Novel Anticoagulant Aids Non-STEMI ACS

BY MARY ANN MOON

Otamixaban, an intravenous anticoagulant, compared well with standard anticoagulant therapy in treating high-risk, non–ST-segment elevation acute coronary syndromes in a phase II study.

Otamixaban was associated with a 40% decrease in the composite outcome of all-cause mortality, myocardial infarction, severe recurrent ischemia requiring urgent revascularization, and "bailout" use of a glycoprotein IIb/IIIa inhibitor for recurrent ischemia or a thrombotic complication during percutaneous coronary intervention. There was no accompanying increase in bleeding events with the drug up to 7 days, study investigators reported.

Moreover, otamixaban has an almost immediate onset of action plus a 30-minute half-life. This allows rapid on-off anticoagulation, "a desirable feature in the setting of invasive management of an acute coronary syndrome," wrote Dr. Marc S. Sabatine of Brigham and Women's Hospital, Boston, and his associates in this trial by the TIMI (Thrombolysis in Myocardial Infarction) Study Group.

Dr. Sabatine presented the results simultaneously with the publication at the annual congress of the European Society of Cardiology in Barcelona.

Otamixaban is a direct, selective inhibitor of factor Xa, "a key component of the prothrombinase complex that drives… the coagulation cascade" in acute coronary syndrome (ACS). Unlike unfractionated heparin, which has been the cornerstone of anticoagulant therapy for acute ACS, otamixaban doesn't cause thrombocytopenia and has predictable pharmacodynamic activity, so it doesn't require anticoagulation monitoring.

In a preliminary, dose-ranging study of 3,241 patients with acute ACS treated at 196 medical centers in 36 countries, study participants were randomly assigned to receive one of five doses of intravenous otamixaban or standard (control) anticoagulation therapy with unfractionated heparin plus eptifibatide. The study was funded by Sanofi-Aventis, the maker of otamixaban.

The two low doses of otamixaban appeared to provide inadequate anticoagulation, as patients who received these doses were at twice the risk as were those who received standard therapy for requiring a bailout glycoprotein IIb/IIIa inhibitor or for developing a thrombotic complication during PCI.

Conversely, the highest dose of otamixaban caused significantly more major or minor bleeding complications than did standard therapy.

The two intermediate doses of otamixaban, however, were associated with a 40% reduction in death, recurrent MI, or additional ischemic complications, compared with standard anticoagulation therapy. At these doses (0.105 and 0.140 mg/kg per hour), bleeding complications were similar between the drug and standard anticoagulation therapy (Lancet 2009 Aug. 30 [doi:10.1016/S0140-6736(09)61454-9]).

Otamixaban has a quick onset of action plus a 30-minute half-life, allowing for rapid on-off anticoagulation.

DR. SABATINE

Otamixaban offers another advantage over heparin plus eptifibatide: With less than 25% excretion through the kidneys, it requires no dose adjustments in patients who have renal impairment, the investigators wrote.

In an editorial comment accompanying this report, Dr. John W. Eikelboom and Dr. Jeffrey I. Weitz of Hamilton (Ont.) General Hospital wrote, "These findings suggest that, like bivalirudin, otamixaban might be a useful alternative to heparin for patients who are undergoing PCI.

"However, do we need another parenteral agent for this indication?" they asked (Lancet 2009 Aug. 30 [doi:10.1016/S0140-6736(09)61529-4]).

"Without safety or convenience advantages, otamixaban would need to show efficacy that is superior not only to heparin but also to bivalirudin, before it would be adopted for clinical use. To our knowledge, there are no ongoing [phase III] trials to explore these possibilities, nor is otamixaban under development for other clinical indications," Dr. Eikelboom and Dr. Weitz noted.

"Most of the attention in acute coronary syndromes has moved away from parenteral anticoagulants, such as otamixaban, and is focused on new oral agents," they added.

Dr. Sabatine reports receiving honoraria and consulting fees from Sanofi-Aventis and Bristol-Myers Squibb Co. The TIMI study group receives research grant support from Sanofi-Aventis, Johnson & Johnson, Bayer Healthcare AG, and Daiichi Sankyo. Dr. Eikelboom has received honoraria, research support, or both from companies that are developing or marketing drugs mentioned in his editorial comment, including Bayer, Bristol-Myers Squibb, Eli Lilly & Co., GlaxoSmithKline, Regado Biosciences Inc., and Sanofi-Aventis.

Dr. Weitz also has received honoraria from companies that are developing or marketing drugs mentioned in his editorial comment, including Bristol-Myers Squibb, Sanofi-Aventis, and the Medicines Company. ■

Reduced Mortality, Events With Ticagrelor

PLATO Trial *from page 1*

vascular death, myocardial infarction, and stroke, compared with a standard clopidogrel regimen in 18,624 patients hospitalized with acute coronary syndrome during a median treatment of 9 months.

The data were presented by Dr. Lars Wallentin, professor of medicine at Uppsala (Sweden) University Hospital, at the annual congress of the European Society of Cardiology. Concurrent with the meeting report, the results appeared online (N. Engl. J. Med. 2009 Aug. 30 [doi:10.1056/NEJMoa0904327]). The study was funded by AstraZeneca, the company developing ticagrelor.

Ticagrelor showed a 1.9% absolute reduction in cardiovascular events, compared with clopidogrel.

DR. WALLENTIN

In addition to this significant 16% relative cut in total cardiovascular events compared with the clopidogrel group, the results showed a significant 21% relative reduction in cardiovascular death alone (a 1.1% absolute drop). The efficacy and safety profile of ticagrelor was similar across the broad range of patients in the study, including a wide range of ages and levels of renal function.

The findings also showed a "unique" effect from ticagrelor, a significant 22% relative (1.4% absolute) reduction in the rate of all-cause death, an outcome not seen for an antiplatelet agent since the aspirin trials 20 years ago, he said.

Dr. Wallentin disclosed he receives lecture and consultant fees and grant support from AstraZeneca and from several other drug companies.

"The reduction in mortality is something that I think we'll all keep coming back to. That's a pretty strong finding, and something that most physicians will want for their patients," said Dr. Christopher P. Cannon, a cardiologist at Brigham and Women's Hospital in Boston and a coinvestigator on PLATO.

One contributor to the total mortality benefit may be the way that ticagrelor cuts ischemic events without boosting bleeds. Because the total mortality benefit is larger than the cut in cardiovascular deaths alone, the drug probably improves outcomes in other ways, too, Dr. Wallentin said.

The extra benefit may result from the drug's mechanism of action, which blocks an adenosine receptor on platelets. In addition to stopping platelet activity, the effect boosts blood adenosine levels, a vasodilatory effect that's potentially beneficial, said Dr. Cannon, who disclosed receiving grant support from AstraZeneca and several other drug companies.

The adenosine effect may also explain the significantly higher rate of dyspnea—14% in the ticagrelor group versus 9% in the clopidogrel group. Still, just 1% of the ticagrelor patients dropped out because of dyspnea. The adenosine effect also may explain the increased, 6% rate of ventricular pauses of 3 seconds or less early during treatment. "These are not oddball toxicities," said Dr. Cannon. They seem related to how the drug works, he said. About the only other notable adverse event was increased blood levels of uric acid, which rose by an average of 15%.

He and other experts especially welcomed the quick reversibility of ticagrelor's effect, with the antiplatelet effect gone within 48 hours of stopping the drug. In contrast, the irreversible platelet inhibition produced by both clopidogrel and prasugrel takes 3-5 days to abate when treatment stops as new platelets enter the circulation.

"As a surgeon, it's the reversibility that interests me the most. That's a major feature of the drug," said Dr. Timothy J. Gardner, a cardiothoracic surgeon and medical director of Christiana Care Health System's Center for Heart & Vascular Health in Wilmington, Del. "It's an impressive drug and an impressive study," added Dr. Gardner, who said he has no relevant disclosures.

Indeed, "[T]he availability of agents for antagonizing platelet ADP receptors may make it possible to individualize antiplatelet therapy," Dr. Albert Shomig wrote in an editorial accompanying the published report. Specifically, "ticagrelor therapy may be preferred in patients whose coronary anatomy is unknown and for whom a CABG procedure is deemed probable." Also, patients taking clopidogrel or prasugrel who are undergoing elective surgery could be switched to tigacrelor 5-7 days beforehand, said Dr. Shomig, of the cardiology department of Deutsches Herzzentrum in Munich (N. Engl. J. Med. 2009 Aug 30 [doi:10.1056/NEJMe0906549).

"Having another [antiplatelet] option will be very be good for clinicians," allowing them to "select the best drug for each patient," commented Dr. Elliott M. Antman, director of the cardiac unit at Brigham and Women's Hospital. Dr. Antman acknowledged that ticagrelor would be an attractive option for patients who may face surgery, but a related disadvantage is that patients who miss just a couple of doses in a row of the b.i.d. drug may lose a significant part of their anti-ischemic protection. Dr. Antman disclosed that he has received consultant fees and research grants from Eli Lilly & Co., the company that markets prasugrel, and he was the lead investigator for the major prasugrel pivotal study. He has also received research grants from AstraZeneca and from several other drug companies. ■