JACC: BASIC TO TRANSLATIONAL SCIENCE
VOL. 2, NO. 4, 2017
ISSN 2452-302X
http://dx.doi.org/10.1016/j.jacbts.2017.07.001

TRANSLATIONAL PERSPECTIVES

Failure to Launch

Targeting Inflammation in Acute Coronary Syndromes

Jennifer A. Rymer, MD, MBA, L. Kristin Newby, MD, MHS

SUMMARY

The importance of inflammation and inflammatory pathways in atherosclerotic disease and acute coronary syndromes (ACS) is well established. The success of statin therapy rests not only on potently reducing levels of low-density lipoprotein cholesterol, but also on the many beneficial, pleiotropic effects statin therapy has on various inflammatory mechanisms in atherosclerotic disease, from reducing endothelial dysfunction to attenuating levels of serum C-reactive protein. Due to the growing awareness of the importance of inflammation in ACS, investigators have attempted to develop novel therapies against known markers of inflammation for several decades. Targeted pathways have ranged from inhibiting C5 cleavage with a high-affinity monoclonal antibody against C5 to inhibiting the activation of the p38 mitogen-activated protein kinase signaling cascades. In each of these instances, despite promising early preclinical and mechanistic studies and phase 2 trials suggesting a potential benefit in reducing post-MI complications or restenosis, these novel therapies have failed to show benefits during large, phase 3 clinical outcomes trials. This review discusses several examples of novel anti-inflammatory therapies that failed to show significant improvement on clinical outcomes when tested in large, randomized trials and highlights potential explanations for why targeted therapies against known markers of inflammation in ACS have failed to launch. (J Am Coll Cardiol Basic Trans Science 2017;2:484–97)

Over the past 2 decades, there has been increasing interest in discovering novel therapeutic agents for reducing residual risk among patients with acute coronary syndromes (ACS), including ST-segment elevation myocardial infarction (STEMI), non-ST-segment myocardial infarction (NSTEMI), and unstable angina. Each year, roughly 1.1 million patients are hospitalized with an ACS event in the United States (1). Although the overall incidence of ACS appears to be declining, the direct and indirect costs associated with treating patients with ACS and its downstream sequelae, including congestive heart failure and repeat revascularization, remain a medical and economic burden (2–4).

Atherosclerotic disease leading to an ACS event is a complex process of atheroma formation and eventual plaque rupture. The 30-day rate of recurrent events post-ACS is estimated to be around 2% (5,6). High-sensitivity C-reactive protein (hsCRP) (a marker of inflammation), can be elevated for several months after an ACS event, and is a marker of risk for subsequent development of heart failure and increased mortality (7). These observations led to a focus on inflammatory pathways as participants in the formation, proliferation, and rupture of atherosclerotic plaques (8). The intersection of ACS pathobiology, inflammation, and high rates of recurrent events post-ACS has generated interest in development of therapeutics that target inflammatory pathways to mitigate the development of post-ACS complications.

In this review, we examine the fate of work over the past decade to develop therapeutics that target

From the Division of Cardiology, Department of Medicine, and Duke Clinical Research Institute, Duke University School of Medicine, Durham, North Carolina. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received July 12, 2017; accepted July 12, 2017.

various inflammatory pathways and their components (Central Illustration). We will focus on therapeutic agents directed at the complement pathway and cleavage of C5, secretory phospholipase A_2 (sPLA2), lipoprotein-associated phospholipase A_2 ($Lp\text{-}PLA_2$), interleukin-1, and the mitogen-activated protein kinase (MAPK) signaling cascades (Table 1). We examine their development from animal models and other preclinical investigations through early and late-phase randomized clinical trials that tested the experimental drugs in ACS patients. We then offer potential explanations for why work targeting these inflammatory components and pathways in ACS has not translated into therapeutic successes and describe current, promising novel therapies that are still under investigation.

CASE STUDIES OF ANTI-INFLAMMATORY AGENTS FOR CARDIOVASCULAR DISEASE

PEXELIZUMAB. Pexelizumab was an early example of an anti-inflammatory therapy for ACS, targeting the C5 component of the complement cascade. Cleavage of the C5 component of the complement pathway results in formation of C5a and C5b-9, the membrane attack complex (9). C5a is proinflammatory, and the membrane attack complex is associated with activation of endothelial cells and leukocytes. Pexelizumab is a single-chain fragment of a humanized monoclonal antibody that binds to C5 with high affinity, preventing its cleavage. Early in vitro and human studies suggested that myocardial cell necrosis during an ACS event triggered the release of subcellular membrane constituents, which resulted in the activation of the complement system (10). For example, in a rabbit model of ischemia induced by ligature to a large marginal branch of the circumflex artery, there was accumulation of the membrane attack complex (C5b-C9) in infarcted myocardium, and rapid activation of the complement pathway occurred during reperfusion (11). One group of rabbits (n = 17) underwent circumflex coronary occlusion for variable time periods (from 0.5 to 29 h) without subsequent reperfusion, whereas the other group (n = 23) underwent coronary occlusion (from 0.5 to 6 h) with subsequent reperfusion. Although C5b-C9 was detected in the infarcted myocardium 5 to 6 h after occlusion without reperfusion, it was detected much earlier (at 30 min) in the group that underwent reperfusion, suggesting that the presence of reperfusion rapidly activates the complement pathway.

In addition to the association of complement activation with infarction and reperfusion injury, in a rat model of myocardial infarction (MI) and reperfusion, infusion of monoclonal antibodies against the rat C5 component prior to ligating the left anterior descending artery for 30 min, followed by reperfusion, significantly reduced left ventricular polymorphonuclear leukocyte infiltration, apoptosis and necrosis, and overall infarct size (12). In another study of myocardial ischemia and reperfusion injury in rats, injection of C5 short hairpin ribonucleic acid 2 days before induction of ischemia inhibited C5 expression, significantly decreased the level of troponin T, and reduced the infarct size by 40% (13). Additionally, in a pig model, infusion of a monoclonal antibody to C5a (at the time of onset of ischemia) followed by 50 min of occlusion of the left anterior descending artery using an occluder catheter and 3 h of reperfusion resulted in significant reduction in infarct size and reperfusion injury (14).

Based on these promising animal data and other early studies, a phase 2 program was launched. The CARDINAL (Complement And ReDuction of INfarct size after Angioplasty or Lytics) phase 2 program included 2 phase 2, parallel group, double-blind, placebo-controlled trials of pexelizumab in STEMI patients. These trials tested the effect of pexelizumab (bolus plus infusion administered <6 h after symptom onset) on infarct size (creatine kinase-MB area under the curve at 72 h) and clinical composite outcomes after fibrinolytic reperfusion therapy in the COMPLY (COMPlement inhibition in myocardial infarction treated with thromboLYtics) trial (15) or primary percutaneous coronary intervention (PCI) in the COMMA (COMplement inhibition in Myocardial infarction treated with Angioplasty) trial (16). The COMPLY investigators found no difference in infarct size or 90-day composite clinical outcomes for pexelizumab versus placebo among STEMI patients who received fibrinolytic therapy. Similarly, in the COMMA trial, among STEMI patients treated with primary PCI, there was no difference in infarct size or the 90-day primary composite of death, heart failure, shock, or stroke between patients treated with placebo versus pexelizumab. However, 90-day mortality was significantly lower among patients who received pexelizumab compared with placebo (1.8% vs. 5.9%; p = 0.014) (Figure 1). Interestingly, this mortality benefit was independent of infarct size, evidence of angiographic or electrocardiographic reperfusion, and extent of ST-segment elevation (17). In addition, the composite of worsening heart failure, shock, and

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndromes

CABG = coronary artery bypass graft

CAD = coronary artery disease

HDL-C = high-density lipoprotein cholesterol

hsCRP = high-sensitivity C-reactive protein

IL = interleukin

LDL-C = low-density lipoprotein cholesterol

$Lp\text{-}PLA_2$ = lipoprotein-associated phospholipase A_2

MAPK = mitogen-activated protein kinase

MI = myocardial infarction

NSTEMI = non-ST-segment myocardial infarction

PCI = percutaneous coronary intervention

PSGL = P-selectin glycoprotein ligand

sPLA2 = secretory phospholipase A2

STEMI = ST-segment elevation myocardial infarction

SVG = saphenous vein grafts

TBR = tissue-to-background ratio