REVIEW ARTICLE

On the value of therapeutic interventions targeting the complement system in acute myocardial infarction

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The complement system plays an important role in the inflammatory response subsequent to acute myocardial infarction (AMI). The aim of this study is to create a systematic overview of studies that have investigated therapeutic administration of complement inhibitors in both AMI animal models and human clinical trials. To enable extrapolation of observations from included animal studies toward post-AMI clinical trials, ex vivo studies on isolated hearts and proof-of-principle studies on inhibitor administration before experimental AMI induction were excluded. Positive therapeutic effects in AMI animal models have been described for cobra venom factor, soluble complement receptor 1, C1-esterase inhibitor (C1-inh), FUT-175, C1s-inhibitor, anti-C5, ADC-1004, clusterin, and glycosaminoglycans. Two types of complement inhibitors have been tested in clinical trials, being C1-inh and anti-C5. Pexelizumab (anti-C5) did not result in reproducible beneficial effects for AMI patients. Beneficial effects were reported in AMI patients for C1-inhibitor, albeit in small patient groups. In general, despite the absence of consistent positive effects in clinical trials thus far, the complement system remains a potentially interesting target for therapy in AMI patients. Based on the study designs of previous animal studies and clinical trials, we discuss several issues which require attention in the design of future studies: adjustment of clinical trial design to precise mechanism of action of administered inhibitor, optimizing the duration of therapy, and optimization of time point(s) on which therapeutic effects will be evaluated. (Translational Research 2016;■:1–20)

Abbreviations: AMI = Acute myocardial infarction; C1-inh = C1-inhibitor; C1s-inh = C1s-inhibitor; C4BP = C4b-binding protein; CK(-MB) = creatine kinase (-MB); CPN = carboxypeptidase-N; CR1 = complement receptor 1; CVF = cobra venom factor; DDA = disodium disuccinate astaxanthin; GAG = glycosaminoglycan; MAC = membrane attack complex; MAP-1 = MBL/ficolin-associated protein 1; MASP = MBL-associated serine protease; MBL = mannose-binding lectin; PMN = polymorphonuclear leukocyte; sCR1 = recombinant sSoluble complement receptor 1

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INTRODUCTION

Acute myocardial infarction (AMI) is an important cause of morbidity and mortality worldwide, forming 7% and 5% of the global disease burden in males and females, respectively.[1] An important factor contributing to AMI-related morbidity and mortality is inflammation. The inflammatory response after AMI is necessary for clearance of the jeopardized infarcted tissue but at the same time may enhance cell death of at that moment still-viable cardiomyocytes, resulting in infarct expansion.[2] The complement system plays an important role herein, both by stimulating inflammation and by directly causing death to reversibly damaged cardiomyocytes (summarized in Fig 1).

In the 1950s, an increase in serum complement was already recognized as a serological marker for AMI.[3] Later, in 1971, a hallmark study by Hill and Ward demonstrated for the first time that cleavage of complement factor C3 occurs in infarcted myocardium following AMI in rats and that depletion of C3 using cobra venom factor (CVF) inhibits polymorphonuclear leukocyte (PMN, neutrophils) infiltration of the infarcted myocardium.[4]

This finding triggered a wide interest in the complement system as potential therapeutic target for AMI. Between 1990 and 2005, a large number of animal studies were published describing positive effects of various complement inhibitors on the outcome of AMI, and complement was considered a promising target for therapy.[5-8] Disappointing results of several clinical trials in the 2000s however dampened the general enthusiasm for complement inhibitors as therapy for AMI patients.

The main objective of this review is to provide a detailed overview on the animal studies and clinical trials that studied complement inhibitors as therapeutic option for AMI. This objective is in contrast to that of other recently published reviews on complement inhibitors in both animal models and clinical trials,[9,10] as these focused on ischemia-reperfusion injury in general. Based on our overview, we aim to elucidate whether or not the concept of complement inhibition as therapy in AMI has been abandoned prematurely, and to provide directions for future research in this field.

STRUCTURE AND FUNCTION OF THE COMPLEMENT SYSTEM

The complement system is part of the humoral innate immune response and forms a cascade of over 30 proteins present in plasma (fluid phase) or bound to the target surface (damaged or infected cells or pathogens). The molecular composition of the complement system has been studied and described in great detail.[11-17] Summarized, the complement system can be activated through 3 pathways: the classical pathway, the lectin pathway, and the alternative pathway (Fig 2). Activation of the classical pathway is mediated by the C1 complex, consisting of C1q, C1s, and C1r, whereas activation of

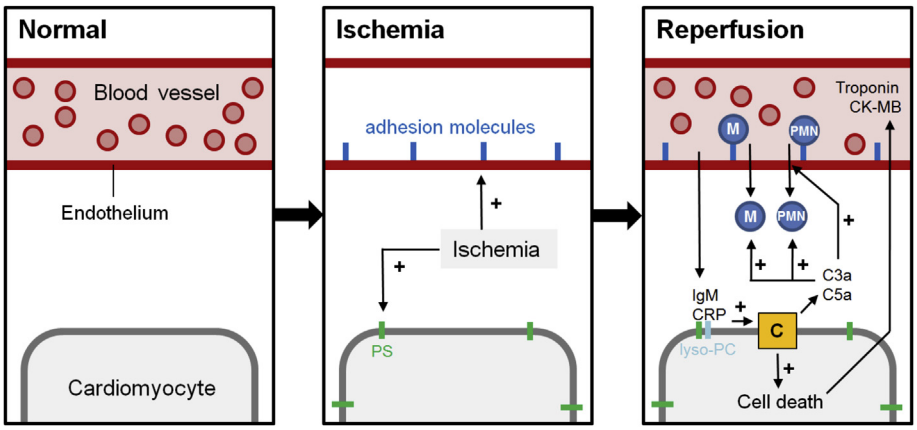

Fig 1. Schematic representation of the effects of complement in the post-AMI myocardium. Following coronary artery occlusion, cardiac ischemia causes exposure of phosphatidylserine (PS) on the cardiomyocyte membrane and upregulation of adhesion molecules, such as ICAM-1, on endothelial cells. When the infarcted myocardium is reperfused, IgM, C-reactive protein (CRP), and complement proteins (C) enter the myocardium from the systemic circulation. PS indirectly triggers exposure of lysophospholipids (Lyso-PC), which function as an attachment site for IgM, CRP, and C to cardiomyocytes that are reversibly damaged by ischemia, after which the complement system is activated. Complement activation results in the death of the damaged cardiomyocytes and release of anaphylatoxins (C3a and C5a). The anaphylatoxins and the adhesion molecules both stimulate extravasation of proinflammatory macrophages (M) and neutrophils (PMN). As result of cardiomyocyte death, cardiac proteins such as troponins and creatine kinase (CK-MB) are released, which can be detected in the systemic circulation. AMI, acute myocardial infarction.