Investigational Oral Antithrombotic Not Superior to Aspirin in Preventing a Second Stroke

Researchers from Paris reported that the primary endpoint (composite rate of fatal or nonfatal ischemic stroke, fatal or nonfatal myocardial infarction [MI], or other nonhaemorrhagic vascular death) showed no difference between terutroban and aspirin (11% versus 11%; HR 1.02, 95% CI 0.94-1.12). There was also no significant difference in efficacy for the secondary or tertiary endpoints. The researchers' conclusion was based on results from the PERFORM study, which was ended prematurely.

The researchers thus concluded that the investigational oral antithrombotic terutroban was not superior to aspirin in preventing a second stroke. Terutroban is a selective thromboxane-prostaglandin receptor antagonist to receptors in platelets and in the vessel wall. Previous preclinical and human research had suggested that terutroban, besides having similar anticlotting effects as aspirin, had potential vascular effects, such as reducing plaque.

The PERFORM *(P*revention of cerebrovascular and cardiovascular *E*vents of ischemic origin with te*R*utroban in patients with a history o*F* ischaemic str*O*ke or t*R*ansient ischae*M*ic attack*)* study, a randomised, double blind, parallel group trial in 802 centres in 46 countries, was thus initiated. Funding for the study was provided by the drug manufacturer. All the researchers had financial relationships with the manufacturer, and two were employees. Because there was no evidence of benefit, the trial was stopped early and the manufacturer of terutroban stopped its development.

There were 19,120 participants in the study, all aged 55 years or older, with a mean age of 67.2 years. 63% were men, and 84% were white. All participants had an ischaemic stroke within the preceding two months, or a transient ischaemic attack (TIA) within the preceding eight days. There were 9,562 randomised patients in the terutroban group, receiving 30 mg a day. There were 9,558 in the aspirin group, receiving 100 mg a day.

There were 2,153 events that fulfilled the primary composite endpoint (92% of the planned target number). Of these, 1,533 were fatal or nonfatal ischaemic strokes (777 in the terutroban group, 756 in the aspirin group); 263 fatal or nonfatal MIs (145 terutroban versus 118 aspirin), and 357 other vascular deaths (169 terutroban versus 188 aspirin). There were no differences related to age, sex, qualifying events, a history of diabetes/coronary artery disease/hypertension, or the use of statins/ACE inhibitors at baseline.

For safety endpoints, there were no significant differences for terutroban compared to aspirin, except for a slight increase in minor bleeding for terutroban compared to aspirin (12% versus 11%; HR 1.11, 95% CI 1.02-1.21). The authors of the PERFORM study concluded that the trial did not meet the "predefined criteria for non-inferiority", and showed similar rates of the primary endpoint with terutroban and aspirin, without safety advantages for terutroban. Based on efficacy, tolerance, and cost, they said that aspirin remains the gold standard antiplatelet drug for prevention of secondary stroke.

17% of patients experienced inadequate control of blood pressure in both arms as the main adverse event, followed by hypercholesterolemia (8% terutroban versus 7% aspirin), and depression (7% terutroban versus 8% aspirin). The researchers also noted that there was no difference between groups in mean blood pressure, heart rate, or laboratory parameters throughout the duration of the study although data for this was not included in the paper.

The main study limitations were the small number of patients randomised acutely after TIA or stroke, the small number of patients followed-up to or more than three years, and the inability to extrapolate data for patients less than 55 years old.

An accompanying commentary postulated that potential explanations for why terutroban did not perform to expectations were related to its varied mechanisms of action. They suggested that 30 mg of terutroban might not be the optimal dose, but even if higher doses were used, any benefit at reducing ischaemic events might be offset by more haemorrhagic episodes. The authors of the commentary said that they while they welcomed studies of novel antiplatelet drugs, they thought that with improving background risk factor control, new antiplatelet agents might not outperform aspirin in efficacy and effectiveness, in view of aspirin's cheapness, broad familiarity, acceptable side effect profile, and single-day dosing. SMA

Sources

1. Bousser M, et al. Terutroban versus aspirin in patients with cerebral ischaemic events (PERFORM): A randomised, double-blind, parallel-group trial. Lancet 2011; DOI: 10.1016/S0140- 6736(11)60600-4.

2. Lee M, et al. Vascular events after stroke: terutroban fails to PERFORM. Lancet 2011; DOI: 10.1016/S0140- 6736(11)60708-3.