRP levels could predict outcomes.[3]

Results from the JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin),[4] PROVE-IT TIMI-22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22),[5] and ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm)[6] trials demonstrated that serum levels of hsCRP might be considered as important as levels of LDL-cholesterol (LDL-C) to define the residual cardiovascular risk in high-risk individuals with hypercholesterolemia. In addition, the JUPITER trial demonstrated that those patients with elevated hsCRP but without hyperlipidemia could significantly benefit from statin therapy, namely rosuvastatin, in terms of reduced incidence of major cardiovascular events in a setting of primary cardiovascular disease prevention.

On the other hand, in a setting of secondary prevention, serum levels of hsCRP in patients with prior myocardial infarction are powerful predictors of subsequent events. It has been reported that rates of recurrent events are up to 60% higher in patients with hsCRP ≥2 mg/L compared to those without a high inflammatory burden, independent from the intensity of statin treatment. Although intensive statins therapy reduces levels of hsCRP, persistently high levels of this inflammatory marker are common in patients after a myocardial infarction, as reported in the PROVE-IT TIMI-22 trial,[5] in which about 43% of patients randomized to receive atorvastatin 80 mg daily had on-treatment, persistently high levels of hsCRP.

Starting from these germinal observations as well as from the further insights derived from these data, the existence of a residual inflammatory risk has been recently proposed, a condition that is different from the postulated residual cholesterol risk[7] and which cannot be assessed and managed in the same way. This innovative pathophysiological hypothesis has been validated by Ridker and coworkers in the recently published results of a proof-of-concept study, CANTOS (Canakinumab Antiinflammatory Thrombosis Outcome Study).[8]

The randomized, double-blind trial assigned patients with a previous myocardial infarction and elevated levels of hsCRP to receive canakinumab every 3 months, a human anti-interleukin (IL)-1β monoclonal antibody (1 of 3 doses of 50 mg, 150 mg, and 300 mg subcutaneously) or placebo. The mean age of patients was 61 years, and approximately 25% were women. Almost 80% of patients had

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hypertension, about 40% had diabetes, and 22% were current smokers, with approximately 93% of the patients being treated with lipid-lowering therapy (91% of patients being treated with a statin). In addition, most of the participants underwent previous coronary artery revascularization (66.7% percutaneous coronary intervention and 14% coronary artery bypass). Median levels of total cholesterol, LDL-C, high-density lipoprotein cholesterol, triglycerides, and hsCRP in patients treated with canakinumab at different dosages were comparable to those of the placebo group. At the end of the follow-up period, canakinumab at the dosage of 150 mg significantly reduced hsCRP levels from baseline, without affecting cholesterol levels, in a median follow-up of 3.7 years. This resulted into a significantly lower incidence of recurrent cardiovascular events as compared with placebo. The incidence rate for the primary endpoint was 4.50 events per 100 person-years in the placebo group and 3.86 events per 100 person-years in the 150 mg group, with a hazard ratio [HR] of 0.85 and 95% confidence interval [CI] of 0.74–0.98 (P = 0.021 compared to placebo). The significant results observed with the 150-mg dose were driven by a 24% relative reduction in risk of myocardial infarction.

The relative hazard reduction of 27% (HR: 0.73, 95% CI: 0.63–0.83, P < 0.001) of the secondary endpoint, which was observed in those patients with 3-month on-treatment hsCRP decrease more than the median value (1.8 mg/L), reveals that this cutoff period could be useful in an attempt to transfer these data to clinical practice and to identify the responders to treatment. In a subgroup analysis, the patients who seemed to benefit most from the treatment were diabetics with a level of hsCRP between 2 and 4 mg/L.

A finding that is consistent with the putative effects of inflammation in the tumoral microenvironment was the surprisingly significant reduction in cancer mortality, substantially driven by a 77% reduction in death from lung cancer with canakinumab 300 mg compared to placebo. Although this stunning result of CANTOS needs to be confirmed by further specific studies, this appears to be the most intriguing finding of the study due to the unexpectedly large reduction of death from lung cancer.

There are important issues to be discussed. The trial seems to identify a potentially new area of therapeutic intervention; in the age of personalized medicine, not all high-risk secondary-prevention patients appear to have the same clinical characteristics. We should focus on individual risk profiles, in the attempt to identify not only those with residual cholesterol risk but also those with persistently high proinflammatory response, despite optimal treatment with statins, who, according to CANTOS results could benefit from anti-inflammatory treatment. This is a breakthrough discovery, and no matter whether the treatment based on canakinumab can be translated to secondary cardiovascular prevention, the road to explore and to consider the role of anti-inflammatory approach in these patients in now open.

It is interesting to note that the median body mass index of the trial participants was at about 29.9, meaning that most patients included in the trial were overweight, with a high proportion (40%) of diabetics. This may indirectly support a contributory role of fat tissue through the release of pro-inflammatory adipokines such as leptin,

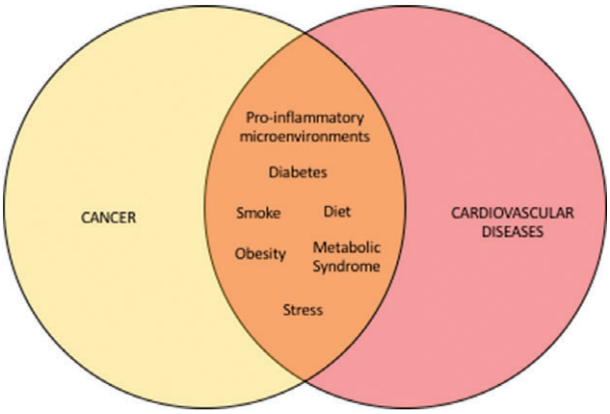

FIGURE 1 Shared risk factors in cardiovascular disease and cancer. Chronic inflammation may contributes to both disease

cytokines, and chemokines such as tumor necrosis factor-α and IL-6,[9] to insulin resistance and low-grade chronic inflammation.

As suggested and shown in the Table 1, based on the results of subgroups analyses, the typology of patients who could benefit most are diabetic subjects 30 days after myocardial infarction, with persistently high C-reactive protein serum levels, mostly smokers, and those on optimal therapeutic treatment. With regard to the side effects reported in CANTOS, we will need more details on fatal infections for a better understanding of which clinical parameters (ie, leukopenia), may be used to promptly identify those who are at high risk for this threatening side effect, thus minimizing the risk of the major adverse effect of canakinumab.

Finally, the therapeutic approach based on a specific and selective intervention on the inflammatory cascade that has been adopted and tested in CANTOS has demonstrated to provide favorable effects on noncardiovascular morbidity and mortality, particularly in reducing the risk of cancer, mostly lung malignancies. This result has two important, though still speculative, consequences. First, these data support the emerging concept of global risk,[10,11] which is biologically more meaningful than just looking at cardiovascular and neoplastic risk, as in separate silos. Second, based on the intriguing hypothesis that inflammatory pathways are relevant both for pathogenesis of cardiovascular events and cancer[12] (Figure 1), a novel multiple target therapeutic approach appears conceivable.

CANTOS data provide the evidence of a completely new therapeutic target, independent of LDL-C, that may provide a reduction in cardiovascular recurrent events, opening the field for new preventive

TABLE 1 CANTOS-based features that may identify patients eligible for anti-inflammatory treatment strategies

Predominantly men, age > 60 years
Previous myocardial infarction, STEMI, or NSTEMI
hsCRP >2 mg/L
Diabetes mellitus
Optimal cardiovascular medical treatment
Current or past smoker

Abbreviations: CANTOS, Canakinumab Antiinflammatory Thrombosis Outcome Study; hsCRP, high-sensitivity C reactive protein; NSTEMI, non–ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

strategies. At this time, another question that remains open is whether the high cost of this novel drug is reasonable in view of its net clinical benefit.

In conclusion, it is necessary to promote other clinical trials to confirm the benefit in lowering hsCRP levels and to investigate other population groups with this approach.

Conflicts of interest

The authors declare no potential conflicts of interest.

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