New oral anticoagulant shows promise in post-myocardial infarction patients

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Asundexian 50 mg administered to post-myocardial infarction patients inhibits factor XIa by more than 90% with no significant increase in bleeding, according to late breaking research presented in a Hot Line

session on 28 August at ESC Congress 2022.

Professor John Alexander of Duke University School of Medicine, Durham, U.S. said, "Asundexian, and other factor XIa inhibitors, may be promising new therapies to potentially reduce ischemic events without significantly increasing bleeding for patients following a myocardial infarction and in other clinical settings where vascular thrombosis or thromboembolism play a role."

Following an acute myocardial infarction, patients are at risk for recurrent ischemic events, including cardiovascular death, myocardial infarction, stroke, and stent thrombosis. Antiplatelet therapy with aspirin and a P2Y12 inhibitor are effective at reducing these events but increase the risk of bleeding. Oral anticoagulation with warfarin or the factor Xa inhibitor rivaroxaban are also effective at reducing recurrent ischemic events, however, they are generally not used because of the increased risk of bleeding with oral anticoagulation on top of antiplatelet therapy.

Asundexian is a new oral anticoagulant that inhibits factor XIa. By working upstream in the contact activation pathway of coagulation, factor XIa inhibitors may prevent pathologic thrombosis, and thus recurrent ischemic events, but not adversely impact haemostasis, and thus not cause bleeding.

The phase 2 PACIFIC-AMI trial assessed the pharmacodynamics, efficacy and safety of three doses of asundexian (10 mg daily, 20 mg daily, and 50 mg daily) compared with placebo in patients treated with dual antiplatelet therapy (aspirin and a P2Y12 inhibitor) following an acute myocardial infarction. The trial was conducted at 157 sites in 14 countries.

Within five days of the myocardial infarction, 1,601 patients aged 45 years and older were randomly allocated to asundexian 10 mg, 20 mg, 50

mg or placebo, with approximately 400 patients in each group. The median age was 68 years and 23% were women. Some 51% had an ST-segment elevation myocardial infarction (STEMI) and 49% had a non-STEMI. Almost all patients (99%) underwent percutaneous coronary intervention as treatment for their myocardial infarction. More patients were treated with prasugrel or ticagrelor (80%) than clopidogrel (20%) as their P2Y12 inhibitor.

Patients were treated for between 6 and 12 months. The median follow up, starting from the first dose, was 368 days. The primary efficacy outcome was a composite of cardiovascular death, myocardial infarction, stroke, or stent thrombosis and the main safety outcome was a composite of Bleeding Academic Research Consortium (BARC) 2, 3, or 5 bleeding. All clinical events were adjudicated by a centralized clinical events classification process.

Asundexian produced a dose related reduction in factor XIa inhibition, with the 50 mg dose resulting in more than 90% inhibition of factor XIa. The primary outcome occurred in 27 (6.8%), 24 (6.0%), and 22 (5.5%) patients in the 10 mg, 20 mg, and 50 mg asundexian groups, respectively, and 22 (5.5%) patients in the placebo group. The main safety outcome occurred in 30 (7.6%), 32 (8.1%), and 42 (10.5%) patients in the asundexian groups, respectively, and 36 (9.0%) patients in the placebo group.

Professor Alexander said, "In this phase 2 study, there was no significant observed increase in bleeding with asundexian at any dose or compared with placebo. There was also no significant reduction in ischemic events with asundexian, although the trial was not designed to be large enough to detect a clinically meaningful reduction in these events."

He concluded, "The trial suggests that asundexian, at a dose of 50 mg daily, will inhibit factor XIa and potentially without a large increase in

bleeding. Plans are underway for larger phase 3 clinical trials to test asundexian in patients with acute myocardial infarction and other conditions where vascular thrombosis or thromboembolism play a role."

Provided by European Society of Cardiology

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