Cardiovascular Outcomes With Anti-Inflammatory Therapies: Review of Literature

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Abstract: Inflammation is a major contributing factor in the development of cardiovascular disease (CVD) and has been a popular topic of discussion as it provides a potential therapeutic target to reduce disease progression. Multiple inflammatory markers have been linked with progressive atherosclerosis which includes interleukin-6, tumor necrosis factor-α, C-reactive protein amongst others, this article aims to review current literature to evaluate the effectiveness of anti-inflammatory therapies in cardiovascular disease. (Curr Probl Cardiol 2022;47:100840.)

Introduction

Over the recent years, inflammation has been the center of attention due to its role in atherosclerotic cardiovascular disease. What we initially thought to be a protective physiologic response, inflammatory markers identified have been linked to vascular disease and endothelial dysfunction.[1,2] Multiple inflammatory markers such as interleukin-6, tumor necrosis factor-α, C-reactive protein have been studied as therapeutic targets to reduce atherosclerotic disease. Firstly, C-reactive

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protein is known to release tumor necrosis factor-a, interleukin 1b and interleukin 6, these pro-inflammatory cytokines play a key role in upregulation of circulating monocytes, lymphocytes, neutrophils and platelets all of which have been linked to expedited atherosclerosis. C-reactive protein also promotes endothelial dysfunction which promotes inflammation in addition to generation of reactive oxygen species.[3-7]

Discussion

CANTOS/Canakinumab Trial

The Interleukin family of cytokines has been one of the major pro-inflammatory mediators related to tissue injury. Within this family, Interleukin 1b is the driver of the interleukin 6 pathway which has been shown to be associated with worsened atherosclerotic disease irrespective of lipid levels.[8,9] Previously, Canakinumab has been approved for use in multiple rheumatologic and immune mediated disorders however its use as an anti-inflammatory agent to prevent worsening atherothrombosis remained initially theoretical.

The Canakinumab Anti-Inflammatory Thrombosis Outcome Study (CANTOS) was a randomized, double blinded trial of Canakinumab which is a monoclonal antibody targeting interleukin-1b. The trial questioned whether patients with a history of prior MI and an elevated C-reactive protein of >= 2 mg/L would benefit from treatment with Canakinumab and potentially reduce cardiovascular events. This trial involved 10,061 patients with a history of myocardial infarction and an elevated C-reactive protein level of >= 2. These patients were assigned to one of 3 doses of 50 mg, 150 mg, 300 mg subcutaneously every 3 months compared to placebo. The primary outcomes included myocardial infarction, stroke or cardiovascular death. The major findings of the study showed that canakinumab reduced hsCRP level from baseline through 48 months; this reduction was also dose dependent. At initial follow up at 3.7 years mark, there was a 0.6% absolute reduction with the 150 mg dose in regards to the primary outcome which was the composite of myocardial infarction, stroke, and cardiovascular death). Additionally, in the 150mg dose group, a modest benefit was also seen in secondary endpoints including reduced hospitalization for unstable angina requiring revascularization. Of note, only the 150 mg dose reached statistical significance which still raises the question as to which dose is ideal. These outcomes further reiterate the benefits of targeting inflammation as a cause of atherothrombosis, more specifically cytokine based therapeutics.[10-11]

CIRT/Methotrexate Trial

For decades statins has been leading for treating atherosclerotic cardiovascular disease. Recently, a new era evolved around the role of anti-inflammatory agents in treating atherosclerotic cardiovascular disease. Methotrexate, a folic acid antagonist used for the treatment of rheumatoid arthritis has been studied for being a potential drug for treatment of atherosclerotic cardiovascular disease. It inhibits enzyme AICAR transformylase, leading to block in Adenosine and Guanine metabolism, this causes Adenosine levels to increase; and because of the anti-inflammatory effect of Adenosine, T-cell activation will be repressed, leading to down-regulation of B-cells, increasing activated CD-95 T cells sensitivity; and repression of methyltransferase activity, inhibition of the binding of beta-1 interleukin to its cell surface receptor.[12] Cardiovascular Inflammation Reduction Trial (CIRT) evaluates whether low-dose methotrexate will reduce rates of myocardial infarction, stroke, or cardiovascular death among patients with a recent history of coronary artery disease and either type II diabetes or metabolic syndrome.[15]

The Cardiovascular Inflammation Reduction Trial (CIRT) is a randomized, double-blind, placebo-controlled, multicenter, event-driven trial that randomized 7,000 men and women from the United States and Canada. The 2 arms include low-dose methotrexate (Tablet, Oral, Target dose 15-20 mg weekly plus 1.0 mg folic acid 6 days/week) or placebo (Tablet, Oral weekly plus 1.0 mg folic acid 6 days/week) over an average follow-up period of 3 to 5 years. The primary end point studied is nonfatal stroke, nonfatal myocardial infarction and cardiovascular death. Secondary endpoint includes subjects who died from any cause, the first occurrence of hospitalization for congestive heart failure, the first occurrence of major adverse cardiovascular event or any coronary revascularization, hospitalization for congestive heart failure or all-cause mortality, the first occurrence of major adverse cardiovascular event, coronary revascularization, new onset type 2 diabetes among those without diabetes at baseline[13]. The final primary end point occurred in 201 patients in the methotrexate group and in 207 in the placebo group (incidence rate, 4.13 vs 4.31 per 100 person-years; hazard ratio, 0.96; 95% confidence interval [CI], 0.79 to 1.16). In conclusion, methotrexate did not result in lower IL-6, IL-1β, or C-reactive protein in comparison to placebo. Also, methotrexate did not result in fewer cardiovascular events than placebo.[14]

COLCOT/Colchicine Trial

It has been established that inflammation plays an important role in atherosclerosis formation.[8,9] Both CANTOS and LoDoCo trials have shown fewer cardiovascular events than those who didn't receive anti-inflammatory medications like Canakinumab or Colchicine, respectively. Canakinumab is not a widely available anti-inflammatory medication and because of this, its use for the risk reduction of atherosclerotic events is limited. The limitations of the LoDoCo trial were: It was not placebo-controlled and only patients with stable coronary artery disease were enrolled. Since acute coronary syndromes are mostly associated with higher risks of recurrent cardiovascular events and exacerbated inflammation, COLCOT (Colchicine Cardiovascular Outcomes) trial was conducted and got published in NEJM in 2019.[11] COLCOT trial was a double-blinded randomized trial that enrolled patients within thirty days of myocardial infarction (MI) to evaluate the effect of colchicine in preventing major adverse cardiac events after MI compared to placebo. This study randomly assigned patients who had MI within the last 30 days to Colchicine 0.5 mg daily (n = 2366,) and placebo (n = 2379). The primary end-point was a composite of death from myocardial infarction, cardiovascular causes, resuscitated cardiac arrest, stroke, or urgent hospitalizations from angina resulting in coronary revascularization. The primary end-point occurred in 5.5% in the colchicine group compared to 7.2 in the placebo group ($P = 0.02$). In conclusion, colchicine was associated with a lower risk of major adverse cardiovascular events compared to placebo. The benefit of colchicine was primary from a reduction in the incidence of urgent hospitalization for unstable angina leading to revascularization and stroke. In this study, it also appeared beneficial among patients with diabetes. The incidence of diarrhea and infection was similar in both groups.

LoDoCo1/2 Trial

Colchicine is a classical antimitotic drug with a wide range of anti-inflammatory activities. The primary mechanism of action of colchicine is tubulin disruption which subsequently prevents the activation and migration of neutrophils and inhibits the activation of interleukin-1. This leads to down regulation of multiple inflammatory pathways and modulation of innate immunity. Colchicine also has anti-fibrotic activities and various effects of endothelial function. These effects account for colchicine efficacy in preventing gout attacks, familial Mediterranean fever and pericarditis. Moreover, a retrospective study was published in 2012

demonstrating a lower incidence of acute coronary syndrome (ACS) in patients with gout on colchicine,[16] which prompted the researchers to conduct multiple prospective, randomized, double-blinded clinical trials to evaluate the possible benefits of colchicine in patients with coronary artery disease.

The first trial, LoDoCo (Low-dose colchicine for secondary prevention of cardiovascular disease) was conducted in 2012[17] to investigate if addition of colchicine to routine medical management would reduce the risk of cardiovascular events in patients with stable coronary artery disease (CAD). A total of 532 patients were randomized to colchicine 0.5 mg/day or observation. The primary outcome was consistent with ACS, cardiac arrest and ischemic cerebrovascular disease (CVA). At a median follow-up of 3 years, the colchicine group had a significant reduction in ACS, CVA and cardiac arrest compared to the control group (5.3% vs 16%, hazard ratio (HR) 0.33, 95% confidence interval (CI) 0.18-0.59; $P < 0.001$), primarily driven by ACS reduction (4.6% vs 13.6%, HR 0.33, 95% CI 0.18-0.63; $P < 0.001$). The reduction in the primary endpoint was significant across different subgroups including age and diabetes. The researchers concluded that adding colchicine 0.5 mg/day to the standard secondary prevention therapies including aspirin, clopidogrel and high-intensity statins appeared effective in reducing the risk of cardiovascular events in patients with stable CAD. However, the trial was limited by its poor design, lack of double-blinding, and lack of placebo control. They didn't also collect any inflammatory biomarkers, which would have been helpful in better understanding of the mechanism of colchicine potential benefit.

A second trial, LoDoCo-MI (The Low Dose Colchicine after Myocardial Infarction) was conducted in 2019[18] after COLCOT trail to assess the role of colchicine in reducing post-MI inflammation and risk of further cardiovascular events through reducing biomarkers of inflammation, mainly C-reactive protein (CRP). A total of 237 patients with recent MI were randomized to colchicine 0.5 mg/day or matching placebo. The primary end-point was the proportion of patients with a residual high sensitivity CRP level $\geq$2 mg/L after 30 days of therapy, a threshold associated with a worse prognosis. At 30 day follow-up, 44% of patients in the colchicine arm compared to 50% of those in the placebo arm, had a CRP level $\geq$2 mg/L ($P = 0.35$). The median CRP in patients in the colchicine arm was 1.6 mg/L compared to 2.0 mg/L in the placebo group ($P = 0.11$). The median absolute reduction in CRP levels in the colchicine arm was -4.3 mg/L compared to -3.3 mg/L in the placebo group. The relative reduction was a fall of 78% compared to a fall of 64% ($P = 0.09$). The

researchers concluded that treatment with colchicine was safe and well tolerated, but was not associated with a statistically significant likelihood of achieving a CRP level of <2 mg/L 30 days after an acute MI.

A third trial, LoDoCo2 (Colchicine in Patients with Chronic Coronary Disease), was conducted recently in 2020[19] to study the beneficial effects of colchicine in patients with chronic coronary artery disease. A total of 5522 patients with chronic CAD underwent randomization to colchicine 0.5 mg/day group (n = 2762) or matching placebo (n = 2760). The primary end-point was a composite of cardiovascular death, spontaneous MI, CVA or ischemia-driven coronary revascularization. The key secondary end-point was a composite of cardiovascular death, spontaneous MI or CVA. At a median follow-up of 28.6 months, A primary end-point event occurred in 6.8% in the colchicine group compared to 9.6% in the placebo group (incidence, 2.5 vs 3.6 events per 100 person-years; HR 0.69; 95% CI 0.57-0.83; $P < 0.001$). A key secondary end-point event occurred in 4.2% in the colchicine group compared to 5.7% in the placebo group (incidence, 1.5 vs 2.1 events per 100 person-years; HR 0.72; 95% CI 0.57-0.92; $P = 0.007$). Researchers also noted significantly lower rates of cardiovascular death or spontaneous MI (composite end-point), spontaneous MI or ischemia-driven coronary revascularization (composite end-point), ischemia-driven coronary revascularization, and spontaneous MI with colchicine than with placebo. However, the incidence of death from noncardiovascular causes was higher in the colchicine group than in the placebo group (incidence, 0.7 vs 0.5 events per 100 person-years; HR 1.51; 95% CI 0.99-2.31; $P = 0.007$). The researchers concluded that the risk of cardiovascular events was significantly lower among patients who received colchicine 0.5 mg/day than those who received placebo. Nevertheless, the unexpected increase in the noncardiovascular deaths is of concern and needs further analysis and explanation. Limitations of the study included: lower percentage of women, lack of baseline data collection on inflammatory biomarkers, lipid levels and blood pressure; the data that would have allowed for further elaboration of risk-factor and outcome collaboration. All of the aforementioned results were consistent and similar. The suggested dose is 0.5 mg/day. Adverse events include: myalgia and increased risk of diarrhea and pneumonia.

Conclusion

In conclusion, inflammation appears to play a role in the development and the progression of cardiovascular disease. Anti-inflammatory agents including colchicine appear to improve outcomes when used for the

chronic CAD or secondary prevention of acute MI. However, further studies and trials are warranted to evaluate possible adverse events.

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