Translational Medicine
ISSN: 2161-1025

Trankle and Abbate, Transl Med (Sunnyvale) 2016, 6:1
DOI: 10.4172/2161-1025.1000e135

Editorial Open Access

PCSK9 Inhibition in Acute Myocardial Infarction: A Novel Opportunity

Cory Trankle and Antonio Abbate*

VCU Pauley Heart Center, Virginia Commonwealth University, Richmond, VA, USA

Editorial

Acute myocardial infarction (AMI) remains a leading cause of mortality and morbidity across the nation and worldwide. While major advances in reperfusion strategies over the past several decades have significantly reduced early mortality rates after AMI, patients who survive the index event are at increasingly risk for adverse cardiac remodeling and the sequelae of heart failure and sudden cardiac death [1]. This problem is accelerated by the aging population, making heart failure a major public health concern. Heart failure indeed currently affects approximately 5 million Americans, with increasing rates of prevalence and incidence.

Anticoagulants, antiplatelet agents, and neurohormonal blockers are standard of care in the treatment of patients with AMI, given their established effects on morbidity and mortality. Drugs lowering low density lipoprotein (LDL) cholesterol, primarily hydroxyl-methyl-glutaryl-coA reductase inhibitors – statins – have been studied as a means not only to reduce LDL cholesterol (and hence the incidence of recurrent AMI), but also as an adjunct to acute AMI therapy to reduce the acute complications. In the MIRACL trial, atorvastatin 80 mg, administered within 24 to 96 hours after presentation with acute coronary syndrome (ACS), significantly reduced the composite endpoint of death, nonfatal AMI, cardiac arrest with resuscitation, or recurrent symptomatic myocardial infarction from 17.4% to 14.8% in the first 16 weeks when compared to placebo (relative risk = 0.84 [0.70 – 1.00], p=0.048) [2].

In the ARMYDA trial, high-dose atorvastatin for 7 days prior to elective percutaneous intervention (PCI) significantly reduced periprocedural myocardial infarction (MI) rates from 18% to 5% (p=0.025) [3]. This was followed by the ARMYDA-ACS trial, showing that initiation of high dose atorvstatin therapy in patients presenting with non-ST elevation ACS sent to early (<48 hours) angiography reduced the composite primary endpoint of death, MI, or target vessel revascularization from 17% to 5% compared to placebo (p=0.010) at 30 days[4].

Proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors are a promising new treatment strategy for LDL cholesterol lowering, demonstrating potent LDL lowering effects in addition to or compared to statins, in stable patients in primary or secondary prevention [5,6]. PCSK9 is predominantly produced in the liver, intestine, and kidney, where it is secreted into the plasma and binds the extracellular component of LDL receptors (LDL-R). Once bound, the LDLR-PCSK9 complex is internalized and directed it to the lysosome for degradation [7]. PCSK9 inhibitors have been formulated as monoclonal antibodies, designed to bind PCSK9 and prevent this series of events. As an effect, LDL-R concentrations on the surface of hepatocytes are increased, and more LDL is removed from the circulation.

Two PCSK9 inhibitors, alirocumab (Praluent™) and evolocumab (Repatha™), are currently approved by the United States of America Food & Drug Administration for primary prevention in patients with heterozygous familial hypercholesterolemia or secondary prevention in patients with clinically stable atherosclerotic cardiovascular disease who require additional lowering of LDL-cholesterol [8,9].

To date, there have been no studies of alirocumab, evolocumab, or any other PCSK9 inhibitor given acutely in patients with AMI. Considering the residual risk of complications and death in patients with AMI, there is an urgent clinical need to investigate new strategies for risk reduction in AMI. A rapid reduction of LDL cholesterol within 2-4 weeks of an AMI could provide additional benefit on top of current standard care, including high-dose statins.

Moreover, a cross-talk between lipoprotein metabolism and systemic inflammation exists. In multiple in vitro studies, PCSK9 has demonstrated influence on receptors other than LDLR, including the VLDL receptor (PCSK9 facilitates its degradation) [10], LDL-R-related protein 1 (LRP-1) [11] and CD36 [12].

LRP-1 is a receptor that is known to bind over 40 ligands, including bacterial toxins and apoptotic cell debris [13], facilitating endosomal transport into phagocytes for degradation [14]. The receptor has been shown to promote resolution of inflammation, at least in part due to its indirect control on the IKK/NF-κB pathway by downregulation of the cell surface expression of tumor necrosis factor-1 receptor [15]. PCSK9 appears to have a similar effect on LRP-1 as it does on LDL-R (i.e. facilitating LRP-1 degradation) [16], suggesting that PCSK9 inhibition would prevent this component of the inflammatory cascade in response to the molecular triggers of LRP-1 (e.g. lipopolysaccharides encountered on Gram negative bacterial surfaces, cell debris released during an acute MI), and thus PCSK9 inhibitors could promote an anti-inflammatory effect.

Macrophages are known to play an important role in atherosclerosis formation [17] and the associated inflammatory pathways [18]. High levels of plasma LDL lead to oxidative modification of those LDL particles in the arterial intima, thus forming oxLDL particles [19]. This oxidized form of LDL is then recognizable to scavenger receptors (SR) on the surface of macrophages, principally SR-CD36 and SR-A18. Once CD36 binds oxLDL, the activated receptor interacts with Toll-like receptor 4 (TLR4) and TLR6 to activate NF-κB and ultimately the inflammasome complex [20], which serves to dramatically amplify the inflammatory response. PCSK9-mediated increases in levels of circulating LDL leaves those LDL particles vulnerable to oxidation. The resulting oxLDL is scavenged by CD36, leading to stimulation of further CD36 upregulation [21]. PCSK9 silencing RNA suppresses oxLDL-induced NF-κB activation of inflammatory pathways in macrophages [22], which appears to be at least partially related to a direct upregulation of CD36 in this cell line [23]. On the other hand, PCSK9 appears to have an opposite effect on CD36 in hepatic cells (i.e. PCSK9 facilitates CD36 degradation) [24], suggesting another mechanism by which oxLDL particles are removed from the circulation, thus reducing the

***Corresponding author:** Antonio Abbate, Department of Pharmacotherapy and Outcome Sciences School of Pharmacy, Virginia Commonwealth University 410 N 12th St, Box 980533 Richmond, VA, 23298, USA, Tel: + 8043988796; E-mail: antonio abbate@vcuhealth.org.

Received November 28, 2015; **Accepted** December 02, 2015; **Published** January 20, 2016

Citation: Trankle C, Abbate A (2016) PCSK9 Inhibition in Acute Myocardial Infarction: A Novel Opportunity. Transl Med 6: e135. doi:10.4172/2161-1025.1000e135

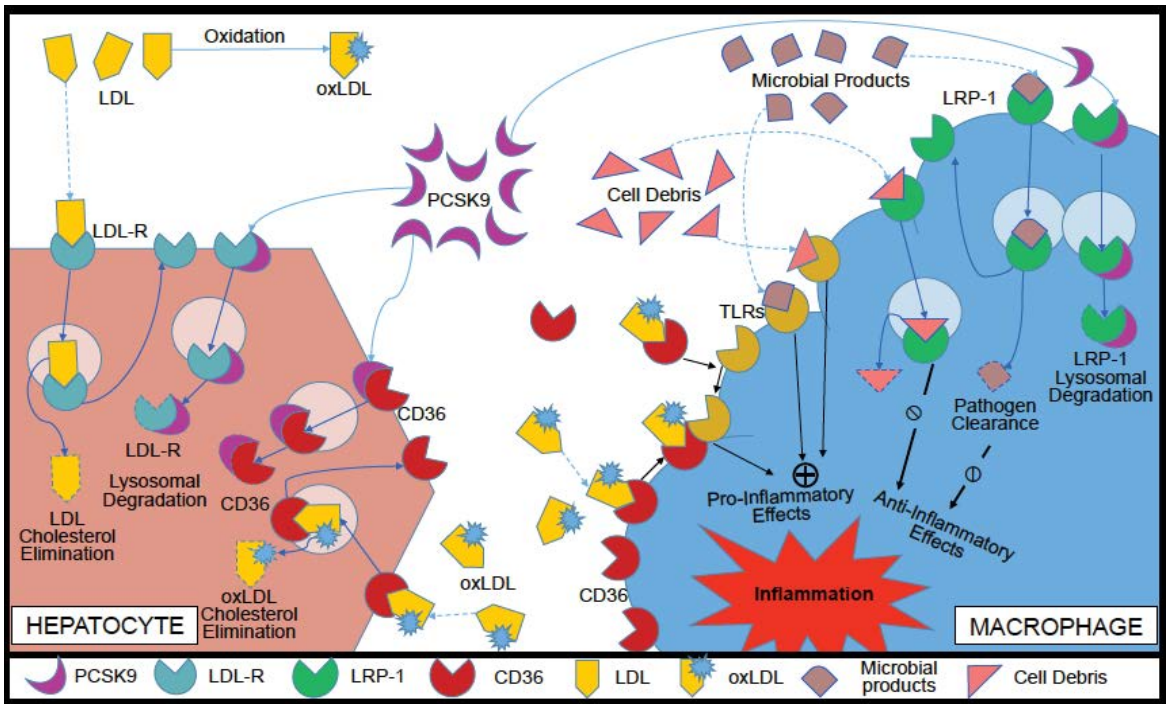

Figure 1: LDL and oxLDL particles bind to their respective receptors on hepatocytes, facilitating their endosomal uptake and elimination. PCSK9 binding to the receptors promotes lysosomal degradation, rather than recycling to the cell surface, making the receptors unavailable for LDL and oxLDL scavenging. Microbial products (e.g. lipopolysaccharide on Gram negative bacterial surfaces) or cell debris bind LRP1 receptor facilitating pathogen clearance and inhibiting the inflammatory response. PCSK9 binding to LRP1 promotes lysosomal degradation of the receptor, thus making the receptor unavailable for pathogen scavenging. Like LDL-R, LRP1 also binds circulating lipoproteins. In macrophages, CD36 functions as a co-factor for TLRs inducing a pro-inflammatory response to ox-LDL. Abbreviations: LDL-R: low density lipoprotein receptor; oxLDL: oxidized LDL; PCSK9: proprotein convertase subtilisin/kexin 9; LRP-1: LDL receptor related protein 1; TLR: Toll-like receptor.

overall inflammatory burden.

The suggested effects of PCSK9 activity on LDL receptors and CD36 in liver cells, as well as LRP-1 and CD36 in macrophages, are summarized in Figure 1.

Overlapping pathways between lipoprotein metabolism and inflammation has a theoretical basis in the innate immune response to pathologic lipoproteic signals (i.e. cell debris during myocardial injury or lipopolysaccharide in Gram negative bacteria). Indeed, in a mouse model of septic shock due to intraperitoneal injection of lipopolysaccharide, PCSK9-knockout mice or mice receiving PCSK9 modulators had a more favorable outcome than their counterparts [25]. Accordingly, retrospective evidence from a large clinical study of septic shock showed a correlation between estimated PCSK9 activity (extrapolated from detected gain of function or loss of function genetic mutations), the measured inflammatory biomarker levels, and survival during septic shock [25].

To our knowledge, there has been no published data from clinical trials on the effects of PCSK9 inhibitors on the inflammatory response in patients with AMI. Efficacy data of PCSK9 inhibitors derives from the primary and secondary prevention studies enrolling patients who are not expected to have high levels of inflammatory biomarkers, thus making any effect of PCSK9 inhibitors on inflammation difficult to detect [26]. Chronic low-grade systemic inflammation (which associates with increased cardiovascular risk in primary and secondary prevention) may indeed be a different pathologic process than the acute inflammatory response to AMI.

Patients suffering from an AMI may, therefore, derive benefit from PSCK9 inhibitors, by way of rapid LDL reduction (stabilizing the LDL-R), a reduction the pro-inflammatory signaling of ox-LDL (reducing the CD36 receptor), and/or facilitation of removal of the pro-inflammatory apoptotic debris and anti-inflammatory cellular signaling (via the LRP1 receptor). They have proven safe and well tolerated in stable outpatient populations, but whether this remains true for patients in the acute setting remains to be seen. Testing this hypothesis in future clinical trial would clarify whether a new therapeutic agent to prevent post-AMI heart failure is already within our reach.

References

1. Velagaleti RS, Pencina MJ, Murabito JM, Wang TJ, Parikh NI et al. (2008) Long-term trends in the incidence of heart failure after myocardial infarction. Circulation 118: 2057-2062.
2. Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF et al. (2001) Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes. J Am Med Assoc 285: 1711-1718.
3. Pasceri V, Patti G, Nusca A, Pristipino C, Richichi G, et al. (2004) Randomized trial of atorvastatin for reduction of myocardial damage during coronary intervention: results from the ARMYDA (Atorvastatin for reduction of myocardial damage during angioplasty) study. Circulation 110: 674-678.
4. Patti G, Pasceri V, Colonna G, Miglionico M, Fischetti D, et al. (2007) Atorvastatin pretreatment improves outcomes in patients with acute coronary syndromes undergoing early percutaneous coronary intervention. Results of the armyda-acs randomized trial. J Am Coll Cardiol 49: 1272-1278.
5. Sabatine MS, Giugliano RP, Wiviott SD, Raal FJ, Blom DJ, et al. (2015) Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. N Engl J Med 372: 1500-1509.
6. Robinson JG, Farnier M, Krempf M, Bergeron J, Luc G et al. (2015) Efficacy and safety of alirocumab in reducing lipids and cardiovascular events. N Engl J Med 372: 1489-1499.

7. Horton JD, Cohen JC, Hobbs HH (2009) PCSK9: A convertase that coordinates LDL catabolism. J Lipid Res 50: S172-S177.

8. Sanofi US (2015) LLC. Praluent (TM) [prescribing information].

9. Amgen Inc. (2015) Repatha (TM) [prescribing information].

10. Poirier S, Mayer G, Benjannet S, Bergeron E, Marcinkiewicz J, et al. (2008) The proprotein convertase PCSK9 induces the degradation of low density lipoprotein receptor (LDLR) and its closest family members VLDLR and ApoER2. J Biol Chem. 283: 2363-2372.

11. Canuel M, Sun X, Asselin M-C, Paramithiotis E, Prat A, et al.(2013) Proprotein convertase subtilisin/kexin type 9 (pcsk9) can mediate degradation of the low density lipoprotein receptor-related protein 1 (LRP-1). PLoS One 8:1-11.

12. Shen L, Peng H-C, Nees SN, Zhao S, Xu DY (2013) Proprotein convertase subtilisin/kexin type 9 potentially influences cholesterol uptake in macrophages and reverse cholesterol transport. Febs Lett 587: 1271-1274.

13. Strickland DK, Gonias SL, Argraves WS (2002) Diverse roles for the ldl receptor family. Trends Endocrinol Metab 13: 66-74.

14. Gardai SJ, McPhillips KA, Frasch SC, et al.(2005) Cell-surface calreticulin initiates clearance of viable or apoptotic cells through trans-activation of LRP on the phagocyte. Cell 123: 321-334.

15. Gaultier A, Arandjelovic S, Niessen S, Overton CD, Linton MF, et al. (2008) Regulation of tumor necrosis factor receptor-1 and the ikk-nf-kb pathway by ldl receptor-related protein explains the antiinflammatory activity of this receptor. Blood 111: 5316-5325.

16. Canuel M, Sun X, Asselin MC, Paramithiotis E, Prat A, et al., (2013) Proprotein convertase subtilisin/kexin type 9 (PCSK9) can mediate degradation of the low density lipoprotein receptor-related protein 1 (LRP-1). PloS One 8: 1-11.

17. Bobryshev YV (2006) Monocyte recruitment and foam cell formation in atherosclerosis. Micron 37: 208-222.

18. McLaren JE, Michael DR, Ashlin TG, Ramji DP (2011) Cytokines, macrophage lipid metabolism and foam cells: implications for cardiovascular disease therapy. Prog Lipid Res 50: 331-347.

19. Lusis AJ (2000) Atherosclerosis. Nature 407: 233-241.

20. Oury C (2014) CD36: Linking lipids to the NLRP3 inflammasome, atherogenesis and atherothrombosis. Cell Mol Immunol 11: 8-10.

21. Han J, Hajjar DP, Febbraio M, Nicholson AC (1997) Native and modified low density lipoproteins increase the functional expression of the macrophage class B scavenger receptor, CD36. J Biol Chem 272: 21654-21659.

22. Tang Z, Jiang L, Peng J, Ren Z, Wei D, et al.(2012) PCSK9 siRNA suppresses the inflammatory response induced by oxLDL through inhibition of NF-kappaB activation in THP-1-derived macrophages. Int J Mol Med 30: 931-938.

23. Shen L, Peng H-C, Nees SN, Zhao SP, Xu D-Y (2013) Proprotein convertase subtilisin/kexin type 9 potentially influences cholesterol uptake in macrophages and reverse cholesterol transport. FEBS Lett 587: 1271-1274.

24. Demers A, Samami S, Lauzier B, Rosiers CD, Sock ET, et al. (2015) PCSK9 induces CD36 degradation and affects long-chain fatty acid uptake and triglyceride metabolism in adipocytes and in mouse liver. Arterioscler Thromb Vasc Biol 35: 2517-2525.

25. Walley KR, Thain KR, Russell JA, et al. (2014) PCSK9 is a critical regulator of the innate immune response and septic shock outcome. Sci Transl Med 6: 258ra143.

26. Gugliano RP, Sabatine MS (2015) Are PCSK9 inhibitors the next breakthrough in the cardiovascular field? J Am Coll Cardiol 65: 2638-2651.