Encouraging Results From New Platelet Inhibitor

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MUNICH — A new antiplatelet drug showed promise as an alternative to today's standard agent, clopidogrel, in a phase II study with about 900 patients.

The new agent, prasugrel, showed comparable safety and efficacy, compared with clopidogrel (Plavix), during 30 days of treatment following percutaneous coronary intervention with coronary stenting. A phase III study with about 13,000 patients is launching this fall to test the two drugs in a definitive match-up in the same clinical setting, Elliot M. Antman, M.D., said at the annual congress of the European Society of Cardiology.

Prasugrel, like clopidogrel, is a thiopyridine drug that interferes with platelet aggregation by blocking the adenosine diphosphate receptor on platelets. But prasugrel may avoid the problem of "clopidogrel resistance" that's seen in as many as 30% of patients who are unable to get a full antiplatelet benefit from clopidogrel, said Dr. Antman, director of the cardiac unit at Brigham and Women's Hospital in Boston.

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Both clopidogrel and prasugrel are prodrugs that must be metabolized to an active form. Clopidogrel is converted to its active form almost exclusively in the liver, one reason why some patients are unable to respond to the drug. "A possible advantage of prasugrel is that it undergoes partial formation of the active metabolite in the intestine and blood," said Dr. Antman, who is also a professor of medicine at Harvard University in Boston. In addition, results from animal studies showed that prasugrel may be more potent than clopidogrel and may also have a more rapid onset of action.

The phase II study enrolled 904 patients at 80 centers in the United States and Canada. The patients had coronary disease, were scheduled for angiography, and were likely to also undergo percutaneous coronary intervention with coronary stenting during 2003. They were randomized to treatment with clopidogrel or one of three prasugrel regimens: low, with a loading dose of 40 mg and a maintenance dosage of 7.5 mg/day; intermediate, with a loading dose of 60 mg and a maintenance dosage of 10 mg/day; and high, with a loading dose of 60 mg and a maintenance dosage of 15 mg/day. Patients in the clopidogrel arm received a standard regimen with a loading dose of 300 mg and a maintenance dosage of 75 mg/day. All patients were also treated with 325 mg/day of aspirin, and patients were stratified so that each randomization group in the study had similar numbers of patients who also received intravenous treatment with a glycoprotein IIb/IIIa inhibitor.

The study's primary end point was the incidence of significant bleeding, not associated with coronary bypass grafting, during 30 days of treatment.

The incidence of significant bleeding was 1.2% among the 254 patients in the clopidogrel group and 1.7% among all 650 patients who received prasugrel, a difference that was not statistically significant. There was also no significant difference in the bleeding rate between the three prasugrel regimens, he reported.

A secondary end point of the study was the incidence of major adverse coronary events—death, myocardial infarction, stroke, target vessel thrombosis, or severe recurrent ischemia—during the 30 days of treatment, although the study did not include enough patients to make a definitive comparison for this measure. The rate of major adverse events was 9.4% in the clopidogrel group and 7.2% in the prasugrel group, a difference that was not statistically significant, Dr. Antman said.

The only measured outcome that showed a significant difference was in the rate of target vessel thrombosis, a measure of either the need for target vessel revascularization or documented total occlusion of the originally stented coronary artery. This rate was 2.4% in the clopidogrel group and 0.6% in the prasugrel group.

The prasugrel clinical studies are sponsored by Eli Lilly and Sankyo, which are collaborating in the drug's development. ■