Commentary

LATITUDE-TIMI: is there still hope for anti-inflammatory therapy in acute myocardial infaction?

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Inflammation is a crucial feature of atherosclerotic plaque formation as well as post myocardial infarction (MI) remodeling and thus thought to play an essential role in the pathogenesis of ischemic heart disease and its complications (1,2). The regenerative processes after MI involve inflammatory, proliferative and maturation phases that are crucial for wound healing and reparation (3). However, an overactive inflammatory and fibrotic response is associated with maladaptive structural and electrophysiological remodeling, leading to systolic as well as diastolic dysfunction and contributing to the development of an arrhythmogenic substrate (2,4). Moreover, elevated cytokine levels also correlate with increased risk for recurrent coronary events in patients with MI (5).

Accordingly, targeting inflammation has emerged as a promising therapeutic approach in the context of post MI remodeling and its complications. So far, however, no anti-inflammatory medication could find its way into the clinical treatment of MI. Corticosteroids showed beneficial effects in several clinical trials, but the risk-benefit ratio appears to be unclear as corticosteroid therapy was suggested to lead to a higher incidence of cardiac rupture due to impaired wound healing in other studies (6). Also treatment with NSAIDs is not recommended after MI as an increased risk of bleeding and excess thrombotic events were observed (7). The TNFα antagonist etanercept was reported to reduce systemic inflammation but increase platelet activation in patients with MI, thus appearing to be rather detrimental (8). Besides that, etanercept also failed to improve clinical outcome in patients with congestive heart failure (9). For the IL-1 receptor antagonist anakinra, pilot studies showed favorable effects on LV remodeling (10,11), but its future value is still uncertain and larger trials are needed.

p38 mitogen-activated protein kinase (MAPK) is an intracellular kinase that is involved in inflammatory processes by enhancing various putatively adverse cytokines and metalloproteinases and was therefore suggested to worsen MI and its complications (12,13). Inhibition of p38 proved beneficial in various animal models regarding atherosclerotic processes and post MI remodeling (14). Losmapimod was the first p38 MAPK inhibitor bearing the potential to enter advanced clinical phases after showing promising results in phase II trials. Treatment resulted in improved vascular function in patients with hypercholesterolemia (15) and reduced vascular inflammation in patients with atherosclerosis (16). In non-ST-segment elevation MI (NSTEMI) patients, losmapimod reduced the acute increase in high sensitivity CRP (hsCRP) as well as in IL-6 and lowered BNP in the long term (17). However, as this study was not powered to assess clinical outcome, it remained open whether the observed reduction in inflammatory markers could translate into clinical benefit.

Very recently, the results of the LATITUDE study, a phase III clinical trial that enrolled a cohort of 3,500 patients with MI (including NSTEMI and STEMI), were published in *JAMA* (18). Patients received either losmapimod (7.5 mg) twice daily or placebo for 12 weeks in addition to standard of care. The primary endpoint was the composite of cardiovascular death, MI, or severe recurrent ischemia requiring urgent coronary artery revascularization. The trial was conducted as an exploratory study in a limited number of patients that was intended to be continued into a second phase with approximately 22,000 patients after

initial safety and efficacy assessment in the leading cohort. Losmapimod was well tolerated, significantly attenuated the acute increase in the inflammatory marker hsCRP and also significantly reduced NT-pro-BNP at 4 and 12 weeks. However, losmapimod treatment did not improve clinical outcome as there was no benefit regarding the primary and all secondary endpoints including all-cause mortality. The results of the exploratory phase predicted the probability for observing a relevant treatment effect in the second phase to be lower than 1% and thus the study was terminated (19).

The LATITUDE trial is clearly dampening enthusiasm in the field of anti-inflammatory treatment of cardiovascular diseases, especially since another recent attempt to target inflammation also failed: the lipoprotein-associated phospholipase A2 inhibitor darapladib did not benefit patients with coronary artery disease and MI (20,21). Nonetheless, our pathophysiological understanding of atherosclerosis and remodeling after MI suggests coherence between overactive immunoresponse and cardiovascular risk (1,3). However, as the inflammatory response involves a complex interplay of a vast number of mediators and a finely tuned timeline of immunoresponse appears to be crucial for sufficient wound healing, targeting these mechanisms is obviously challenging. Refinement of therapeutic approaches in this field is essential—such as specificity, dose and timepoint of intervention. Moreover, one has to consider interindividual differences in inflammatory reactions, which might limit a global anti-inflammatory medication for all patients, implying a more personalized therapy. Finally, the efficacy of existing therapies may well mask the effect of additional anti-inflammatory interventions. These challenges will be hard to tackle, and improved preclinical studies, potentially including large animal models, may be necessary to define target and time point. Yet such aspects will have to be addressed before the conceptually promising anti-inflammatory approach can translate into clinical success.

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Footnote

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References

1. Tousoulis D, Oikonomou E, Economou EK, et al. Inflammatory cytokines in atherosclerosis: current therapeutic approaches. Eur Heart J 2016;37:1723-32.
2. Francis Stuart SD, De Jesus NM, Lindsey ML, et al. The crossroads of inflammation, fibrosis, and arrhythmia following myocardial infarction. J Mol Cell Cardiol 2016;91:114-22.
3. Frangogiannis NG. The inflammatory response in myocardial injury, repair, and remodelling. Nat Rev Cardiol 2014;11:255-65.
4. Streitner F, Kuschyk J, Veltmann C, et al. Role of proinflammatory markers and NT-proBNP in patients with an implantable cardioverter-defibrillator and an electrical storm. Cytokine 2009;47:166-72.
5. Ridker PM, Rifai N, Pfeffer M, et al. Elevation of tumor necrosis factor-alpha and increased risk of recurrent coronary events after myocardial infarction. Circulation 2000;101:2149-53.
6. Giugliano GR, Giugliano RP, Gibson CM, et al. Meta-analysis of corticosteroid treatment in acute myocardial infarction. Am J Cardiol 2003;91:1055-9.
7. Schjerning Olsen AM, Gislason GH, McGettigan P, et al. Association of NSAID use with risk of bleeding and cardiovascular events in patients receiving antithrombotic therapy after myocardial infarction. JAMA 2015;313:805-14.
8. Padfield GJ, Din JN, Koushiappi E, et al. Cardiovascular effects of tumour necrosis factor α antagonism in patients with acute myocardial infarction: a first in human study. Heart 2013;99:1330-5.
9. Mann DL, McMurray JJ, Packer M, et al. Targeted anticytokine therapy in patients with chronic heart failure: results of the Randomized Etanercept Worldwide Evaluation (RENEWAL). Circulation 2004;109:1594-602.
10. Abbate A, Kontos MC, Grizzard JD, et al. 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.e1.

11. 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.
12. Denise Martin E, De Nicola GF, Marber MS. New therapeutic targets in cardiology: p38 alpha mitogen-activated protein kinase for ischemic heart disease. Circulation 2012;126:357-68.
13. O'Donoghue ML, Glaser R, Aylward PE, et al. Rationale and design of the LosmApimod To Inhibit p38 MAP kinase as a TherapeUtic target and moDify outcomes after an acute coronary syndromE trial. Am Heart J 2015;169:622-30.e6.
14. Clark JE, Sarafraz N, Marber MS. Potential of p38-MAPK inhibitors in the treatment of ischaemic heart disease. Pharmacol Ther 2007;116:192-206.
15. Cheriyan J, Webb AJ, Sarov-Blat L, et al. Inhibition of p38 mitogen-activated protein kinase improves nitric oxide-mediated vasodilatation and reduces inflammation in hypercholesterolemia. Circulation 2011;123:515-23.
16. Elkhawad M, Rudd JH, Sarov-Blat L, et al. Effects of p38 mitogen-activated protein kinase inhibition on vascular and systemic inflammation in patients with atherosclerosis. JACC Cardiovasc Imaging 2012;5:911-22.
17. Newby LK, Marber MS, Melloni C, et al. Losmapimod, a novel p38 mitogen-activated protein kinase inhibitor, in non-ST-segment elevation myocardial infarction: a randomised phase 2 trial. Lancet 2014;384:1187-95.
18. O'Donoghue ML, Glaser R, Cavender MA, et al. Effect of Losmapimod on Cardiovascular Outcomes in Patients Hospitalized With Acute Myocardial Infarction: A Randomized Clinical Trial. JAMA 2016;315:1591-9.
19. No Improvements with Losmapimod After Heart Attack. American College of Cardiology Foundation. Available online: https://www.acc.org/about-acc/press-releases/2016/04/11/15/59/no-improvements-with-losmapimod-after-heart-attack?w_nav=S
20. O'Donoghue ML, Braunwald E, White HD, et al. Effect of darapladib on major coronary events after an acute coronary syndrome: the SOLID-TIMI 52 randomized clinical trial. JAMA 2014;312:1006-15.
21. Wallentin L, Held C, Armstrong PW, et al. Lipoprotein-Associated Phospholipase A2 Activity Is a Marker of Risk But Not a Useful Target for Treatment in Patients With Stable Coronary Heart Disease. J Am Heart Assoc 2016;5. pii: e003407.

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