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CRITICAL ANALYSIS OF THE STUDIES THAT HAVE CHANGED RECENT CLINICAL PRACTICE: INFLAMMATION AND CORONARY ARTERY DISEASE

ANÁLISE CRÍTICA DOS ESTUDOS QUE MUDARAM A PRÁTICA CLÍNICA RECENTE: INFLAMAÇÃO E DOENÇA CORONARIANA

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ABSTRACT

Studies with statins involving clinical endpoints have shown that, in spite of achieving lipid goals, patients with high levels of C-reactive protein are at higher risk for cardiovascular events. Atherosclerotic coronary artery disease has also presented greater regression in studies with statins when, in addition to an effective reduction in LDL cholesterol, a reduction in C-reactive protein was achieved. In recent years, two important studies involving anti-inflammatory therapies reported divergent results. The CANTOS study, with the human monoclonal antibody canakinumab, showed a decrease in the primary objective composed by cardiovascular death, non-fatal myocardial infarction or non-fatal stroke and the magnitude of that benefit was associated with the degree of reduction in the inflammatory markers, such as C-reactive protein and interleukin-6. In the CIRT study, patients who received the anti-inflammatory methotrexate did not have a decrease in cardiovascular outcomes, but the treatment did not decrease these inflammatory biomarkers. Taken together, these results suggest that the specific blockade of an inflammatory pathway, such as that of cytokine,may be more relevant than the antiinflammatory effect per se and reveal a promising way to reduce the residual inflammatory risk.

Keywords: Interleukin 1; Canakinumab; Methotrexate.

RESUMO

Os estudos com estatinas envolvendo desfechos clínicos mostraram que, mesmo atingindo as metas lipídicas, os pacientes que persistem com níveis aumentados de proteína C-reativa, têm maior risco de eventos cardiovasculares. A doença aterosclerótica das coronárias também apresentou maior regressão nos estudos com estatinas, quando ocorreu além de redução efetiva de LDL-colesterol, redução da proteína-C reativa. Nos últimos anos, dois importantes estudos com terapias anti-inflamatórias mostraram resultados divergentes. O estudo CANTOS, com o anticorpo monoclonal canaquinumabe, mostrou redução do evento combinado de morte cardiovascular, infarto ou acidente vascular cerebral não fatais, e a magnitude do benefício foi associada ao grau de diminuição de marcadores inflamatórios, como proteína C-reativa ou interleucina 6. No estudo CIRT, os pacientes que receberam o anti-inflamatório metotrexato não tiveram redução de desfechos cardiovasculares, mas tampouco tiveram redução dos mencionados marcadores inflamatórios. Esses resultados, em conjunto, sugerem que o bloqueio específico de uma via inflamatória, como a citocina, pode ser mais relevante do que efeito anti-inflamatório per se e revela um caminho para diminuição do risco inflamatório residual.

Descritores: *Interleucina 1; Interleucina 6; Canaquinumabe; Metotrexate.*

INTRODUCTION

Atherosclerosis was already seen as a combination of inflammatory and proliferative mechanisms in the mid-nineteenth century by Virchow.[1] In the twentieth century, inflammation and endothelial dysfunction formed the pathophysiological basis of atherosclerosis by Ross.[2]

More recently, particularly after standardization of high-sensitivity C-reactive protein (hsCRP) quantification, the link between inflammation and cardiovascular outcomes, especially coronary events, has been proven.[3]

Further, prospective, randomized clinical trials with active controls treatment, proving the association of

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cardiovascular outcomes.[4,5] Subsequently, a greater regression of atherosclerosis was found when statin therapy was accompanied by a decrease in hsCRP.[6,7] Not only baseline levels of hsCRP, but over time in its association with cardiovascular outcomes, attention to this biomarker has been renewed following high-risk cardiovascular patients, as recently shown in VISTA-16 study, in patients with recent acute coronary syndrome.[8]

JUPITER[9] study was a milestone in the primary prevention of cardiovascular disease as it demonstrated the benefit of statin therapy in patients with relatively normal cholesterol levels but identified as high risk due to increased levels of hsCRP.[10] However, rosuvastatin treatment reduced both cholesterol and inflammation, making data interpretation difficult if due to lower LDL-C or hsCRP.[11]

Thus, the definitive evidence for the inflammatory theory of atherosclerosis required specific treatment that reduced cardiovascular outcomes decreasing inflammation without changes in cholesterol levels, in high-risk patients fully treated with statins and other proven effective therapies, such as beta blockers, angiotensin renin system blockers, and antiplatelet agents.[12,13] At the same time that studies with this proposition were implemented, the inflammatory basis of atherosclerosis was better understood[14,15] and mendelian randomization studies confirmed the causal role of interleukin-6 in cardiovascular disease.[16]

MAIN STUDIES FOCUSING ON ANTI-INFLAMMATORY THERAPY

CANTOS Study

CANTOS[17] study (Canakinumab Anti-inflammatory Outcomes Study) involved 10,061 patients with a history of myocardial infarction who had hsCRP levels ≥ 2 mg/L with at least four weeks from the acute coronary event. Anti-inflammatory treatment was performed with the use of human monoclonal antibody canaquinumab (highly specific antibody to 1-beta interleukin). Canakinumab therapy was randomized at a dose of 50 mg, 150 mg or 300 mg and compared with placebo at a 1:1:1:1.5 ratio. Clinical follow-up had a median of 3.7 years. Dose-dependent reduction of hsCRPas was observed (26%, 37% and 41%, respectively, for the 50, 150 and 300 mg doses of monoclonal antibody) and the study proved that exposure to treatment did not modify cholesterol, LDL -cholesterol or HDL-cholesterol.[17] The primary endpoint of the study (combination of cardiovascular death, nonfatal myocardial infarction or stroke) was not significantly reduced with the 50 mg dose (HR 0.93, p = 0 , 30); but reduced by 15% (p = 0.021) at the 150 mg dose and by 14% (p = 0.031) at the 300 mg dose. Only 150 mg dose met all pre-specifications of the study's statistical analysis in reducing primary endpoint outcomes. Canakinumab exposure was associated with a small but significant increase in infectious cause mortality (one case per 1000 patients) and there was no significant reduction in all-cause mortality.[17] However, a pre-specified analysis of the relationship between the reduction of hsCRP to less than 2 mg/L was accompanied by a 25% reduction in the primary endpoint (p = 0.0004) even after multiple adjustments, as well as a 31% reduction in mortality (p <0.0001).[18] Another study analysis involved patients exposed to canakinumab treatment who reduced interleukin-6 below the median (1.65 ng/L).[19] Even with multiple adjustments, these patients had a 32% reduction in the primary endpoint and a 30% reduction in the secondary endpoint which included, in addition to cardiovascular death, nonfatal myocardial infarction or CVA, hospitalization for unstable angina requiring urgent revascularization. In this same analysis of interleukin-6 below the median, cardiovascular mortality was reduced by 52% and total mortality by 48% (both p <0.0001).[19] The study also showed a reduction in cancer mortality, particularly lung cancer, bringing a new link of inflammation, in this case in relation to tumor invasion of tissues and metastasis mechanisms.[20]

CIRT Study

CIRT (Cardiovascular Inflammation Reduction Trial) study involved 4786 subjects who had previous myocardial infarction or multivascular coronary disease in addition to diabetes or metabolic syndrome.[21] Patients were randomly assigned to methotrexate (15-20 mg/week) or placebo and followed up for a median of 2.3 years after premature discontinuation of the study for futility. There was no reduction in the primary endpoint of the study (cardiovascular death, nonfatal myocardial infarction or CVA) and there was a higher incidence of adverse events among patients exposed to methotrexate, such as elevated liver enzymes, reductions in leukocyte and hematocrit counts, and higher incidence of skin cancer.[21] In the study, there was no reduction in interleukin-1 beta, hsCRP or interleukin-6 levels.[21]

HOW TO INTERPRET DIFFERENT RESULTS OF THESE CONTEMPORARY STUDIES

CANTOS study showed that interleukin-1-beta-mediated blockade of the inflammatory pathway reduces cardiovascular outcomes even in the absence of any effect on cholesterol or blood pressure. Treatment effectively reduced inflammatory markers such as hsCRP and interleukin-6, and the reduction of these inflammatory markers was accompanied by significant benefit in reducing cardiovascular outcomes and mortality.[17-19] Thus, CANTOS study was the proof of concept that reducing ithe Interleukin 1-beta-mediated inflammatory pathway is effective in reducing cardiovascular outcomes. On the other hand, CIRT study clearly showed that methotrexate anti-inflammatory therapy possibly involving adenosine-mediated signaling does not seem relevant for atherothrombotic outcomes.[22] These divergent results between two anti-inflammatory strategies clearly reveal that specific therapies against cytokines implicated in cardiovascular disease are promising and not the anti-inflammatory effect per se.[23-25] Chart 1 shows the main differences between the two CANTOS and CIRT studies and summarizes the main differences between them and possible reasons for the results obtained.

In conclusion, in recent years, the existence of residual inflammatory risk has become clear, despite all clinical and technological advances in cardiovascular disease therapy. The two main studies with anti-inflammatory therapies for high-risk cardiovascular patients, CANTOS and CIRT studies added important contributions and allowed

Chart 1. Major differences between CANTOS and CIRT studies in inflammatory response.

CANTOS study
• Inhibition of inflammation by human canaquinumab monoclonal antibody (1-beta interleukin inhibitor)
• Reduces 1-beta interleukin
• Reduces interleukin 6
• Reduces C-reactive protein
• Reduces cardiovascular outcomes*
• Does not change cholesterol and fractions levels
• Reduces incidence of cancer (especially lung)
CIRT Study
• Inhibition of inflammation by methotrexate (possibly via adenosine)
• Does not reduce 1-beta interleukin
• Does not reduce interleukin 6
• Does not reduce C-reactive protein
• Does not reduce cardiovascular outcomes*
• Increased incidence of cancer (especially skin)

* Combined outcomes of cardiovascular death, nonfatal stroke or stroke as well as the described outcome plus hospitalization for unstable angina requiring urgent revascularization.

a great advance in understanding the most relevant aspects in the treatment of these patients. The inflammatory pathway triggered by the cellular inflammatory complex (inflammasome), which includes interleukin-1 beta release and interleukin-6 mediated pathway activation is the most promising therapy. In fact, by blocking interleukin-1 beta with the canaquinumab monoclonal antibody, the proof of concept of the validity of the treatment of inflammation has been proven because the reduction in outcomes was not due to lipid, glycemic or blood pressure changes, and indeed occurred in patients with full use of the therapeutic arsenal consisting of statins, beta-blockers, antiplatelet agents and renin-angiotensin blockers.

CONFLICTS OF INTEREST

Dr. FAHF reports participation as a member of the steering committee and national leader of JUPITER and CANTOS studies. Dr. MCOI mentions participation as a clinical researcher for JUPITER and CANTOS studies.

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