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ACUTE CORONARY SYNDROMES

Promising data for losmapimod in NSTEMI

A novel p38 mitogen-activated protein kinase (MAPK) inhibitor, losmapimod, has been shown to be well tolerated and to reduce levels of inflammatory biomarkers in patients with non-ST-segment elevation myocardial infarction (NSTEMI). These findings from the phase II SOLSTICE trial are reported in *The Lancet*.

"Despite guideline-recommended acute and secondary prevention therapies, ... death, myocardial infarction, or stroke occur at a rate of 4–5% per year after an acute coronary syndrome (ACS)," explains lead investigator L. Kristin Newby. p38 MAPK is induced by stress in macrophages and myocardial and endothelial cells. In preclinical studies, inhibition of this enzyme has been shown to reduce infarct size and limit postinfarction remodelling. Losmapimod competitively inhibits both the α and β forms of p38 MAPK and, therefore, "seemed a promising compound to explore in ACS, to begin to address its potential utility in fulfilling an unmet clinical need," says Professor Newby.

In the SOLSTICE trial, 535 patients aged ≥45 years with NSTEMI were randomly assigned to receive one of two loading doses of losmapimod (7.5 mg or 15.0 mg) followed by 7.5 mg of the drug twice daily, or to receive placebo, for 12 weeks. A subgroup of patients ($n = 93$) who had a creatine kinase-MB level twice the upper limit of normal were enrolled in an MRI substudy.

The median duration of treatment was 84 days; however, 32–40% of patients in each group did not complete the full 12-week regimen. The rate of adverse events (elevations in alanine aminotransferase concentrations and cardiac events) did not differ between the two groups. The primary efficacy end points were C-reactive protein (high-sensitivity assay; hs-CRP) concentration at 12 weeks, and troponin I concentration at 72 h, as indicators of inflammation and infarct size, respectively. Although hs-CRP levels were lower in the losmapimod groups than the placebo group (64.1 mmol/l vs 110.8 mmol/l; $P = 0.0009$) at 72 h, the difference was no longer significant at 12 weeks. The troponin I concentration did not differ between the groups. The level of B-type natriuretic peptide (BNP) was also measured to assess cardiac remodelling and ventricular strain. Although no early differences in BNP levels between the groups were recorded, the level was significantly lower in the losmapimod groups than the placebo group at 12 weeks (37.2 ng/l vs 49.4 ng/l; $P = 0.0359$). In the MRI substudy, infarct size was numerically smaller and left ventricular ejection fraction significantly higher in losmapimod-treated patients compared with placebo. "The results of the SOLSTICE trial support further randomized clinical trials of losmapimod ... as a potential novel treatment for patients with ACS," concludes Professor Newby.

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Original article Newby, L. K. *et al*. Losmapimod, a novel p38 mitogen-activated protein kinase inhibitor, in non-ST-segment elevation myocardial infarction: a randomised phase 2 trial. *Lancet* doi:10.1016/s0140-6736(14)60417-7