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REVIEW ARTICLE

Inflammation in Cardiovascular Disease: From Basic Concepts to Clinical Application

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Abstract

Although low-density lipoprotein cholesterol is central to the development and progression of atherosclerosis, the role of inflammation in the atherosclerotic process is becoming better understood and appreciated. Chronic inflammatory conditions such as rheumatoid arthritis, lupus, psoriasis, HIV infection, and inflammatory bowel disease have all been shown to be associated with an increased blood levels of inflammatory biomarkers and increased risk of cardiovascular events. Evidence from observational studies suggests that anti-inflammatory therapy decreases this risk in these conditions. Clinical trials of anti-inflammatory drugs in patients with coronary disease have yielded mixed results. Drugs that have failed in recent trials include the P38 MAP kinase inhibitor losmapimod, the phospholipase A2 inhibitors darapladib and varespladib, and methotrexate. Canakinumab, an interleukin-1β inhibitor, reduced cardiovascular events in patients with coronary disease in the Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS). Canakinumab increased the rate of fatal infections in CANTOS and is very expensive; it is thus unlikely to be widely used for risk reduction in cardiology. On the other hand, colchicine is a safe and inexpensive anti-inflammatory drug. In the Colchicine Cardiovascular Outcomes Trial (COLCOT), where patients within 30 days of a myocardial infarction were randomized to low-dose colchicine or placebo and followed for a median of almost 2 years, colchicine treatment was associated with a 23% reduction (p=0.02) in cardiovascular events. Newer studies with anti-inflammatory drugs have the potential to improve outcomes of patients with atherosclerosis, just as low-density lipoprotein cholesterol-lowering drugs have done over the past two decades.

Keywords

Lipoproteins,LDL, Atherosclerosis; Cardiovascular Diseases; Inflammation; Arthritis, Rheumatoid; Coronary Disease; Anti-Inflammatory Agents/therapeutic use; Colchicine/therapeutic use; Canakinumab/therapeutic use; Risk Factors.

Introduction

Atherosclerosis is a slowly progressive condition that eventually affects perfusion of various organs, most importantly the heart and brain. The classical risk factors that accelerate atherosclerosis include diabetes, hypertension, smoking, and hyperlipidemia, which are in turn influenced by genetic factors, diet and physical activity levels. Interactions among these factors are complex, and the pathogenesis of atherosclerosis is still incompletely understood.

Nevertheless, the central role of low-density lipoprotein cholesterol (LDL-C) has been clearly established, as detailed in a recent consensus statement from the European Atherosclerosis Society.[1]

A key feature of early atherosclerosis is the uptake of LDL-C particles by the arterial wall, where LDL-C is oxidized and stimulates an inflammatory response.[1] Inflammation thus becomes a powerful contributor to the progression of atherosclerosis. While the centrality of LDL-C to the development of atherosclerosis has long been recognized, and LDL-C lowering has been a goal of therapy, the role of inflammation has been a focus of attention only more recently.

This review addresses two aspects of inflammation and cardiovascular (CV) disease. In the first section we review the body of evidence showing that chronic inflammatory diseases are associated with an increased risk of CV events, and that anti-inflammatory therapy

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reduces this risk. In the second section we summarize the clinical trials that assessed the effects of anti-inflammatory treatments on CV events in patients without underlying inflammatory conditions.

Inflammatory Conditions with Increased Cardiovascular Risk

Rheumatoid Arthritis

Some of the inflammatory conditions associated with increased risk of CV events and supporting studies[2-6] are listed in Table 1. The link between rheumatoid arthritis (RA) and increased CV risk is particularly clear. In a meta-analysis[2] including eight studies and a total of 788 patients with RA and 1,641 controls, the presence and severity of coronary artery disease (CAD) was assessed with coronary computed tomography angiography (CCTA). Compared with controls, there was an increased risk of CAD (relative risk [RR] = 1.26, 95% confidence interval [CI] 1.04-1.52), and a higher prevalence of a coronary calcium score >100 and multivessel CAD. RA disease activity was linked to high-risk (non-calcified or mixed) coronary plaques. Methotrexate treatment was associated with an absence of CAD.

Other studies have shown that the presence of RA increases the incidence of coronary and cerebrovascular events. In a report from the Taiwan National Health Insurance Research Database, 10,568 patients with RA were compared to 42,272 controls matched for age, sex, urbanization and income.[7] During a six-year follow-up, an increased risk was seen for ischemic stroke (HR 3.48, 95% CI 2.16-5.61), coronary heart disease (HR 2.77, 95% CI 2.32-3.32), atrial fibrillation (HR 2.90, 95% CI 1.17-7.20), and heart failure (HR 2.88, 95% CI 2.01-4.14).

Not only are CV events more likely in patients with RA, they are more severe. In a matched cohort study from Sweden, RA subjects more frequently presented with sudden cardiac death and ST-segment elevation myocardial infarctions (STEMI),[8] and had higher levels of troponin and more in-hospital complications compared with controls. The seven-day mortality after acute coronary syndrome (ACS) was also higher in RA patients compared to controls: HR 1.65 (95% CI 1.32-2.08).

As summarized by Klingenberg and Lüscher,[9] circulating T cells of patients with ACS and of patients with RA are characterized by clonal restriction, with increased CD4+CD28^{null} T cells. Clonal restriction indicates a reduced repertoire of antigens recognized by the T cell receptor complex and reveals similar autoimmune responses against specific antigens in ACS and RA.

An army of cytokines, including TNF-α, IL-1β, IL-6, and IL-17, contribute to the inflammatory joint damage in RA and are current or potential targets of therapy.[10] Some of these inflammatory mediators have been implicated in the pathogenesis of ACS, including TNF-α. TNF-α antagonists are now widely used in the treatment of RA, and have been shown to have a beneficial effect on cardiac risk factors,[11] and on surrogate markers of atherosclerosis such as endothelial function[12] and carotid intima-media thickness.[13]

Based on the aforementioned data, one might expect that TNF-α inhibition would reduce CV events

Tabela 1 – Chronic inflammatory conditions that increase the risk of cardiovascular events

Condition	Type of Study	Study Endpoint	Number of Patients	RR/HR (95% CI)
Rheumatoid arthritis[2]	Meta-analysis 8 studies	Coronary Ca^{+} Score	785 pts 1641 controls	1.26 (1.04-1.52)
Lupus[3]	Meta-analysis 9 studies	Incident CAD	3320 pts	3.19 (2.15-5.35)
Psoriasis[4]	Prospective cohort	Myocardial infarction	130,976 pts 556,995 controls	1.11 (1.07-1.17)* 1.43 (1.18-1.72)^
HIV[5]	Meta-analysis 80 studies	Incident CVD	793,635 pts	2.16 (1.68-2.77)
Inflammatory Bowel Disease[6]	Meta-analysis 6 studies	Incident IHD	123,907 pts	1.18 (1.08-1.31)

** hazard ratio for mild psoriasis vs controls; ^ hazard ratio for severe psoriasis vs controls*

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in patients with RA. This was in fact demonstrated among 10,156 RA patients enrolled in the Consortium of Rheumatology Researchers of North America RA registry (CORRONA).[14] Patients were treated with TNF-α antagonists, methotrexate, or non-biological disease-modifying antirheumatic drugs (DMARDs). During a median follow-up of 22.9 months, 88 CV events occurred. Using a TNF-α antagonist reduced the adjusted risk of a CV event (HR 0.39, 95% CI 0.19-0.82) compared with users of DMARDs, while methotrexate was not associated with an adjusted reduced risk.

Although all studies examining this issue do not yield concordant results, findings from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis recently confirmed the benefit just described in the North American registry. A total of 14,258 patients were analyzed, 11,200 receiving TNF-α inhibitors and 3,058 receiving DMARDs.[15] There were 58 verified first MIs during a median follow-up of 3.5 years in the DMARD cohort and 194 MIs during a median follow-up of 5.3 years in the TNF-α inhibitor cohort. The risk of myocardial infarction (MI) in the TNF-α inhibitor cohort was 0.61 (95% CI 0.41-0.89) compared with the DMARD cohort.

To summarize for RA, the risk of CV events is increased, which is likely related to inflammation, and is reduced by anti-inflammatory treatment.

Systemic Lupus Erythematosus

The prevalence of lupus is much lower than that of RA, and thus the relationship between lupus and CV events has not been as well documented. In a meta-analysis of nine studies (eight cohort and one case-control), including 3,320 lupus patients, the RR of CAD compared to controls was 3.39, 95% CI 2.15-5.35.[16] This meta-analysis, however, has limitations; for example, most of the included studies did not account for treatment, and a common treatment for lupus, glucocorticoids, can by itself increase the risk of CV events.

Lupus patients at highest risk for CV events are those with lupus nephritis. Atherosclerotic plaques in the carotid and femoral arteries have been reported to be more common in patients with lupus compared to controls, with the excess risk comparable to that seen in RA or in diabetes.[17] Endothelial dysfunction is a common feature of lupus, even in mild cases and early in the disease.[18] This has been attributed to a variety of mechanisms including impaired clearance of apoptotic cells, oxidative stress, circulating autoantibodies, different subtypes of T lymphocytes, and a cascade of cytokines.[18]

A distinct subset of lupus proinflammatory neutrophils, termed low-density granulocytes (LDGs), appear to play a key role in enhancing CV risk in lupus. In a recent study, lupus subjects and healthy controls underwent 18F-fluorodeoxyglucose–PET/CT imaging to measure vascular inflammation, a mechanism of arterial dysfunction, and CCTA to determine plaque burden; LDGs were quantified by flow cytometry and cholesterol efflux capacity was also measured.[19] Vascular inflammation, arterial stiffness, and noncalcified plaque burden were all increased in lupus patients compared to controls, even after adjustment for traditional risk factors. In lupus subjects noncalcified plaque burden was directly associated with LDGs and negatively associated with cholesterol efflux capacity in fully adjusted models.[19] These associations suggest that LDGs may contribute to vascular damage and unstable coronary plaque in the setting of lupus.

Psoriasis

In a cohort study from the United Kingdom with 130,976 psoriasis patients and 556,995 controls, 13,625 MIs were documented during a mean follow-up of 5.4 years.[4] Risk of MI was elevated in subjects with psoriasis and was highly dependent on age and severity of psoriasis (Figure 1). For example, for a 30-year-old patient with mild or severe psoriasis, the adjusted RR of having a MI was 1.29 (95% CI, 1.14-1.46) and 3.10 (95% CI, 1.98-4.86), respectively. For a 60-year-old patient with mild or severe psoriasis, the adjusted RR of having a MI is 1.08 (95% CI, 1.03-1.13) and 1.36 (95% CI, 1.13-1.64), respectively.[4]

In a more recent study, subjects with psoriasis were shown to have more noncalcified coronary plaque and more high-risk plaques by CCTA compared to healthy volunteers.[20] Moreover, improvement in skin disease severity after one year was associated both with a reduction in circulating levels of proinflammatory cytokines such as TNF-α and IL-1β, and with improvement in total coronary plaque burden and noncalcified plaque, unexplained by traditional risk factors.[20] Thus, control of peripheral inflammation appeared to have a salutary effect on coronary disease. These findings raise the question: would anti-inflammatory therapy in psoriasis reduce the risk of CV events?

The answer to this question seems to be yes. A Danish cohort study of 6,902 patients with severe psoriasis

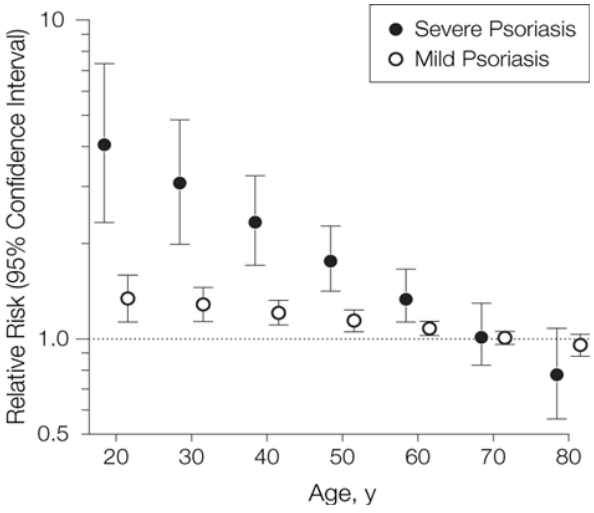


Figure 1 – Adjusted relative risk of myocardial infarction in patients with psoriasis based on age and disease severity. Adjusted relative risk is depicted on a log scale (y axis). From reference #4.

showed that relative to other therapies, methotrexate (HR 0.53, 95% CI 0.34-0.83) and TNF-α inhibitors (HR 0.46; 95% CI 0.22-0.98) were associated with reduced risk of the composite CV endpoint.[21]

HIV

In a recent meta-analysis including 80 studies of 793,635 people living with HIV and a total follow-up of 3.5 million person-years, the RR for CV disease was 2.16 (95% CI, 1.68-2.77) compared with individuals without HIV.[5] As shown in Figure 2, this risk is similar to the risk of hypertension, diabetes, lipids and smoking.[22,23]

Several factors increase the risk for CV disease in persons living with HIV in addition to inflammation.[24] Smoking is more prevalent in subjects with HIV in many countries. Antiretroviral treatment may increase the risk of CV events directly or by inducing or worsening lipid abnormalities, most frequently hypertriglyceridemia.[25] Improvements in antiretroviral therapy in recent years has led to better control of infection; the HIV population is aging, and thus at higher CV risk.

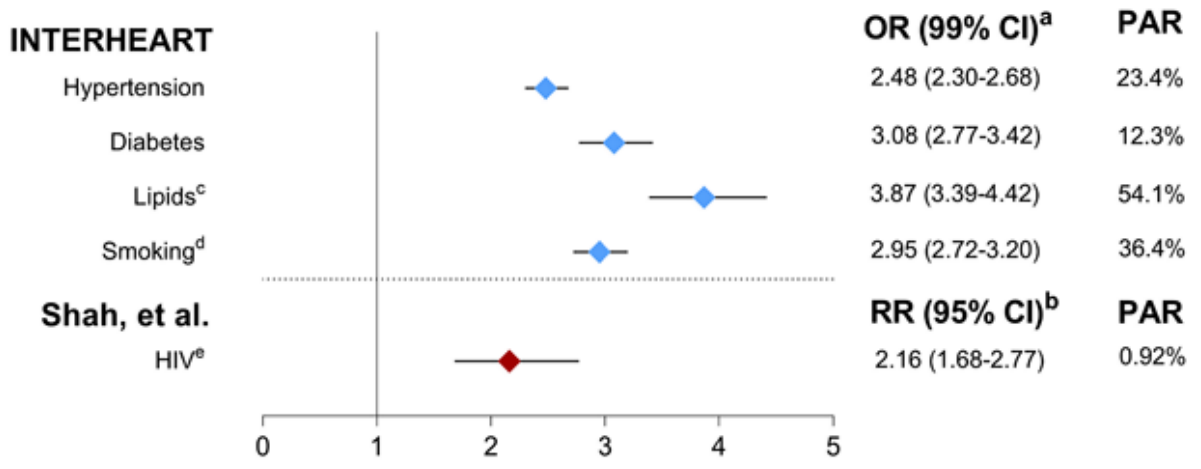
The mechanisms leading to HIV atherosclerosis are complex and poorly understood. Even when HIV infection is controlled, low-level transcription of HIV genes continues and HIV-encoded proteins induce inflammation and endothelial dysfunction.[24] Second, immune abnormalities persist in successfully treated subjects, and these abnormalities are predictive of CV events.[24] For example, one such abnormality, the CD4:CD8 ratio, is a marker of immunosenescence. Third, co-infection with cytomegalovirus has been linked to an increased CV risk through different potential mechanisms.[24] CMV-specific T cell responses correlate with increased carotid intima-media thickness,[25] a surrogate marker of increased CV risk. Fourth, an early feature of HIV infection is impairment of the gut barrier, such that microbial products leak through the intestinal barrier and cause immune activation, a process termed microbial translocation.[24] Markers of microbial translocation, specifically plasma levels of soluble CD14 and lipopolysaccharide, predict progression and mortality of HIV disease, and are associated with higher levels of the inflammatory markers TNF-α and IL-6.

All the aforementioned mechanisms increase inflammation. High plasma levels of inflammatory and coagulation markers, such as C-reactive protein (CRP), IL-6 and d-dimer, strongly predict CV events and all-cause mortality in subjects with HIV infection.[24] These relationships suggest that anti-inflammatory treatment might reduce the risk of CV events in persons with HIV infection.[26] Although this hypothesis has not yet been tested in a randomized clinical trial, a small pilot study of canakinumab, a monoclonal antibody targeting IL-1β, showed a significant reduction of plasma IL-6 and CRP levels.[27] This was paralleled by reductions in leukopoietic activity, monocyte cytokine production, and arterial inflammation as assessed by FDG-PET CT.

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD), comprising Crohn's disease and ulcerative colitis, is a risk factor for both stroke and coronary disease. In a meta-analysis of five studies reporting 2,424 cerebrovascular events in 98,240 IBD patients, IBD conferred an increased risk (adjusted OR, 1.18, 95% CI 1.09-1.27).[6] Similarly, the risk of a coronary event was increased across six studies reporting 6,478 ischemic heart disease events in 123,907 patients with IBD (adjusted OR 1.18, 95% CI 1.08-1.31).[6] For both cerebrovascular and ischemic heart disease endpoints, the increased risk was present for both Crohn's disease and ulcerative colitis, and appeared to be greater in women than in men.

In a Danish registry-based study IBD patients had an increased risk of MI during flares (RR 1.49, 95% CI 1.16-1.93), and during persistent activity (RR 2.05, 95% CI:1.58-2.65), but no increased risk during remission (RR 1.01,



[a]Risk of acute MI; adjusted for age, sex, and smoking. Because ORs can give inflated estimates of risk when the outcome is common,[12] it is likely that the RRs of traditional risk factors in INTERHEART are smaller, and thus closer to that of HIV.
[b]Risk of ASCVD (CVD, stroke, or MI); adjustment for confounders was limited to those available in the primary studies.
[c]High ApoB/ApoA1 ratio.
[d]OR (99% CI) for current smoking; PAR for any smoking.
[e]PAR for 2015 using prevalence data for HIV for the 15-49 year age group.

Cardiovascular risk of HIV compared with traditional risk factors. The odds ratios for hypertension, diabetes, lipids and smoking are taken from the INTERHEART study23 and the relative risk for HIV from Shah et al.5 Odds ratios are not directly comparable to relative risk and should be adjusted downward slightly for comparison.
a risk of acute MI, adjusted for age, sex, and smoking.
b risk of ASCVD (CVD, stroke, or MI).
c high ApoB/ApoA1 ratio.
d OR (99% CI) for current smoking; PAR for any smoking.
e PAR for 2015 using prevalence data for HIV for the 15- to 49-year-old group. Apo indicates apolipoprotein; ASCVD, atherosclerotic cardiovascular disease; CVD, cardiovascular disease; HIV, human immunodeficiency virus; MI, myocardial infarction; OR, odds ratio; PAR, population attributable risk; and RR, risk ratio. From reference #22.

95% CI 0.89-1.15).[28] Studies reporting surrogate endpoints such as carotid intima-media thickness or arterial stiffness in IBD patients are sparse or inconclusive.[29]

In contrast to some of the other inflammatory conditions already discussed, the effect of anti-inflammatory therapy on CV events in IBD has not been well documented. A common treatment for IBD, 5-aminosalicylic acid (5-ASA), which might possess aspirin-like anti-platelet properties, has been reported to be associated with a reduced risk of CV events in IBD patients.[30] In the same study a trend toward fewer CV events among IBD patients treated with TNF-α inhibitors was also seen, but the authors cautioned that this relationship may have been underestimated due to confounding by indication, because sicker patients were more likely to be treated with this drug.

Anti-inflammatory Drugs That Reduce CV Events

As discussed in the preceding section, a wide range of chronic inflammatory diseases are associated with an increased risk of CV events. The evidence is strong for some of these conditions that anti-inflammatory therapy reduces CV risk; for others, the evidence is weaker.

However, even the strong evidence is drawn mainly from observational studies and is thus subject to bias.

These data form a basis for consideration of the role of anti-inflammatory therapy for the prevention of CV events in subjects without concurrent inflammatory conditions. Table 2 lists some of the anti-inflammatory drugs that have been tested to date in clinical trials.[31-37] Older failed trials with the P38 MAP kinase inhibitor losmapimod[31] and the phospholipase A2 inhibitors darapladib[32,33] and varespladib[34] will not be discussed further, except to note that these drugs reduced markers of inflammation and inhibited biomarkers that were predictive of CV events. The results of trials with statins, methotrexate, canakinumab and colchicine will be discussed in the remainder of this article.

Statins

The reduction in CV events with statin treatment is proportional to the amount of LDL-C reduction; specifically, each mmol/L (38.6 mg/dl) reduction in LDL-C is expected to produce a 22% reduction in CV events, slightly less during the first year, and slightly more thereafter.[38] In addition to LDL-C lowering, statins exert anti-inflammatory effects through a wide variety of mechanisms. Statins reduce inflammatory markers including C-reactive protein CRP, cytokines (IL-1β, IL-6, IL-8, TNF-α), and adhesion molecules (P-selectin, ICAM-1).[39] They reduce T cell activity and monocyte activation and increase nitric oxide levels.[39] These anti-inflammatory effects may contribute to event reduction, despite the close relationship between LDL-C reduction and event reduction. PCSK9 inhibitors lack some of the anti-inflammatory properties of statins, and this has been suggested as an explanation for why they do not reduce CV events as much as expected, based on their degree of LDL-C lowering.[40]

In the JUPITER trial (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin), healthy subjects with LDL-C levels below 130 mg/dl and CRP levels of 2 mg/L or higher were randomized to rosuvastatin 20 mg/day or placebo and followed for a median of 1.9 years.[41] The primary endpoint, a composite of MI, stroke, arterial revascularization, hospitalization for unstable angina, and CV death was reduced in the active treatment group (HR 0.56, 95% CI 0.49-0.69). Thus, targeting subjects with evidence of inflammation without hyperlipidemia markedly reduced CV events.

In patients with ACS, levels of inflammatory markers are high, and are reduced more rapidly and to lower levels by potent statins compared to placebo.[42] Statins reduce CV events early post-ACS, and this event reduction has been attributed more to a decline in inflammatory markers than to a decline in LDL-C levels.[43] Although the anti-inflammatory effects of statins cannot be disentangled from their cholesterol-lowering effects, it is reasonable to assume that part of the benefit of this class of drugs is related to their effect on inflammation.

Methotrexate

Methotrexate is a folic acid antagonist with broad anti-inflammatory effects. As previously noted, methotrexate use was associated with a reduction in CV events by nearly half in a large Danish series of patients with

Tabela 2 – Anti-inflammatory drugs for the prevention of cardiovascular events

Drug	Mechanism of Action	Clinical Trial	Result
Losmapimod	P38 MAP kinase inhibitor	LATITUDE-TIMI 60[31]	No benefit
Darapladib	Lipoprotein-associated phospholipase A2 inhibitor	SOLID-TIMI 52[32] STABILITY[33]	No benefit
Varespladib	Secretory phospholipase A2 inhibitor	VISTA-16[34]	Stopped early for probable harm
Methotrexate	Folic acid antagonist	CIRT[35]	Stopped early for futility
Canakinumab	IL-1β inhibitor	CANTOS[36]	15% reduction at higher doses (p=0.007)
Colchicine	inhibition of NLRP3 inflammasome	COLCOT[37]	23% reduction in primary endpoint (p=0.02

severe psoriasis.[21] In a cohort study of patients with RA, where information about CV events was obtained by questionnaire, prolonged methotrexate use was associated with a 15% reduction in CV morbidity.[44] Similarly, a 21% reduction in CV events was reported with methotrexate treatment in a meta-analysis of patients with various rheumatologic diseases.[45] Based upon this body of evidence, a trial of methotrexate to prevent CV events in patients with coronary disease seemed promising.

The Cardiovascular Inflammation Reduction Trial (CIRT) randomized 4,786 patients with previous MI or multivessel coronary disease who also had type 2 diabetes or metabolic syndrome, to low-dose methotrexate or placebo.[35] The trial was terminated by the Data and Safety Monitoring Board after a median follow-up of 2.3 years because it had crossed the prespecified boundary for futility and because methotrexate did not lower IL-1β, IL-6, or CRP levels compared to placebo. No reduction in CV events was seen with methotrexate. Thus, the CIRT failed to reproduce, in patients with coronary disease, positive results with anti-inflammatory drugs reported in non-randomized studies on patients with chronic inflammatory conditions. Baseline CRP levels were not elevated in CIRT patients, and as pointed out by the authors, this may have accounted for both the lack of CRP lowering and the lack of clinical benefit with methotrexate.

Canakinumab

Anakinra is a humanized monoclonal antibody that decreases signaling via both IL-1α and IL-1β.[46] It is used to treat RA and has been shown in pilot studies to reduce CRP and IL-6 after MI, as well as improve other surrogate measures.[46] A limitation of anakinra is that it affects IL-1α and IL-1β, thereby interfering with immune function. Canakinumab, another humanized monoclonal antibody, neutralizes IL-1β specifically, and thus has the potential to favorably affect atherosclerosis without affecting immune function.[46] In a pilot study of 556 patients with diabetes, canakinumab reduced CRP, fibrinogen, and IL-6 with no negative effects on serum lipids.[47]

The Canakinumab Anti-inflammatory Thrombosis Outcome Study (CANTOS) randomized 10,061 patients with previous MI and a high-sensitivity CRP level of ≥2 mg/L to placebo or to one of three doses of canakinumab (50 mg, 150 mg, or 300 mg, administered subcutaneously every three months).[36] The primary efficacy end point was nonfatal MI, nonfatal stroke, or CV death. More than 90% of study patients took statins and median LDL-C levels at baseline were 82 mg/dl with no change during follow-up. Compared to placebo, CRP levels were reduced by 26%, 37% and 41% with increasing doses of canakinumab ($p<0.001$ for all).

At a median follow-up of 3.7 years, the HR was, in the 50-mg group, 0.93 (95% 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). The 150-mg dose, but not the other doses, met the prespecified threshold for statistical significance adjusted for multiple comparisons. Canakinumab was associated with a higher incidence of fatal infection compared to placebo and there was no significant difference in all-cause mortality for all canakinumab doses versus placebo. These results demonstrate that targeting the IL-1β pathway with canakinumab reduced CV events among post-MI patients with elevated CRP levels.

Outcomes in CANTOS were related to on-treatment CRP levels. Trial participants allocated to canakinumab who achieved a CRP concentration of <2 mg/L had a 25% reduction in major adverse CV events (adjusted HR 0.75, 95% CI 0.66-0.85), whereas no significant benefit was observed among those with an on-treatment CRP concentration of ≥2 mg/L (adjusted HR 0.90, 95% CI 0.79-102, p=0.11).[48]

The effects of canakinumab on IL-6 and IL-18, and the prognostic value of these interleukins were assessed in a subset of CANTOS patients who had these measurements at baseline and at three months of follow-up.[49] The reductions in IL-6 at three months were 24.8%, 36.3%, and 43.2% for the 50, 150, and 300 mg doses of canakinumab, but there was no change in IL-18 levels. Nevertheless, both on-treatment IL-6 and IL-18 levels were predictive of prognosis. For example, for major adverse cardiac events, each tertile increase in IL-18 was associated with a 15% increase in risk (95% CI 3-29%, p=0.016), and each tertile increase in IL-6 was associated with a 42% increase in risk (95% CI 26-59%, p<0.0001). These findings suggest that IL-6 and IL-18 are still useful biomarkers to predict risk in canakinumab-treated patients, but more importantly, that an inhibitor of IL-18 might also reduce risk.

Colchicine

Colchicine is one of the most ancient of all drugs, so that its safety and side effect profile are well established. However, its anti-inflammatory effects are complex and under ongoing investigation. Colchicine has anti-

mitotic activity and inhibits neutrophil migration.[50] In gout, urate crystals activate the NLRP3 inflammasome and colchicine inhibits it.[51] Multiple mechanisms have been described through which colchicine inhibits the NLRP3 inflammasome[50] and these mechanisms are active not only against urate crystals in gouty joints but also against cholesterol crystals in atherosclerotic coronary arteries. In a study where inflammatory markers were simultaneously measured in the coronary sinus and aorta in patients with ACS, trans-coronary gradients of IL-1β, IL-6 and IL-18 were observed, and were reduced by colchicine pretreatment.[52] Thus, coronary production of the inflammasome-specific IL-1β and IL-18, and the more downstream IL-6, were blocked by colchicine in ACS.

In a retrospective cross-sectional study of 1,288 patients with gout, the prevalence of MI was 1.2% in colchicine users and 2.6% in non-users (p=0.03).[53] In a small (n=59) randomized trial, pre-operative colchicine administration significantly reduced peak troponin and creatine kinase-MB levels after coronary bypass surgery.[54] In a pilot study of 151 patients randomized to colchicine or placebo for 5 days after ST-elevation MI, infarct size as assessed by area under the creatine-kinase-MB curve and by MRI in a substudy of 60 patients was significantly reduced in the colchicine group.[55]

The Low-Dose Colchicine (LoDoCo) trial randomized 532 patients with stable coronary disease to colchicine 0.5 mg/day or no colchicine and followed them for a median of 36 months.[56] The primary outcome, a composite of ACS, out-of-hospital cardiac arrest, or non-cardioembolic ischemic stroke, occurred in 15 of 282 colchicine patients (5.3%) and in 40 of 250 (16.0%) of those who did not (HR 0.33, 95% CI 0.18-0.59). Such a large treatment effect is likely to be a consequence of the small number of outcome events, and an exaggeration of any benefit of the drug. In the absence of placebo treatment in the control group, the adverse effect rate cannot be accurately ascertained; however, 32 patients (11%) assigned to colchicine discontinued the drug within 30 days due to intestinal intolerance.

The Colchicine Cardiovascular Outcomes Trial (COLCOT) randomized 4,745 within 30 days of MI to colchicine 0.6 mg/day or to placebo.[37] The primary efficacy endpoint was a composite of CV death, resuscitated cardiac arrest, MI, stroke, and urgent hospitalization for angina leading to coronary revascularization. Patients were followed for a median of 22.6 months. The primary endpoint occurred in 5.5% of colchicine patients and 7.1% of placebo patients (HR 0.77, 95% CI 0.61-0.96, p=0.02). Figure 3 depicts the Kaplan-Meier curves for the primary outcome. Although COLCOT was underpowered to demonstrate a significant reduction in individual components of the composite endpoint, stroke and urgent hospitalization for angina leading to coronary revascularization were reduced by large, statistically significant margins, while the reductions for CV death and MI were much less impressive.

The incidence of diarrhea in COLCOT was not significantly higher in the colchicine group (9.7% versus 8.9%, p=0.35); however, pneumonia occurred more often in colchicine-treated patients (0.9% versus 0.4%, p=0.03). Although this difference may be only a chance finding, pneumonia has been reported more frequently in colchicine users in a large database study from Taiwan.[57]

Other randomized trials of colchicine in different populations of coronary patients are either complete or in their later stages. The COLCHICINE-PCI trial randomized 714 patients to 1.2 mg of colchicine or placebo two hours before percutaneous coronary intervention.[58] The primary outcome of PCI-related myocardial injury was seen in 57.3% of colchicine-treated and 64.2% of placebo-treated subjects (p=0.19), and there was no difference in CV event rates at 30 days.[58] The Low-Dose Colchicine 2 trial (LODOCO2) randomized 5,322 patients with stable CAD who tolerated 0.5 mg of colchicine for one month to colchicine or placebo.[59] This trial is event-driven and is nearing completion. CLEAR-SYNERGY is a randomized two-by-two factorial design trial comparing colchicine 0.5 mg BID, spironolactone 25 mg/day, and corresponding placebos in 4,000 STEMI patients receiving a SYNERGY stent (ClinicalTrials.gov NCT03048825). The estimated completion date for this trial is December 2021.

Future Directions

Targeted anti-inflammatory drugs are not yet part of the treatment guidelines for patients with atherosclerosis, but it is possible to imagine a future where is the case.[60,61] In addition to canakinumab, other IL-1β inhibitors including anakinra, gevokizumab, and rilonacept, and the IL-6 inhibitors tocilizumab, sarilumab, sirukimab, and olokizumab, as well as IL-18 inhibitors may one day become part of our therapeutic arsenal alongside more familiar drugs such as statins.

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