

Do p38 mitogen-activated protein kinase inhibitors have a future for the treatment of cardiovascular disease?

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Acute coronary syndrome (ACS) is associated with a significant risk of cardiovascular death, and recurrent ischemic events including myocardial infarction (MI). Therapeutic interventions for the management of ACS utilize a thrombolytic approach, although this is associated with an increased risk of bleeding. The incidence of ischemic events in ACS usually results from disruption of atherosclerotic lesions (1). Atherosclerosis is a degenerative disease of the coronary arteries where excessive circulating lipoprotein leads to plaque formation through intimal inflammation, necrosis, fibrosis, and calcification. After years and decades of gradual progression, these plaques may cause coronary thrombosis presenting as ACS. Vulnerable plaques are associated with markers of systemic inflammation, such as C-reactive protein (CRP), serum amyloid A and interleukin 6 (IL-6), all predictive of subsequent adverse ischemic events (2). Furthermore, these biomarkers are strongly implicated in the pathogenesis of ACS (3), hence a therapeutic approach utilized to reduce the inflammatory response associated with ACS may provide novel treatment options.

p38 mitogen-activated protein kinase (p38 MAPK) is an inflammatory signalling cascade that leads to activation of cytokine production during ACS. Since the late 1990's it was discovered that p38 MAPK, a stress activated protein kinase, played a crucial role in inflammation and cardiovascular disease (4-6). Activation of p38 MAPK occurs in response to stress mediators including hypertension, oxidized low density lipoprotein cholesterol, ischemia, and vascular injury (7). In animal studies it has been demonstrated that early post-MI

p38 MAPK activity is increased, whereas activation subsequently tends to be cyclical, most likely corresponding to triggers such as remodeling or heart failure (8). In patients with end-stage heart failure and ischaemic heart disease, increased p38 MAPK activity has been associated with inflammatory, fibrotic, hypertrophic, and apoptotic processes (9), important mediators of cardiac remodeling.

The beneficial effects derived from inhibiting p38 MAPK activity have been demonstrated in cell culture and animal studies, in a number of cardiovascular diseases, including atherosclerosis, stroke, MI and chronic heart failure (10). Improved cardiac function post-MI has been demonstrated with small molecule inhibitors and is accompanied by reduction in hypertrophy, interstitial fibrosis, apoptosis, macrophage infiltration, plasma cytokine levels and superoxide production (11-13). Furthermore, these changes occur independently of changes in blood pressure, suggesting that small molecule p38 MAPK inhibitors could be a useful adjunct to neurohormonal blockade especially in heart failure patients with borderline hypotension.

The use of p38 MAPK inhibitors in man has previously been limited to patients with rheumatoid arthritis (RA), although the disease modifying benefits of the early generation drugs were offset by adverse events including elevations in liver enzyme activity, increased incidence of infections and skin rashes. However with discovery of the structural features of the enzyme, a resurgence in the development more specific p38 MAPK inhibitors has emerged (14), with trials for indications such as RA,

chronic pulmonary disease, malignancies, neuropathic pain, depression, glomerulosclerosis as well as atherosclerosis and ACS (15). Generally the results have been encouraging, showing positive outcomes, with apparently fewer adverse events (15).

Recently, the p38 MAPK inhibitor losmapimod was evaluated for its effect on inflammation and infarct size in the SOLSTICE study (16). The results from this randomised phase 2 multi-centre trial demonstrated beneficial effects of losmapimod (7.5 mg b.d.) in reducing circulating inflammatory markers, namely high sensitivity C-reactive protein (hs-CRP) and IL-6 within 72 hours of treatment initiation. Furthermore concentrations of plasma B-type natriuretic peptide (BNP), a marker of wall stress, were reduced at the end of the 12 week treatment period in losmapimod treated-patients, suggesting a potential beneficial effect on cardiac remodeling. Supportive evidence from the magnetic resonance imaging (MRI) sub-study reported improved left ventricular ejection fraction with increased end systolic and end diastolic volumes at the conclusion of the treatment period (16). Although the trial was not powered to determine clinical outcomes, a non-significant trend toward a lower incidence of major adverse cardiovascular events (MACE) was observed in losmapimod treated subjects compared with placebo.

Following on from the promising result of SOLSTICE, LATITUDE-TIMI 60, a phase 3 multicentre centre trial was designed to assess the incidence of MACE in subjects presenting with ACS treated with losmapimod (7.5 mg, bid, N=1,738) and compared with placebo (N=1,765), when added to standard of care therapy. The results of this trial have recently been published in *The Journal of the American Medical Association* (17) and discussed here. The primary objective was to evaluate the efficacy of losmapimod on the time to first occurrence of a MACE defined as cardiovascular death, MI or severe recurrent ischemia requiring urgent coronary artery revascularization during the 12 weeks of therapy. The principle secondary endpoint was to evaluate the efficacy on the time to first occurrence of adjudicated cardiovascular death or MI. Safety objectives recorded the incidence of adverse events. Patients with non-ST-segment elevation MI (NSTEMI) and ST-segment elevation MI (STEMI) were randomized in a placebo-controlled, double-blind, parallel group trial. The trial was designed in 2 stages, part A enrolled 3,503 patients to provide an initial assessment of safety and exploratory efficacy. A larger efficacy trial was planned for part B (approximately 22,000 patients) should a signal be identified

from the initial study. This multistage approach allows commencement of the phase III trial with an interim review of the patient safety profile and provides preliminary insight into drug efficacy before expanding into the larger cohort.

The overall results of losmapimod in part A were neutral when compared with placebo. The primary end point of MACE was unchanged between both groups (HR 1.16; 95% CI, 0.91–1.47; P=0.24). The principle secondary endpoint, composite of cardiovascular death or MI was not significant (HR 1.13; 95% CI, 0.88–1.47). Other secondary end points did not show a difference between the groups. Despite this neutral result, sub-group analyses of the primary end point indicate losmapimod may be potentially beneficial in STEMI patients (HR 0.84; 95% CI, 0.51–1.40), however this result was in a small subgroup of patients (N=432) and would need to be validated in a separate appropriately powered trial before confirming this effect.

The effect of losmapimod on biomarkers reduced levels of acute inflammation at 48 hours (P<0.001) indicated by the biomarker hs-CRP, and at the 4 week (ratio of the mean for losmapimod compared with placebo, 0.76; 95% CI, 0.62–0.91; P=0.004) and 12 week time points (ratio of the mean for losmapimod compared with placebo, 0.73; 95% CI, 0.61–0.87; P<0.001). Similarly N-terminal pro-BNP plasma concentration was reduced at 4 and 12 weeks (P<0.001). No significant difference was observed for serious adverse events between losmapimod (16.0%) and placebo (14.2%). Although the incidence level was low, the liver enzyme alanine aminotransferase (ALT) was consistently higher in the losmapimod group compared with placebo, with a doubling in the number patients with ALT levels more than five times the upper limit of normal (1.0% vs. 0.5%).

One factor that may have proved important to the outcome of this trial is the optimal timing for the commencement of therapy. Subjects were administered drug as early as possible after hospitalization and prior to coronary vascularization or reperfusion. The median time from symptom onset to randomization for STEMI patients was 3.8 hours (IQR: 2.5–6.6 hours) and 20.3 hours for NSTEMI patients (IQR: 13.0–27.7 hours). We can only hypothesize that earlier treatment may have resulted in improved clinical outcomes. Other factors may include dose, dosing interval and duration. Perhaps higher and/or frequent doses may have resulted in a greater anti-inflammatory effect, or additionally inhibited other pathways, i.e., anti-fibrotic, anti-apoptotic which may have provided different outcomes.

Losmapimod reduced inflammation and levels of wall stress, indicated by lower hs-CRP and N-terminal pro-BNP levels respectively, however unlike SOLSTICE, there was no supportive evidence in the form of an MRI or echocardiography to gauge an improvement in cardiac remodeling. Furthermore, this study was only of 12 weeks duration, conceivably a longer course of treatment may have yielded better clinical outcomes in terms of primary and secondary endpoints besides improving cardiac remodeling effects.

To determine the clinical efficacy of losmapimod and other p38 MAPK inhibitors in ACS, STEMI patients may provide a more pertinent cohort. However to overcome the limitations of the current study, a prolonged and more investigative trial needs to be initiated with a larger sample size. This may also include higher doses, assessment of cardiac function, measurement of wall stress and inflammatory markers. In addition, the timing for the commencement of therapy may need to be optimized. Furthermore, safety monitoring of this drug needs to be ensured in future trials to minimize adverse events.

Evaluation of p38 MAPK inhibition in cardiovascular disease associated with inflammation and cardiac remodeling has yielded beneficial results from animal studies, however translation to the clinic has proved more difficult. Nevertheless, these drugs may play an important role in the prevention of cardiovascular disease progression and further trials are warranted.

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Footnote

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