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EDITORIAL COMMENT

Interleukin-1 Blockade in Acute Myocardial Infarction and Heart Failure

Getting Closer and Closer*

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Acute myocardial infarction (AMI) and heart failure (HF) are characterized by an intense inflammatory response that contributes to progression of the injury and dysfunction [(1)]. Tissue injury stimulates the formation of the inflammasome and the production of interleukin (IL)-1β [(2,3)], the prototypical cytokine involved in virtually every local and systemic inflammatory response, also known as the "fever molecule" [(4)] (**Figure 1**).
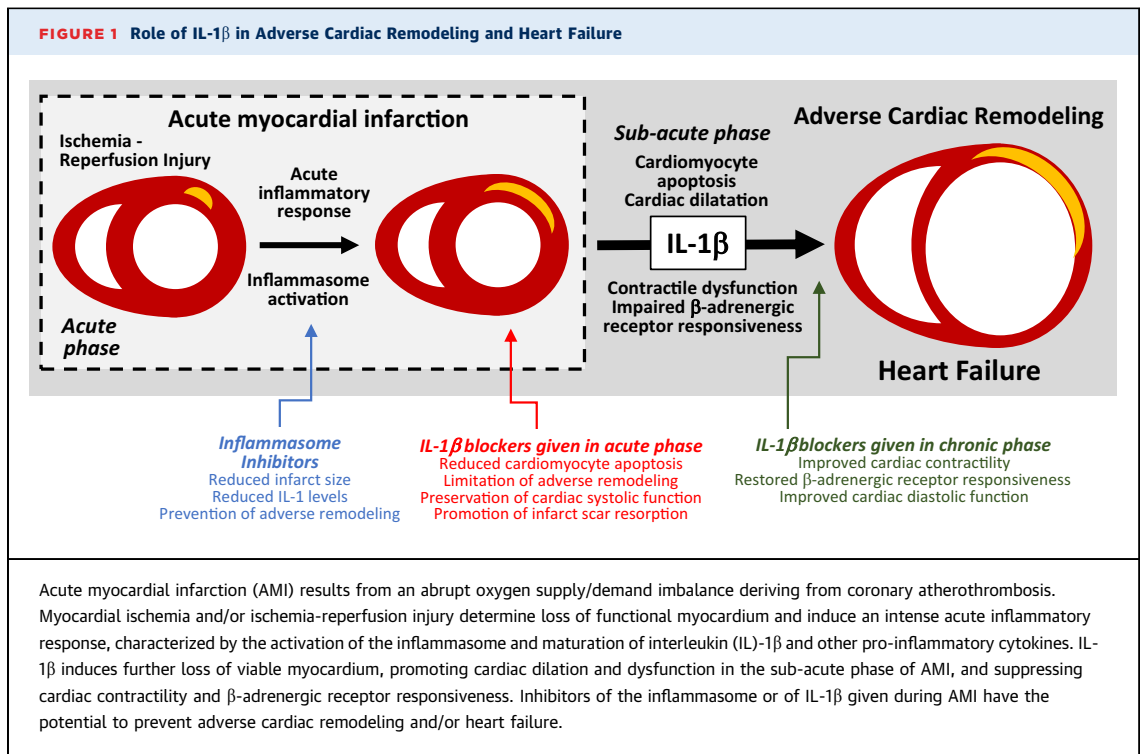
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In this issue of *JACC: Basic to Translational Science*, Harouki et al. [(5)] show that neutralization of IL-1β using the monoclonal antibody gevokizumab initiated shortly after reperfusion (1 h) or late (7 days) significantly improved cardiac remodeling and systolic and diastolic function in nondiabetic as well as diabetic rats with AMI due to ischemia-reperfusion injury. Furthermore, when gevokizumab was administered 83 days after reperfusion, and when cardiac dilation and dysfunction had already been established, IL-1β blockade resulted in an

improvement in systolic function. These beneficial effects of IL-1β blockade in preventing adverse cardiac remodeling after AMI had been, in part, already described [(3)]. A murine analog of gevokizumab was tested in mice with large nonreperfused AMI showing similar results [(6)]. Another IL-1β-blocking antibody, a murine analog of canakinumab, was also shown to improve cardiac function in mice early and late after large nonreperfused AMI [(7,8)]. The current study by Harouki et al. [(5)] confirms prior findings, deriving for the most part from a single laboratory and significantly expanded prior findings by exploring the AMI model with reperfusion and including experiments in rats with diabetes. The addition of reperfusion adds a clear clinical translational value as most of the patients with AMI nowadays receive reperfusion. It is important to note that the treatment occurred 1 h after reperfusion and not before reperfusion. This makes it a clinically relevant model, avoiding the dilemma of whether treatment after reperfusion, as occurs in practice, would jeopardize benefit [(9)]. They also added 2 treatment groups for rats with established cardiac dysfunction at 7 and 83 days after reperfusion, confirming that the beneficial effects of IL-1β blockade on cardiac contractility are, at least in part, time-independent. They show also a smaller infarct scar size measured on day 90, with gevokizumab given early, which, combined with prior data of no-infarct sparing effect of another IL-1β antibody [(10)], suggests an effect on infarct resorption. Studying rats with diabetes is also very clever because patients with AMI are often diabetic. Gevokizumab also improved acetylcholine-induced coronary relaxation and significantly reduced oxidative stress, providing a potential molecular mechanism. The reported effects of the IL-1β pathway in AMI are described in **Figure 1**.

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FIGURE 1 Role of IL-1β in Adverse Cardiac Remodeling and Heart Failure

Acute myocardial infarction (AMI) results from an abrupt oxygen supply/demand imbalance deriving from coronary atherothrombosis. Myocardial ischemia and/or ischemia-reperfusion injury determine loss of functional myocardium and induce an intense acute inflammatory response, characterized by the activation of the inflammasome and maturation of interleukin (IL)-1β and other pro-inflammatory cytokines. IL-1β induces further loss of viable myocardium, promoting cardiac dilation and dysfunction in the sub-acute phase of AMI, and suppressing cardiac contractility and β-adrenergic receptor responsiveness. Inhibitors of the inflammasome or of IL-1β given during AMI have the potential to prevent adverse cardiac remodeling and/or heart failure.

The data presented by Harouki et al. (5) come at a very appropriate time in the clinical development of IL-1β blockers in heart disease (3). Anakinra, a recombinant IL-1 receptor antagonist, has been tested in a pilot feasibility study of 10 patients with ST-segment elevation AMI (11) and in an additional follow-up proof-of-concept study of 30 patients (12), showing a favorable safety and tolerability profile, a significant blunting of the inflammatory response, and a promising signal of heart failure incidence (13). Small proof-of-concept studies in patients with systolic heart failure treated with anakinra also showed a promising improvement in exercise capacity and quality of life (14,15). On June 22, 2017, Novartis Pharma announced in a press release that the large phase III clinical trial of canakinumab, an IL-1β antibody, in 10,061 patients with prior AMI (CANTOS [Canakinumab Anti-inflammatory Thrombosis Outcomes Study]), met its primary endpoint, meaning that the treatment significantly reduced the composite endpoint of cardiovascular death, nonfatal AMI, and nonfatal stroke (16). The bench-to-bedside translation for IL-1β blockade is therefore becoming a reality. Based on preclinical data in AMI and HF, including the data presented herein (5) and the promising data in the CANTOS trial (16), it is foreseeable that IL-1β blockers will be further explored as a treatment strategy also for patients with AMI and/or symptomatic HF in the near future.

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REFERENCES

1. Seropian IM, Toldo S, Van Tassell BW, Abbate A. Anti-inflammatory strategies for ventricular remodeling following ST-segment elevation acute myocardial infarction. J Am Coll Cardiol 2014;63:1593–603.

2. Toldo S, Mezzaroma E, Mauro AG, Salloum F, Van Tassell BW, Abbate A. The inflammasome in myocardial injury and cardiac remodeling. Antioxid Redox Signal 2015;22:1146–61.

3. Van Tassell BW, Toldo S, Mezzaroma E, Abbate A. Targeting interleukin-1 in heart disease. Circulation 2013;128:1910–23.

4. Dinarello CA. Interleukin-1 in the pathogenesis and treatment of inflammatory diseases. Blood 2011;117:3720–32.

5. Harouki N, Nicol L, Remy-Jouet I, et al. The IL-1β antibody gevokizumab limits cardiac remodeling and coronary dysfunction in rats with heart failure. J Am Coll Cardiol Basic Trans Science 2017;2:418–30.

6. Abbate A, Van Tassell BW, Seropian IM, et al. Interleukin-1beta modulation using a genetically engineered antibody prevents adverse cardiac remodeling following acute myocardial infarction in the mouse. Eur J Heart Fail 2010;12:319–22.

7. Toldo S, Mezzaroma E, Van Tassell BW, et al. Interleukin-1β blockade improves cardiac remodelling after myocardial infarction without interrupting the inflammasome in the mouse. Exp Physiol 2013;98:734–45.

8. Toldo S, Mezzaroma E, Bressi E, et al. Interleukin-1β blockade improves left ventricular systolic/diastolic function and restores contractility reserve in severe ischemic cardiomyopathy in the mouse. J Cardiovasc Pharmacol 2014;64:1–6.

9. Trankle C, Thurber CJ, Toldo S, Abbate A. Mitochondrial membrane permeability inhibitors in acute myocardial infarction: still awaiting translation. J Am Coll Cardiol Basic Trans Science 2016; 1:524–35.

10. Sager HB, Heidt T, Hulsmans M, et al. Targeting interleukin-1β reduces leukocyte production after acute myocardial infarction. Circulation 2015;132:1880–90.

11. Abbate A, Kontos MC, Grizzard JD, et al., for the VCU-ART Investigators. Interleukin-1 blockade with anakinra to prevent adverse cardiac remodeling after acute myocardial infarction (Virginia Commonwealth University Anakinra Remodeling Trial [VCU-ART] Pilot study). Am J Cardiol 2010;105:1371–7.

12. Abbate A, Van Tassell BW, Biondi-Zoccai G, et al. Effects of Interleukin-1 blockade with anakinra on adverse cardiac remodeling and heart failure after acute myocardial infarction (from the Virginia Commonwealth University-Anakinra Remodeling Trial (2) (VCU-ART2 pilot study). Am J Cardiol 2013;111:1394–400.

13. Abbate A, Kontos MC, Abouzaki NA, et al. Comparative safety of Interleukin-1 blockade with anakinra in patients with ST-segment elevation acute myocardial infarction (from the VCU-ART and VCU-ART2 pilot studies). Am J Cardiol 2015; 115:288–92.

14. Van Tassell BW, Arena RA, Toldo S, et al. Enhanced interleukin-1 activity contributes to exercise intolerance in patients with systolic heart failure. PLoS One 2012;7:e33438.

15. Van Tassell B, Canada J, Carbone S, et al. Interleukin-1 blockade in recently decompensated systolic heart failure: the recently decompensated heart failure anakinra response trial (REDHART). Eur J Heart Fail 2017;19 Suppl:368.

16. Novartis. Novartis phase III study shows ACZ885 (canakinumab) reduces cardiovascular risk in people who survived a heart attack. Available at: https://www.novartis.com/news/media-releases/novartis-phase-iii-study-shows-acz885-canakinumab-reduces-cardiovascular-risk. Accessed July 13, 2017.