MedicalXpress

Safety and tolerability of the oral Xa inhibitor darexaban for secondary prevention after acute coronary syndromes

August 30 2011

A phase II dose-finding study has found that the new oral Factor Xa inhibitor darexaban was associated with a two to four-fold increase in bleeding when added to dual antiplatelet therapy in patients following an acute coronary syndrome.

Professor Gabriel Steg from the Hôpital Bichat in Paris, presenting results from the RUBY-1 trial in a Hot Line session of the ESC Congress today, said the study produced no other safety concerns and that "establishing the role of low-dose darexaban in preventing major cardiac events after ACS now requires a large phase III trial".

The recurrence of ischaemic events after ACS remains high, with rates of up to 9.1% recorded at six months. Long-term antithrombotic therapy with vitamin K antagonists (such as warfarin) has proved beneficial in ACS patients, although, said Steg, "fraught with problems related to their narrow therapeutic margin, need for monitoring, frequent interactions with drugs and food, and delay in onset and offset of action".

New more selective oral anticoagulants - such as direct thrombin and factor Xa inhibitors - have several advantages over vitamin K antagonists. Darexaban, a new direct oral inhibitor of Factor Xa, has been shown to have predictable pharmacokinetics, minimal interaction with food and no drug–drug interactions. Its potential benefit has already been indicated in venous thromboembolic disease and is now being

explored in the prevention of stroke in subjects with non-valvular atrial fibrillation. The RUBY-1 trial reported today aimed to explore the safety, tolerability and optimal dosing regimen in the secondary prevention of ischaemic vascular events in subjects with recent ACS.

RUBY-1 was a multicentre, double-blind, randomised, parallel-group study in 1279 patients with recent high-risk non-ST-segment elevation and ST-segment elevation ACS. after discontinuation of parenteral antithrombotic therapy, they received one of six darexaban regimens: 5 mg twice daily (bid), 10 mg once daily (qd), 15 mg bid, 30 mg qd, 30 mg bid or 60 mg qd, or placebo, in addition to dual antiplatelet treatment (aspirin and clopidogrel) for 24 weeks.

The primary outcome of the study (major or clinically relevant non-major bleeding events) was numerically higher in all darexaban arms than in the placebo group (pooled HR 2.275, 95% CI 1.13-4.60, p=0.022). Using placebo as reference (with a bleeding rate of 3.1%), there was a dose-response relationship (p=0.009) for increased bleeding rates with increasing darexaban dose (6.2, 6.5 and 9.3% for 10, 30 and 60 mg daily, respectively). This increase was statistically significant for the 30 mg bid dose (p=0.002).

There was no decrease in rates of efficacy outcome (a composite of death, stroke, myocardial infarction, systemic thromboembolic events and severe recurrent ischaemia) with darexaban versus placebo, but the study was underpowered to evaluate efficacy. There were no other significant drug-related safety concerns associated with darexaban.

Provided by European Society of Cardiology