ACUTE CORONARY SYNDROMES

A new factor Xa inhibitor for acute coronary syndrome

A phase II clinical trial has shown that otamixaban, a selective inhibitor of factor Xa, reduces the risk of death or other adverse cardiovascular outcomes in patients with acute coronary syndromes. Otamixaban could prove to be more effective than currently available anticoagulant therapies.

Acute coronary syndromes often occur as a consequence of thrombus formation following atherosclerotic plaque rupture, which results in bleeding and stimulation of the clotting cascade. Anticoagulant therapy has long been part of the standard treatment regimen aimed at reducing adverse outcomes for patients with acute coronary syndromes undergoing percutaneous coronary intervention. Although beneficial, anticoagulant agents that are currently available are far from ideal as they lack selectivity and show variable effects, requiring frequent monitoring. Efforts to improve the efficacy and safety of anticoagulant therapy have focused on factor Xa as a potential therapeutic target, as it directly stimulates thrombin production, which leads to the formation of the fibrin clot, and also promotes platelet aggregation. Otamixaban is a new, selective and direct inhibitor of factor Xa that is currently being assessed for efficacy and safety in the SEPIA-ACS1 TIMI 42 trial, a randomized, double-blind, active-controlled phase II study, which was designed to determine the optimal dose range.

The trial was conducted at 196 sites in 36 countries and included 3,241 patients with non-ST-segment elevation acute coronary syndromes. Patients were randomly assigned to receive one of five intravenous doses of otamixaban (an initial bolus dose of 0.08 mg/kg, followed by infusions of 0.035, 0.07, 0.105, 0.14 or 0.175 mg/kg/h) or the standard combination therapy of heparin (initial bolus dose of 60 IU/kg followed by an infusion of 12 IU/kg/h) and eptifibatide (initial bolus dose of 180 μg/kg followed by an infusion of 1–2 μg/kg/min). Efficacy was assessed on the basis of a composite end point of all-cause death, myocardial infarction, ischemic complications requiring revascularization or the need for alternative anticoagulant treatment; safety was assessed on the basis of bleeding.

Soon after commencement of the trial, the lowest dose of otamixaban was found to be ineffective and was discontinued at the recommendation of the Data Safety Monitoring Committee. The four remaining groups of otamixaban-treated patients were able to continue treatment for the duration of the study. Analysis of the results showed a 40% decrease in the rate of the primary efficacy end point (death, myocardial infarction or ischemic complications) in patients who received the intermediate doses of 0.105 or 0.140 mg/kg/h, compared with those receiving standard therapy. The beneficial effects of otamixaban were maintained for at least 6 months. A gradient of increasing bleeding with increasing doses of otamixaban was observed; however, the rates of bleeding at 0.105 or 0.140 mg/kg/h of otaxamixaban were similar to those observed in the patients treated with standard heparin and eptifibatide combination therapy.

"The data show that intermediate doses of otamixaban may offer a substantial reduction in major coronary complications in patients presenting with an acute coronary syndrome, with bleeding rates comparable to current therapy," says Marc Sabatine, principal investigator of the study, adding, "these findings will need to be tested in a large phase III trial to establish the definitive role of otamixaban in the treatment of acute coronary syndromes."

Sharmini Rajanayagam

Original article Sabatine, M. S. *et al.* Otamixaban for the treatment of patients with non-ST-elevation acute coronary syndromes (SEPIA-ACS1 TIMI 42): a randomised, double-blind, active-controlled phase 2 trial. *Lancet* **374**, 787–795 (2009)