Hopes dashed for an agent to prevent reperfusion injury

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The administration of an experimental agent known as TRO40303 to patients who have had a heart attack, with the hope of preventing tissue damage when impaired blood flow is corrected (reperfusion), was disappointingly ineffective according to results of a European study of patients with acute ST-elevation myocardial infarction (STEMI) presented today as a Hot Line the ESC Congress 2014 with simultaneous publication in the *European Heart Journal*.

Calling it "yet another nail in the coffin" of reperfusion injury prevention, Dan Atar MD, PhD, principal investigator of the MITOCARE study and professor of cardiology at the University of Oslo, Norway said "reperfusion injury in STEMI patients remains an enigma that has not been amenable to any therapeutic intervention – despite 30 years of intense research."

Results for TRO40303 are a surprising contrast to promising earlier studies that had generated high hopes for the agent.

"Negative studies rarely lead to phenomenal breakthroughs and monumental change-of-practice, but it is important to be aware that negative studies increase our understanding of disease and of therapeutic options," he said.

The study's finding of lack of benefit of TRO40303, "provides important information on current state-of-the-art STEMI treatment, and may reflect the fact that the high quality of modern care leaves little

room for improvement."

TRO40303 has been shown in animals and laboratory models to block mitochondrial permeability that leads to reperfusion injury.

When blocked vessels that cause a heart attack (infarct) are cleared, allowing reperfusion, cardiac muscle may be injured causing what is known as an infarct expansion. Mitochondrial permeability has been shown to play an important role in this process.

MITOCARE, a 10-center, double-blind study, randomised 163 patients with STEMI to receive an intravenous injection (6mg/kg at 35 mL/min) of either TRO40303 (n=83) or placebo (n=80) within 6 hours of pain onset and prior to reperfusion with primary percutaneous coronary intervention (PCI).

The primary endpoint of the study was size of the infarct, assessed by creatine kinase (CK) and troponin I (TnI) levels during the first three days of the infarction.

Secondary endpoints, measured with gadolinium-enhanced cardiac magnetic resonance (CMR) imaging at 3-5 days post infarction included size of the infarct, the myocardium salvage index (MSI) expressed as the size of the infarct/ myocardium at risk, and left ventricular ejection fraction (LVEF)

Safety outcomes were also assessed from day one through day 30.

For the primary endpoint, the study found no difference between the TRO40303 and placebo groups for the size of the infarct, whether calculated according to CK levels (mean 77558.4 vs. 74455.3 U/L , p=0.98), or Tn1 levels (mean 3377.6 vs. 3084.9 ng/mL, p=0.57).

Infarct size measured with CMR was also not significantly different (21.9 vs 20.0g respectively, or 17% vs 15% of LV mass), and neither was MSI (51% vs. 58% , p=0.1000), or LVEF (46% vs. 48%). Echocardiographic assessment of LVEF at 30 days confirmed these data (mean 51.5% vs. 52.2%).

Unexpectedly, compared to the placebo group, a greater number of patients in the TRO40303 group had a failed primary PCI (12% vs. 6%), meaning the attempt at clearing the blocked vessel was not successful.

"This was most likely due to a play of chance," said Dr. Atar, and likely explains the higher rate of adjudicated serious adverse events (SAEs) such as death, cardiogenic shock, heart failure and ventricular arrhythmias observed in the TRO40303 arm of the trial (n=26 vs. 11).

While this finding could also possibly reflect a deleterious effect of TRO40303, such an effect was not observed in a previous study, and no evidence of clotting problems has been observed with this agent, he explained.

The high standard of care in MITOCARE including a mean door-to-PCI time of 38-minutes, as well as preservation of the left ventricle as documented by the 30-day LVEF "appears to leave limited room for further infarct size reduction," Dr. Atar concluded. "In fact, one might question the entire concept of reperfusion injury in humans: what we predominantly see in today's clinical practice is 'reperfusion benefit', not injury."

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