Editorial

Losmapimod does not reduce cardiovascular events in patients with acute myocardial infarction

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The recently published results of LATITUDE-TIMI 60 (*Effect of Losmapimod on Cardiovascular Outcomes in Patients Hospitalized With Acute Myocardial Infarction: A Randomized Clinical Trial*) investigated the effect of losmapimod, a p38 mitogen-activated protein kinase (MAPK) inhibitor, on major cardiovascular events in patients with acute myocardial infarction (MI) (1). The p38 MAPK is activated in the setting of myocardial ischemia, hypertension, and heart failure, resulting in amplification of cytokines [cyclooxygenase 2, interleukins 1 and 6 (IL1, IL6), metalloproteinases, and tumor necrosis factor-α (TNF-α)] (2). Future vascular events correlate with elevated levels of IL-6 and TNF-α, which lead to downstream production of C-reactive protein (CRP) in the liver (3,4).

Small scale preliminary trials have shown promise for targeted anti-inflammatory agents, such as losmapimod, to reduce cardiovascular events. A recent meta-analysis of multiple inflammatory cytokines showed that two were significant and independent risk factors for future vascular events: TNF-α [hazard ratio (HR) 1.32 per 1 SD higher baseline level] and high-sensitivity CRP (HR 1.69 per 1 SD higher baseline level) (5). Statin therapy has been shown to provide clinical benefit in those with the highest levels of inflammation as measured by CRP in the JUPITER (Justification for the use of Statins in Prevention: an intervention Trial Evaluating Rosuvastatin) study (6). Similarly, reducing serum low-density lipoprotein cholesterol to <70 mg/dL and hs-CRP to <1 mg/L with aggressive statin therapy had the greatest relative risk reduction in the PROVE-IT TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22) trial (7).

The LATITUDE-TIMI 60 trial attempts to identify if losmapimod can mitigate the maladaptive component of the inflammatory response in the setting of acute coronary syndrome, a complex and redundant cascade which involves both the innate and acquired immune system (8). A small clinical trial prompting the initiation of LATITUDE-TIMI 60 demonstrated that the levels of CRP and IL6 were reduced with administration of losmapimod prior to percutaneous coronary intervention (PCI) (9). Follow-up cardiac magnetic resonance imaging demonstrated improved left ventricular function, as well as left ventricular remodeling (smaller left ventricular dimensions at end -diastole and at end -systole), in treated patients (9). Losmapimod was also shown to decrease uptake of 15F-fluorodeoxyglucose on positron emission tomography-computed tomography and improvement in nitric oxide-mediated vasodilation in patients with hypercholesterolemia (10,11).

LATITUDE-TIMI 60 was a two-part trial. An initial cohort (A) of 3,503 patients would be randomized to the treatment drug or placebo in a double-blinded fashion, and if safety and efficacy were demonstrated, a second cohort (B) of approximately 22,000 patients would then be randomized (12). This was an international study involving 322 sites in 34 countries. Eligible patients were those presenting with non-ST segment elevation myocardial infarction (NSTEMI) within 24 hours of symptoms, or ST-segment elevation myocardial infarction (STEMI) within 12 hours of onset (12). The treatment arm received 7.5 mg of losmapimod orally twice daily, started at the time of study enrollment (prior to PCI) and continued for 12 weeks. A composite endpoint of cardiovascular death, MI, or severe recurrent ischemia requiring urgent revascularization at 12 weeks after

randomization was the primary endpoint.

The treatment period was 12 weeks, and follow-up was performed for an additional 12 weeks. The final analysis for the leading cohort A for the primary outcome demonstrated a neutral result, with 7.0% of the placebo group and 8.1% of the treatment group experiencing events (HR, 1.16; 95% CI, 0.91–1.47; P=0.24). This failure to meet the primary endpoint at 12-week and at 24-week follow-up occurred despite losmapimod reducing serum levels of pre-specified inflammatory biomarkers. Levels of CRP were lower at both 4 weeks (ratio of means 0.76; 95% CI, 0.62–0.91; P=0.004) and 12 weeks (ratio of means 0.73; 95% CI, 0.61–0.87; P<0.001) in the treatment arm. Similarly, NT-pro-BNP (N-terminal pro b-type natriuretic peptide) levels were significantly reduced at these time points (P<0.001 for both) in those receiving losmapimod. However, these reductions did not result in a clinical benefit in this population presenting with acute coronary syndromes. Secondary analysis demonstrated a signal that losmapimod may have some benefit in STEMI patients (HR, 0.84; 95% CI, 0.51–1.40), potentially due to a more robust inflammatory response in these patients. This study was not powered to draw conclusions stratified by presenting myocardial infarction type.

Despite the promising preliminary data on losmapimod, the LATITUDE-TIMI 60 study does not satisfy the unmet need of targeted treatment for the maladaptive effects of the inflammatory response in acute coronary syndromes NSTEMI and STEMI. The outcomes of small studies were indeed suggestive of potential benefit of losmapimod. However, these data again highlight the limitations of small exploratory trials that use surrogate endpoints for cardiovascular outcomes. The TIMI group should be commended for their multistage design, which provided valuable data to halt what would have been a costly and time-intensive cohort B large-scale trial. This approach may be useful for future trials as we search for agents that will likely provide small additive benefits in the era of primary PCI and efficacious optimal medical therapy.

Despite these neutral results, the interest in targeted anti-inflammatory therapy in cardiovascular disease will remain, with multiple agents currently being investigated in clinical trials. Agents in trial include those that target IL-6 dependent pathways, such as canakinumab, methotrexate, anakinra, tocilizumab, and etanercept, as well as non-IL-6 dependent pathways, such as varespladib, darapladib, inclacumib, and succinobucol. In addition to the disappointing results of LATITUDE TIMI-60, two trials investigating darapladib, an inhibitor of lipoprotein-associated phospholipase A (2), were also negative (13,14). Both the STABILITY (the Stabilization of Atherosclerotic Plaque by Initiation of Darapladib Therapy) and SOLID-TIMI 52 (Stabilization of Plaques using Darapladib-Thrombolysis in Myocardial Infarction 52) trials failed to meet the primary composite endpoint of improving cardiovascular death, MI, or stroke (13,14). With the disappointing results of LATITUDE TIMI-60, STABILITY, and SOLID-TIMI 52, it remains to be seen if a targeted anti-inflammatory agent can have a meaningful impact on cardiovascular morbidity and mortality.

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Footnote

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