Reperfusion Injury: How Can We Reduce It?

Hyun-Jai Cho, MD, PhD

Cardiovascular Center, Department of Internal Medicine, Seoul National University Hospital

Infarct size reduction after acute myocardial infarction (AMI) has been a dream of cardiologists since 1960s. Even though many preclinical studies showed promising results, there is no effect therapy for myocardial salvage, except for prompt revascularization (emergent primary PCI) within 12 hours of symptom onset.

After appropriate revascularization therapy to treat MI, reperfusion itself may paradoxically cause a wide variety of injuries to the myocardium. The net effect of reperfusion is a reduction in infarct size, however, the introduction of blood flow into an ischemic zone generates reactive oxygen species (ROS), calcium ion (Ca2+) influx, and a rapid correction of acidosis, all of which induce the opening of the mitochondrial permeability transition pore (mPTP). Therefore, during reperfusion, a damaged myocardium suffers additional necrotic cell death and increase in infarct size, known as myocardial ischemia-reperfusion (I/R) injury.

Cyclosporine A (CsA) has been known for its protective effect against myocardial I/R injury through the inhibition of mPTP opening. Recently, two large scale trials were reported in the purpose of infarct size reduction and I/R injury prevention. Disappointingly, CIRCUS (Cyclosporine to ImpRove Clinical oUtcome in STEMI patients) trial of 975 patients, which applied CycloMulsion, a new formulation of cyclosporine A, reported no significant difference between the CsA and placebo groups in the primary endpoint, a composite of 1-year all-cause mortality, rehospitalization for heart failure (HF) or HF worsening, and LV adverse remodeling. CYCLE (CYCLosporinE A in reperfused myocardial infarction) trial of 410 patients, which administered Sandimmun, an original drug of cyclosporine A, demonstrated no effect on ST-segment resolution or hs-cTnT, and did not improve clinical outcomes or LV remodeling up to 6 months.

We introduced the novel necrosis inhibitor, NecroX ((tetrahydropyran-4-yl)-[2-phenyl-5-(1,1-dioxothiomorpholin-4-yl)methyl-1H-indol-7-yl]amine; C25H32N4O4S2), is an indole-derivative that has a strong scavenging activity against mitochondrial ROS and we confirmed the powerful inhibitory effect of the necrosis inhibitor on mPTP opening and Ca2+ overload *in vitro* and the therapeutic efficacy using a *in vivo* rat MI/reperfusion model. The cardioprotective effect of the necrosis inhibitor was substantially superior to that of CsA, with nearly twice the area of protected myocardium. In the context of clinical translation, the safety profiles of NecX were favorable in a phase I clinical trial which was completed without any serious adverse events. A phase II/a trial for STEMI patients (NEXsteMI trial) was successfully performed and a phase II/b trial is ongoing now.