CLINICAL REVIEW

Relationship between Atherosclerosis and Inflammation

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Atherosclerotic cardiovascular disease (ASCVD) is a complex phenomenon now believed to be a manifestation of dyslipidemia and chronic inflammation of the arteries.[1-9] However, studies are still being conducted to elucidate the exact risks of the inflammatory process on ASCVD. ASCVD begins with endothelial activation by dyslipidemia and other factors that leads to secretion of chemokines and expression of endothelial adhesion proteins. Chemokines allow for recruitment of monocytes, which then differentiate into macrophages at the intimal layer of the arterial wall, while endothelial adhesion proteins allow for macrophages to infiltrate the intimal layer of the arterial wall. Simultaneously, endothelial activation also exposes the accumulated low-density lipoprotein (LDL) to oxidizing agents that leads to oxidation of the LDL.

Macrophages begin to uptake the oxidized LDL via pattern recognition receptors on their surface, forming lipid laden foam cells, which can be seen as a fatty streak on the arterial wall in the early stages of the disease. As oxidized LDL accumulates, foam cells begin to lyse as a result of apoptosis which not only forms a necrotic core, but promotes the inflammatory response. This enhanced inflammatory response is characterized by smooth muscle cells from the media layer of the arterial wall migrating to the intima where they proliferate, uptake oxidized LDL and secrete extracellular matrix proteins that stabilizes the plaque and forms a fibrotic cap.[10,11]

However, ongoing inflammation destabilizes this newly formed plaque by three different mechanisms: decreased production of extracellular matrix proteins from the smooth muscle cells, increased action of macrophage-secreted matrix metalloproteinases which break down extracellular matrix proteins, and decreased inhibition of matrix metalloproteinases.[12] Unstable plaques are susceptible to subsequent rupture and thrombosis, which leads to acute coronary syndrome.

Significance of Relationship between Atherosclerosis and Inflammation

By understanding that a relationship exists between inflammation and ASCVD, researchers have searched for methods to monitor the inflammatory process through imaging modalities to help better risk stratify patients with ASCVD. Some data from prior studies suggests that the degree of coronary calcification may correlate with local vascular inflammation.[13-15] Using this principle, along with the proposed association of inflammation and atherosclerosis, researchers have attempted to use coronary artery calcium (CAC) measurement to risk stratify patients.[16-23] Clinically significant ASCVD can be excluded by the absence of CAC in an asymptomatic adult.[24,25] On the other hand, a significantly high CAC score can be associated with an approximately 10-fold increased risk of adverse coronary events after multivariable adjustment.[26] In addition, investigators have found that CAC scores improves classification of patients into appropriate clinical risk groups.[24]

An example of a study using CAC scores is the South Bay Heart Watch prospective cohort study, which was conducted by Park et al.[25] They found that CAC scores and CRP levels were associated with ischemic cardiovascular events in previously asymptomatic nondiabetic adults. More specifically, their analysis demonstrated approximately a 6-fold difference in the risk of MI and cardiac death and a 7-fold difference in the risk of any cardiovascular event between the lowest-risk (defined as the lowest tertile calcium score and normal CRP levels) and the highest- risk (defined as the highest tertile of calcium score and elevated CRP levels) groups. Furthermore, the investigators found a lack of interaction in nondiabetics between CRP levels and CAC scores in their study. Using this finding, along with the complementary predictive power of the 2 tests, they suggested that the CAC scores and CRP levels assess different mechanisms that result in cardiovascular events.[25] They further explain that inflammation may lead to vulnerable plaques rupturing or eroding to cause these coronary events.[25,26]

In another prospective study, Detrano et al. also found that an increased CAC measurement is associated with increased risk for future coronary events.[23] While there are many risk factors associated with CAC development and progression, one study demonstrated inflammatory markers were weakly associated with CAC burden. In the Multi-Ethnic Study of Atherosclerosis (MESA) population.[27,28] Zeb et al. assessed the relationship between inflammatory mediators (high sensitivity CRP (hsCRP), interleukin-6 (IL-6), fibrinogen) and CAC development and progression.[1] Univariate analysis demonstrated that elevated levels of IL-6 and fibrinogen were associated with the development of CAC and its progression. After multivariable-adjusted linear regression analyses however, only hsCRP was associated with a significantly higher risk of CAC progression in patients with a baseline CAC greater than 0, while the other inflammatory mediators demonstrated a non-significant association with incident CAC.[1]

A prior study, conducted by Okwuosa et al., also initially found

an association between inflammatory mediators and the development and progression of CAC, but the association lost significance once adjusted for traditional risk factors.[29] A cross-sectional study using MESA participants conducted by Jenny et al. demonstrated a weak association between IL-6 and fibrinogen with CAC presence after multivariable-adjusted analyses, but CRP statistical significance was lost.[28] This is inconsistent with the study conducted by Zeb et al., which found a statistically significant increased risk of CAC development and progression with hsCRP, while the association of IL-6 and fibrinogen with CAC progression and development was lost after adjustment.[1]

Zeb et al., describe some limitations to their study that may have led to the results not completely agreeing with their initial hypothesis, which was that the inflammatory markers would play a role in the development of incident CAC and increase the risk of progression. These limitations are as follows: authors including patients free of clinical cardiovascular disease at baseline, not including all inflammatory markers such as matrix metalloproteinases, tumor necrosis factor, resistin, and others that play a role in atherosclerosis, and obtaining inflammatory markers and lipid subfractions at baseline, which change over time.[1] Despite these limitations, however, an important finding of this study and the one conducted by Jenny et al. is that for patients with existing atherosclerosis (i.e., baseline CAC >0), inflammatory mediators may help stratify risk for atherosclerosis progression. Another important contribution from Zeb's study is their discussion on exploring treatments aimed at reducing inflammation in an attempt to attenuate atherosclerosis progression. Such treatment options include statins and other novel pharmacologic anti-inflammatory agents.[30]

One study that investigated whether treatment with rosuvastatin as compared with placebo would decrease the rate of first major cardiovascular events was The Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial.[31] This randomized control trial demonstrated a significantly reduced rate of first major cardiovascular event and death from any cause in patients with LDL-C <130 mg/dL and hsCRP ≥2 mg/L on rosuvastatin. Following this study, a separate analysis conducted by Blaha et al., tried to determine whether CAC scores may further risk stratify a JUPITER-eligible population, in addition to comparing CAC scores to hsCRP for risk prediction in this population.[32] They found that participants in this population who had a CAC score of 0 experienced a very low 6- year event rate, while nearly all coronary artery events occurred in patients with CAC. Thus, they concluded with their analysis that CAC may help risk stratify JUPITER-eligible patients and may be used to identify a subgroup of patients who may be able to derive the most, and the least, absolute benefit from statin therapy.

Another trial that supports the existence of the relationship between inflammation and atherosclerosis is the Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) trial.[33] In this double-blind, randomized trial, patients were randomly assigned to receive 40 mg of pravastatin vs. 80 mg of atorvastatin, and intravascular ultrasound was used to measure progression of atherosclerosis. The results showed that baseline LDL was more reduced in the atorvastatin group than the pravastatin group. In addition, CRP decreased by 5.2% with pravastatin vs. 36.4% with atorvastatin. As far as the primary endpoint, defined as the percentage change in atheroma volume, progression of coronary atherosclerosis occurred in the pravastatin group when compared with baseline. At the same time, progression did not occur in the atorvastatin group when compared with baseline. The authors of this study also found the progression rate at any level of LDL-C reduction to be lower with atorvastatin than pravastatin, which suggests that other factors may have played a role in the reduction of atherosclerotic progression. One of these factors may be the larger reduction in CRP seen in the atorvastatin group. In fact, progression of the plaque occurred in the pravastatin group even when lowered LDL-C levels was below the recommended goal of 100 mg/dL, supporting the possibility of other factors, such as the anti-inflammatory effects of atorvastatin, influencing the findings of this trial.

Treating Inflammation to Reduce Risk of Atherosclerosis Progression

Studies have already begun to look at slowing progression of atherosclerosis via pharmacological modulation of inflammation aside from statins. One study conducted by Gaztananga et al. looked at the effect of VIA-2291 (Atreleuton), a 5-lipoxygenase inhibitor involved in the leukotriene (LT) biochemical pathway, on vascular inflammation using fluorodeoxyglucose–positron emission tomography.[34-39] However, they did not observe a significant anti-inflammatory effect by VIA-2291.[38] Following this study, a double-blinded prospective study conducted by Matsumoto et al. looked at the effect of VIA-2291 as compared with placebo on atherosclerotic inflammation.[39] The study evaluated the effect of VIA-2291 on various coronary plaque types, such as fibro-fatty plaque (FF), fibro-calcified plaque (FC), dense calcified plaque (DC), and low-attenuation plaque (LAP), all of which were identified by cardiac computed tomography angiography (CCTA). Their study was based on the premise that reducing the inflammatory process may reduce atherosclerotic progression. They found that VIA-2291 significantly reduced each component of a noncalcified plaque, such as FF, FC, and LAP, and slowed the progression of DC plaque, compared to placebo at 6 months. They concluded that VIA-2291 resulted in slowed plaque progression compared with placebo across different plaque subtypes in patients with recent ACS. It is also important to note that while the researchers used a novel method to measure plaque known to have highly reproducible results,[40] newer CT scanners can potentially improve the ability of CCTA to monitor atherosclerosis due to advancements in image acquisition and processing.[41] For the time being however, this study supports the current literature on the usefulness of CCTA in understanding plaque progression and evaluating the effectiveness of interventions, such as statins, on ASCVD.

Another study that looked into reducing inflammation as a means to reduce the risk of ASCVD is The Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS).[30] The pharmacological agent that was investigated was canakinumab, a monoclonal antibody that inhibits IL-1β, which is activated by the NOD-like receptor protein 3 (NLRP3) inflammasome.[42-44] The CANTOS trial was a randomized, double-blind study that tested canakinumab at three different doses (50 mg, 150 mg, and 300 mg) against placebo in patients with a previous myocardial infarction (MI) and a hsCRP level of 2 mg/L or greater. The primary efficacy endpoint was defined as nonfatal MI, nonfatal stroke, or cardiac death. The trial demonstrated a statistically significant decrease in hsCRP and IL-6 from baseline in the canakinumab groups as compared with placebo. Furthermore, this occurred with no significant reduction in lipid levels from baseline. Despite these positive findings however, there was no significant difference between the experimental groups and the placebo group in all-cause mortality.[30] Additional findings include the 150 mg canakinumab group demonstrating a statistically significant reduction in both the risk of the primary end point and key secondary endpoints by 15% and 17% respectively when compared to the placebo group. The 50 mg and 300 mg canakinumab groups did not show a statistically significant effect on the primary end point when compared to placebo, but pooled and trend analyses of all canakinumab doses showed a possible beneficial effect of canakinumab on cardiovascular outcomes.[30] Canakinumab is not without its adverse events, however, as investigators discovered a higher risk of fatal infection, sepsis, and a reduced platelet count with no increased bleeding risk in the canakinumab group when compared to placebo.[30]

There are other implications regarding the future of anti-inflammatory therapy on reducing ASCVD risk that can be taken away from this trial. Despite well-controlled LDL levels in the participants of the CANTOS trial, rates of both the primary end point and key secondary cardiovascular endpoints were higher in the placebo group. Every patient in the CANTOS trial also had some residual inflammatory risk as demonstrated by a hsCRP equal to or greater than 2 mg/L at baseline. This data suggests that statin-treated patients with residual inflamemation may be at some risk of a cardiovascular event and thus may benefit from anti-inflammatory therapy.[30,45] It was mentioned before, in the study conducted by Matsumoto et al., one concern regarding their findings was that other medications like statins may have impacted the results they obtained. These findings in the CANTOS trial supports the possibility that VIA-2291 did in fact play a role on ASCVD risk due to the anti-inflammatory effects of this agent.

Future Anti-Inflammatory Trials to Monitor

Another anti-inflammatory agent shown to be effective in reducing the risk of ASCVD is colchicine, an anti-inflammatory agent that acts via multiple mechanisms, including inhibition of microtubule polymerization and NLRP3.[46-48] In a randomized, double-blinded trial known as the LoDoCo trial conducted by Nidorf et al., patients with stable coronary disease receiving aspirin and/or clopidogrel, along with statins, were randomly assigned colchicine 0.5 mg/day or no colchicine. They demonstrated that colchicine was effective in the prevention of cardiovascular events in patients with stable coronary artery disease, but acknowledge that larger studies are necessary to confirm whether colchicine actually reduces the risk of ASCVD.[46,49,50] In a recent prospective nonrandomized observational study conducted by Vaidya et al., low dose colchicine therapy was associated with significantly reduced plaque volume via CCTA assessment, which was attributed to reduction in hsCRP as opposed to changes in lipoproteins.[51] However, this study was also conducted with a small sample size and a short follow-up time period of 12 months. Fortunately, the Colchicine Cardiovascular Outcomes Trial (COLCOT), a randomized clinical trial looking at patients with stable coronary artery disease on a typical medical regimen (i.e., statins, aspirin, and/or clopidogrel) compared to patients on a typical medical regimen plus a low dose of colchicine, is designed to confirm these results.[52] Additionally, Nidorf et al. are currently enrolling patients for a larger and more robust study that follows their initial pilot design in a trial known as the LoDoCo2 trial.[53] Another study currently looking at the efficacy of anti-inflammatory agents in reducing ASCVD is the cardiovascular inflammation reduction trial (CIRT), a randomized clinical trial which is allocating stable patients diagnosed with coronary artery disease who show persistent elevations of hsCRP to placebo or a very-low-dose-methotrexate group, an anti-inflammatory agent that reduces tumor necrosis factor-α, IL-6, and CRP levels.[54,55]

Conclusion

In conclusion, there have been steep advancements in understanding the relationship between inflammation and the progression of ASCVD. While researchers have historically struggled to identify inflammatory markers to act as surrogate markers for atherosclerosis, recent new findings have identified hsCRP as having potential to play this role. Studies have also suggested that CAC correlates with local vascular wall inflammation and atherosclerosis, and advancements in imaging techniques have helped investigators better quantify the degree of CAC and identify therapeutic benefits of anti-inflammatory agents on ASCVD. Some trials have begun to show efficacious anti-inflammatory agents on reducing the risk of ASCVD and have provided encouraging prospects for future studies. Perhaps other anti-inflammatory pharmacological agents that target a different step of the inflammatory pathway than the ones mentioned in this article may show benefit in reducing the risk of ASCVD.[30,56-58]

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