Ameliorating reperfusion injury in STEMI: dead or alive?

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This editorial refers to ‘Inhibition of delta-protein kinase C by delcasertib as an adjunct to primary percutaneous coronary intervention for acute anterior ST-segment elevation myocardial infarction: results of the PROTECTION AMI Randomized Controlled Trial’†, by A.M. Lincoff et al., on page 2516

Reperfusion therapy reduces infarct size and improves left ventricular function in ST-segment elevation myocardial infarction (STEMI). Despite restoration of epicardial perfusion and commensurate reductions in morbidity and mortality, residual hazard persists. Restoration of coronary blood flow after prolonged ischaemia may exhibit a ‘double edge’ characterized as reperfusion injury with resulting cell death that can account for up to half of the final infarct size. The pathophysiology of reperfusion injury is probably multifactorial and includes distal embolization/platelet plugging of the microvasculature, release of toxic inflammatory mediators, production of oxygen free radicals, and accumulation of intracellular calcium. Whereas various cytoprotective agents have shown promise in animal models, to date translation of this benefit has been disappointing at best. Hence, combating reperfusion injury remains one of the final therapeutic frontiers in STEMI management.

Because protein kinase C (PKC) isoenzymes modulate myocardial protection, their potential for therapeutic intervention has been of interest. However, counter-regulatory cardioprotective activity has been reported with specific PKC isoenzymes. This ‘ying–yang’ counterpoint is represented by activation of εPKC which provides cardioprotection whereas activation of δPKC induces myocardial cell damage following ischaemia. Application of this pathway to myocardial protection led to the development of the selective δPKC antagonist, delcasertib, which reduced infarct size and improved microvascular function following reperfusion in animal models.

Given the experimental promise of delcasertib, a phase II dose-escalation study of 154 patients with acute anterior STEMI was undertaken. DELTA MI included patients with an occluded left anterior descending artery who were randomized in a 2:1 fashion to receive one of four doses of delcasertib (0.05, 0.5, 1.25, or 5.0 mg) vs. placebo given in two divided doses using an intracoronary route (before and after reperfusion was established). The incidence of serious adverse events was similar in all groups, establishing the safety of delcasertib. However, non-significant reductions in myocardial biomarkers and ST segment indices of ischaemic recovery provided enough optimism to generate continuing clinical study of this novel compound.

Lincoff et al. now report the results of the PROTECTION AMI trial, a phase II dose-finding study, testing the effects of delcasertib in 1010 patients presenting within 6 h of STEMI. Patients were randomized to either placebo or one of three doses of delcasertib (50, 150, or 450 mg/h) given by an i.v. infusion initiated before primary percutaneous coronary intervention (PCI) and continued for ~2.5 h after the procedure. There were no differences in the treatment groups according to the primary efficacy endpoint of infarct size measured by the CK-MB (creatine kinase MB form) area under the curve. Additionally, no differences were seen in the secondary endpoints of infarct size, electrocardiogram (ECG) ST segment recovery area under the curve, time to stable ST segment recovery, or left ventricular ejection fraction, after 3 months. Although this trial was not powered for clinical endpoints, no signal for benefit was evident in death, heart failure, or serious ventricular arrhythmias.

PROTECTION AMI was a well-conducted study that again highlights the failure to translate experimental promise of a novel agent to clinical practice. This theme is reminiscent of many other pharmacological agents shown to be effective in animal models yet ineffective in humans. Specifically, free radical antagonists, inhibitors of intercellular calcium overload, and inhibitors of the inflammation—neutrophil injury pathway have failed to show benefit in human clinical trials. Such one example was the APEX AMI phase III trial which was performed in 5745 patients who presented with an STEMI and underwent primary PCI. Pexelizumab, an anti-CS complement antibody, did not modify the primary endpoint of all-cause mortality at 30 days despite robust animal data and promising phase II clinical results.
What might explain the current result? The PROTECTION MI investigators chose an i.v. route as opposed to the intracoronary route for delcassertib administration used in DELTA MI. More directed administration, specifically targeting the jeopardized region of myocardium subserved by the infarct-related artery (IRA), may have enhanced this agent’s effectiveness. Equally important would have been confirmation of the biological efficacy of one of the three escalating i.v. doses of delcassertib initiated before PCI, as underdosing may have been a possibility. The i.v. formulation was started a median of 16 min prior to PCI. Given that the steady state of this agent can take up to 30 min to achieve, it is feasible this was too late for cardioprotection once reperfusion had been established. Earlier administration in the emergency department (or even pre-hospital administration) may have allowed time to achieve optimal pharmacodynamic effects prior to reperfusion.

Given the various contemporary adjunctive treatments of STEMI patients undergoing primary PCI, it would be useful to understand the impact of other concomitant therapies administered according to investigator preference. Specifically, the timing of P2Y12 receptor antagonists as antiplatelet agents used in the early hours of patient care (pre-load or during angiogram) would be relevant to help evaluate the contribution to clinical outcome. Could unexpected drug–drug interactions have attenuated the efficacy of this short-acting isoenzyme? Of interest were the high rates of spontaneous reperfusion (pre-PCI TIMI 3 flow) seen in the anterior STEMI patient population (19–22%). Presumably the more favourable clinical outcomes of those with pre PCI TIMI 3 flow may limit the efficacy of agents directed at reperfusion injury. Perhaps future investigations should be aimed at patients with completely occluded culprit vessels (TIMI 0 flow) to target a phenotype that provides the best substrate for testing proof of concept. It is of note that the DELTA MI phase I study only included patients with a completely occluded IRA, employed intracoronary administration, and studied a population with a total ischaemic time at least 1 h longer that in PROTECTION MI. Although the PROTECTION MI investigators assessed their results according to pre-PCI TIMI 0/1, the lower number of patients in this category may have left them underpowered to rule out a treatment effect.

The ECG ST-segment area under the curve for the anterior MI cohort was numerically lower across all delcassertib-treated patients as compared with the placebo group. Interestingly when outcomes were partitioned according to culprit artery patency (pre-PCI TIMI 0/1 vs. pre-PCI TIMI 2/3), the ST-segment outcomes were substantially less impressive in subjects with an open IRA. Since the counter-regulatory role of αPKC may be active in the pre-conditioning process, it is conceivable this may have been operative when pre-PCI coronary patency was established. 14

What patient population is the most appropriate for further studies of reperfusion injury? The low risk, promptly treated STEMI cohort in the current study may not be the most appropriate. Moreover when total ischaemic times are long, there is a commensurate decline in myocardial salvage, and reperfusion injury more often ensues. As shown in Figure 1, cardioprotective strategies commenced later during ischaemia (e.g. at 3–6 h or even later) may be best aligned with the most opportune window to limit reperfusion injury. In our view, future clinical trials investigating novel cardioprotective agents should account for total ischaemic times and pre-reperfusion injury of the culprit vessel so as to optimize cardioprotective opportunities.

Overall, although delcassertib in PROTECTION MI showed limited promise as a cardioprotective agent for reducing reperfusion injury in STEMI, we should not bury alive the potential of PKC isoenzymes or other opportunities to ameliorate reperfusion injury.

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References

Atherosclerotic changes in coronary aneurysms post-Kawasaki disease: in vivo demonstration with near-infrared spectroscopy and intravascular ultrasound

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In a 25-year-old patient treated with covered stents for a giant aneurysm of the LAD post-Kawasaki (arrowhead in Panel A), intravascular ultrasound was used to confirm the size and characteristics of a smaller aneurysm in the mid-RCA (Panels B and C). No treatment was performed as the maximal aneurysm diameter was 5.5 mm with a napkin’s ring of calcium in the mid-segment causing a moderate lumen narrowing with a lumen diameter of 2.2 mm (Panel D). Distal to the aneurysm near infrared spectroscopy showed two quadrants of lipid deposition (maximum lipid core burden index of 341) behind a shell of superficial calcium (Panel E). The patient had no risk factors for CAD (total cholesterol 3.9 with 2.0 mMol/L LDL) nor evidence of wall thickening or calcification neither distal nor proximal to the aneurysmal segment (Panel F) in a pull-back of 12 cm along the entire LAD and RCA. Near infrared spectroscopy has the unique ability to generate a chemogram of the vessel wall components not affected by the presence of calcium and is, for the detection of lipids, a technique much more robust than virtual histology, the only other method used so far to demonstrate in vivo the link between inflammation and early atherosclerosis in Kawasaki disease (Mitani et al., Circulation 2009; 119(21):2829–2836). This case image highlights the role of lipid precipitation in the progression to calcification and wall changes leading to the development of aneurysms and stenoses in Kawasaki disease.

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