HHS Public Access

Author manuscript

Nat Rev Cardiol. Author manuscript; available in PMC 2019 May 01.

Published in final edited form as:

Nat Rev Cardiol. 2019 February ; 16(2): 74–75. doi:10.1038/s41569-018-0144-3.

Targeting inflammation in CVD: advances and challenges

Kathryn J. Moore

Leon H. Charney Division of Cardiology, Department of Medicine, New York University School of Medicine, New York, NY, USA. kathryn.moore@nyumc.org

Considerable evidence supports a role for low-grade chronic inflammation in the atherothrombotic process, from plaque initiation to acute plaque rupture preceding myocardial infarction. Publications in 2018 revealed both the promise and challenges of targeting inflammation to treat atherosclerotic cardiovascular disease and highlighted the importance of understanding the mechanistic diversity of inflammatory pathways contributing to atherosclerosis.

In the past 2 decades, numerous studies have established that activation of both innate and adaptive immune responses in the setting of hypercholesterolaemia contributes to the development and progression of atherosclerosis. As a result, targeting inflammation for the primary and secondary prevention of atherosclerotic cardiovascular disease (CVD) has been an area of intense investigative focus. The past year has seen substantial advances in the development of immunotherapies for atherosclerosis, but has also revealed the challenging landscape ahead. Specifically, the results from two large-scale clinical trials — CANTOS[1] and CIRT[2] — demonstrated that different approaches to targeting inflammation can have dramatically different effects on cardiovascular risk reduction. A comparison of these trials provides a useful framework for guiding future drug development efforts in atherosclerotic CVD and points to a critical role for the cytokine IL-1β in the risk of CVD. In 2018, we also saw a new twist in our understanding of the mechanism of action of IL-1β, with the demonstration of a role for this cytokine in epigenetic reprogramming of immune cells to heighten the inflammatory response[3], a process known as ‘innate immune training’. Finally, the question of whether inflammation remains an independent risk factor for atherothrombosis in the era of LDL-cholesterol (LDL-C) lowering to very low levels was addressed by a post-hoc analysis of two trials of PCSK9 inhibitors[4].

In the CANTOS trial[1], investigators repurposed canakinumab, an IL-1β monoclonal antibody approved for the treatment of rare autoinflammatory syndromes, by testing its capacity to reduce cardiovascular events in patients with a history of myocardial infarction who were determined to have ‘residual inflammatory risk’, as defined by elevation in the inflammatory biomarker high-sensitivity C-reactive protein (hsCRP >2 mg/l). In support of this approach are the multiple known proatherogenic functions of IL-1β, including promotion of immune cell adhesion to vascular endothelial cells, triggering of smooth muscle cell proliferation and stimulation of the production of IL-6, another pro-

Competing interests

The author declares no competing interests.

inflammatory cytokine that drives the acute phase response, including the release of CRP[5]. In this 10,000-patient trial, participants were receiving background therapy of lipid-lowering medications (median LDL-C level at baseline was 82 mg/dl) and were randomly allocated to receive either placebo or canakinumab at a dose of 50 mg, 150 mg or 300 mg given subcutaneously every 3 months. Of note, study participants receiving either of the two highest doses of canakinumab had a 15% reduction in major adverse cardiovascular events compared with placebo, with no change in LDL-C level[1]. A secondary analysis showed that although baseline clinical characteristics of the CANTOS participants did not influence the effect of canakinumab on clinical outcomes, the magnitude of hsCRP reduction achieved following a single dose of canakinumab was a predictor of those individuals who were likely to receive the largest benefit in CVD risk reduction[6]. Participants who achieved on-treatment hsCRP concentrations <2 mg/l within the first 3 months of receiving canakinumab had 30% reductions in cardiovascular mortality and all-cause mortality, whereas no significant reduction in those end points was observed in participants with on-treatment hsCRP levels >2 mg/l[6]. These findings provide the first definitive evidence that directly targeting inflammation, in the absence of additional lipid lowering, is beneficial for the secondary prevention of atherosclerotic CVD. Moreover, they support guiding therapy according to inflammatory status in clinical trials and contemporary practice to reduce CVD risk.

Despite the encouraging results from CANTOS that inhibiting inflammation can prevent cardiovascular events, not all immune-based therapies have shown benefit in protecting from atherosclerosis. The CIRT trial[2] tested an alternate approach to reducing inflammation in atherosclerosis with the use of low-dose methotrexate — an inexpensive and widely used treatment for inflammatory conditions such as rheumatoid arthritis, psoriatic arthritis and juvenile idiopathic arthritis. Methotrexate was considered a promising anti-inflammatory approach because observational data had consistently shown an association between low-dose methotrexate use and fewer cardiovascular events in patients with rheumatoid or psoriatic arthritis. However, in a randomized, double-blind trial in nearly 5,000 patients with previous myocardial infarction or multivessel coronary disease, treatment with either 15 mg or 20 mg of methotrexate weekly did not reduce cardiovascular events compared with placebo[2]. Moreover, methotrexate treatment was associated with modest adverse effects, including elevations in liver enzyme levels and decreases in leukocyte counts and haematocrit levels, as well as a higher incidence of non-basal cell skin cancers than with placebo.

Understanding the differences between CANTOS, CIRT and trials of other immune therapies for CVD is likely to be informative in designing future therapeutics for atherosclerosis. One critical difference between CANTOS and CIRT is that treatment with canakinumab led to significant reductions in hsCRP and IL-6 levels, as well as IL-1β, whereas no changes in these inflammatory markers were observed with low-dose methotrexate. Interestingly, studies of other anti-inflammatory agents that had neutral outcomes on CVD, such as darapladib (a phospholipase inhibitor)[7] and losmapimod (a p38 mitogen-activated protein kinase inhibitor)[8], similarly showed no long-term effects on hsCRP, IL-6 or IL-1β levels. In the past decade, hsCRP has proved to be a useful clinical biomarker of inflammation and CVD risk, but extensive investigation suggests that CRP is not directly involved in the atherosclerosis process. By contrast, human genetic data

implicate the IL-6 signalling pathway as being causal in atherothrombosis[9], with IL-1β production thought to lie upstream of IL-6 activation, placing greater emphasis on these cytokines as direct targets for decreasing inflammatory risk.

IL-1β was one of the first inflammatory cytokines to be identified and has been studied in the context of atherosclerosis for >30 years. Multiple triggers of the NLRP3 inflammasome, which controls the production of mature IL-1β, have been identified in atherosclerosis, including cholesterol crystals, hypoxia and turbulent blood flow[5]. Although IL-1β has been known for some time to have pro-atherosclerotic effects on multiple cell types in the plaque (reviewed previously[5]), a new role for the NLRP3–IL-1β pathway was recently defined in mediating 'trained immunity', a form of innate immune memory that leads to augmented inflammatory responses. Latz and colleagues showed that feeding mice a high-fat, high-cholesterol diet induced systemic inflammation, as measured by increased circulating levels of cytokines and chemokines, with these biomarkers returning to baseline levels soon after mice were returned to a chow diet[3]. By contrast, myeloid cell responses to subsequent innate immune stimuli were broadly elevated, reminiscent of the functionally adapted immune response observed in myeloid cells previously challenged with a microbial ligand. Investigators showed that a high-cholesterol diet induced broad transcriptomic and epigenetic reprogramming of myeloid progenitor cells that resulted in increased proliferation and augmented inflammatory responses that were maintained over prolonged times after return to a low cholesterol diet. Quantitative trait locus analysis in human monocytes exposed to oxidized LDL and subsequently challenged with lipopolysaccharide identified the NLRP3–IL-1β pathway as an important mediator of innate immune reprogramming, and mice lacking *Nlrp3* no longer showed diet-induced trained immune responses. These findings expand our understanding of the pro-atherosclerotic functions of IL-1β and specifically implicate this cytokine in heightening inflammation in response to a cholesterol-enriched diet, even after cholesterol levels are controlled.

An important question is whether inflammation remains an important risk factor after plasma LDL-C levels have been aggressively reduced, as is now possible with PCSK9 inhibitors in combination with other lipid-lowering therapies. An approach to addressing this question was taken by Pradhan and colleagues in a post-hoc analysis of the SPIRE-1 and SPIRE-2 trials[4]. Investigators measured plasma levels of LDL-C and hsCRP in high-risk patients receiving moderate-intensity or high-intensity statins and the PCSK9 antibody bococizumab. At 14 weeks after initiation of drug therapy, patients achieved a 60% mean reduction in LDL-C levels, with a median LDL-C of 35 mg/dl in the bococizumab-treated group compared with 98 mg/dl in the placebo group. Despite this large reduction in atherogenic lipids, little on-treatment change in hsCRP levels occurred (–6.6% change), and half of the patients receiving bococizumab were determined to have residual inflammatory risk, as defined by hsCRP levels <2 mg/l. Furthermore, a continuous gradient in CVD risk according to hsCRP level remained, with patients with on-treatment hsCRP >3 mg/l having a 60% greater risk of future CVD events than those without evidence of subclinical inflammation, despite a mean LDL-C level of 42 mg/dl. Indeed, among patients receiving bococizumab, elevated hsCRP levels were significantly associated with increased rates of nonfatal myocardial infarction, cardiovascular death and all-cause mortality. These findings have several important implications. First, they indicate that even after low levels of LDL-C

are achieved in high-risk patients, inflammation remains a major CVD risk factor. Second, although several studies have linked LDL oxidation to vessel-wall inflammation, the above finding suggests that multiple factors are likely to promote subclinical inflammation in atherosclerosis at low LDL-C levels.

In summary, as targeting of inflammation in atherosclerosis enters the clinical realm, new challenges and opportunities are being revealed. A comparison of the CANTOS and CIRT trials argues that reductions in IL-1β and IL-6 might be important for effective mitigation of inflammation risk. Although genetic analyses implicate IL-6 as a causative factor in the development of atherosclerosis, whether specifically targeting IL-6 would prove to be beneficial in reducing CVD risk remains unclear. If the newly identified role for IL-1β in heightening atherosclerotic inflammation via innate immune training contributes substantially to its inflammatory mechanism, targeting IL-6, which lies downstream of IL-1β, would miss this target. Finally, although treatment with canakinumab and statins was effective at reducing CVD risk, the patients in the CANTOS trial still had a high rate of cardiovascular events. Genetic analyses reveal the potential benefit of targeting nodes that lie outside of the LDL and IL-1β–IL-6 pathways to address this residual risk, and early studies of investigational agents targeting lipoprotein(a), angiopoietin-related protein 3, angiopoietin-related protein 4 and apolipoprotein C-III are underway.

Acknowledgements

K.J.M.'s work is supported by the NIH (grants R35HL135799 and P01HL131478).

References

1. Ridker PM et al. Antiinflammatory therapy with canakinumab for atherosclerotic disease. N. Engl. J. Med 377, 1119–1131 (2017). [PubMed: 28845751]
2. Ridker PM et al. Low-dose methotrexate for the prevention of atherosclerotic events. N. Engl. J. Med 10.1056/NEJMoa1809798 (2018).
3. Christ A et al. Western diet triggers NLRP3-dependent innate immune reprogramming. Cell 172, 162–175.e114 (2018). [PubMed: 29328911]
4. Pradhan AD, Aday AW, Rose LM & Ridker PM Residual inflammatory risk on treatment with PCSK9 inhibition and statin therapy. Circulation 138, 141–149 (2018). [PubMed: 29716940]
5. Grebe A, Hoss F & Latz E NLRP3 inflammasome and the IL-1 pathway in atherosclerosis. Circ. Res 122, 1722–1740 (2018). [PubMed: 29880500]
6. Ridker PM et al. Relationship of C-reactive protein reduction to cardiovascular event reduction following treatment with canakinumab: a secondary analysis from the CANTOS randomised controlled trial. Lancet 391, 319–328 (2018). [PubMed: 29146124]
7. O'Donoghue ML et al. Effect of darapladib on major coronary events after an acute coronary syndrome: the SOLID-TIMI 52 randomized clinical trial. JAMA 312, 1006–1015 (2014). [PubMed: 25173516]
8. O'Donoghue ML et al. Effect of losmapimod on cardiovascular outcomes in patients hospitalized with acute myocardial infarction: a randomized clinical trial. JAMA 315, 1591–1599 (2016). [PubMed: 27043082]
9. IL6R Genetics Consortium Emerging Risk Factors Collaboration. Interleukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis of 82 studies. Lancet 379, 1205–1213 (2012). [PubMed: 22421339]

Key advances

- Selective neutralization of the cytokine IL-1β reduces cardiovascular disease events, particularly in those individuals who achieved the highest reduction in inflammation as measured by high-sensitivity C-reactive protein (hsCRP) levels[1].
- Low-dose methotrexate does not protect against cardiovascular disease events and, interestingly, also does not reduce IL-1β, IL-6 or hsCRP levels in high-risk patients[2].
- Studies in mice indicate that a high-cholesterol diet can induce long-term reprogramming of haematopoietic reservoirs or ‘innate immune training’ to set the stage for higher inflammation via a mechanism involving IL-1β[3].
- Inflammation remains an important risk factor after levels of LDL cholesterol have been aggressively reduced, as is now possible with PCSK9 inhibitors in combination with other lipid-lowering therapies[4].

Pull quotes

directly targeting inflammation … is beneficial for the secondary prevention of atherosclerotic CVD

a new role for the NLRP3–IL-1β pathway was recently defined in mediating ‘trained immunity’

even after low levels of LDL-C are achieved in high-risk patients, inflammation remains a major CVD risk factor