Myocardial Infarct Size Reduction With Pexelizumab

The Role of Chance Is Patently Clear*

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The goal of ST-segment elevation myocardial infarction (STEMI) management is rapid and sustained reperfusion of the infarct-related artery (1–3). Primary percutaneous coronary intervention (PCI) is the preferred reperfusion method if it can be performed promptly and by an experienced operator (4). Despite widespread improvements in clinical pathways to improve door-to-balloon time and the development of novel antiplatelet and antithrombotic agents and subsequent improved clinical outcomes, STEMI remains a cause of considerable morbidity and mortality (5). As such, numerous pharmacologic and device-based strategies have been developed with the aim of improving outcomes among STEMI patients.

Although primary PCI sufficiently restores epicardial patency in the majority of STEMI patients, a large subset suffer from impaired myocardial perfusion, which has been associated with larger infarct size and a higher incidence of adverse cardiovascular events (6). Impaired myocardial perfusion may result from embolization of thrombotic and atherosclerotic debris and platelet microaggregates, endothelial dysfunction, inflammatory changes, or a combination of these events that occur in the myocardial microcirculation downstream of ruptured plaque.

The role of inflammation, specifically the complement pathway, in myocardial injury following STEMI has been an area of active investigation (7). The C5 component of the complement pathway, when cleaved via activation of more proximal components of the pathway, yields C5a, a proinflammatory cytokine, and C5b, which initiates production of the membrane attack complex, a multimeric protein that inserts itself into the cell membrane and leads to membrane destabilization and, ultimately, cell death. Therefore, inhibition of the cleavage of C5 into C5a and C5b would appear to be an attractive target in the reduction of infarct size and, potentially, adverse clinical events following STEMI.

Pexelizumab, a humanized monoclonal antibody that binds C5, showed promise in a phase 2 study of STEMI patients undergoing primary PCI, the COMMA (COMplement inhibition in Myocardial infarction treated with Angioplasty) trial (8). Paradoxically, administration of intravenous pexelizumab following primary PCI did not lead to a significant reduction in enzymatic infarct size, but was associated with a significant reduction in mortality (5.9% vs. 1.9%, p < 0.014). The authors postulated that although pexelizumab had no effect on infarct size, as might have been expected, its anti-inflammatory properties must have had some unmeasured pleiotropic effect(s) in order to lead to a reduction in mortality. Unfortunately, a subsequent phase 3 trial of high-risk STEMI patients, the APEX-AMI (Assessment of Pexelizumab in Acute Myocardial Infarction) study, did not confirm this reduction in either mortality or in the composite of death, shock, and congestive heart failure at 30 or 90 days following STEMI (9).

In this issue of JACC, Patel et al. (10) present the cardiac magnetic resonance (CMR) substudy of the APEX-AMI trial. In this 99-patient substudy, the administration of pexelizumab was associated with a significant reduction in infarct size and a higher left ventricular...
ejection fraction compared with placebo, a surprising result, considering administration of pexelizumab had no significant effect on mortality, shock, or congestive heart failure in the entire study population.

At first blush, the results of this substudy appear to present the opposite paradox from what was seen in the COMMA trial: in COMMA, pexelizumab did not reduce enzymatic infarct size but was associated with a significant reduction in mortality; in APEX-AMI, pexelizumab was associated with a reduction in CMR infarct size but had no effect on mortality.

The authors present 3 possible explanations for the significantly smaller infarct size in the pexelizumab group: 1) that pexelizumab does, in fact, reduce infarct size, but has some unknown deleterious effect; 2) that CMR may have been inaccurate; or 3) that there was selective bias inherent in this subgroup analysis.

Upon closer inspection of the patients enrolled in the CMR substudy of APEX-AMI, however, it becomes readily apparent why patients who received pexelizumab had, on average, smaller infarct size: they were significantly and substantially more likely to have a patent culprit artery at the time of initial angiography (42.9% with Thrombolysis In Myocardial Infarction [TIMI] flow grade 2 or 3 in the pexelizumab group versus 14.6% in the placebo group). Although pexelizumab was administered prior to balloon inflation, it is unlikely that it had such a dramatic effect on culprit artery patency and far more likely that the disparate baseline characteristics occurred because of chance. Moreover, there was no significant difference in initial TIMI Flow Grade in the entire study population between the pexelizumab and placebo groups.

Although pexelizumab likely had little effect on either infarct size or clinical outcomes among patients with STEMI—only anterior infarct location and initial TIMI flow grade were significantly associated with infarct size in a multivariate analysis—the results presented in this analysis further emphasize the importance of early epicardial patency in the management of STEMI.

Numerous studies have shown a significant association between initial TIMI flow grade at the time of primary PCI and both infarct size and clinical outcomes (11). Efforts to increase early patency, most specifically those aimed at improving door-to-reperfusion time, have been associated with improved clinical outcomes (12). Further pharmacologic strategies to improve early epicardial patency, namely in the form of fibrinolytic therapy prior to PCI, have, however, been met with disappointing results to date (13).

Likewise, APEX-AMI failed to demonstrate any tangible benefit of complement inhibition in the management of STEMI. Although this CMR substudy suggests that perhaps pexelizumab leads to a significant reduction in infarct size, this may reflect, at least in part, an imbalance in baseline characteristics between the small patient populations. What this substudy does support, however, is the continued pursuit of early epicardial patency as a means to reduce morbidity and mortality in STEMI.

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REFERENCES


Key Words: ST-segment elevation myocardial infarction • myocardial perfusion • TIMI flow grade.