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Scientific Update™

Clinical Efficacy and Safety of Otamixaban, an Intravenous, Selective Factor Xa Inhibitor for the Treatment of Non-ST-Elevation Acute Coronary Syndromes: Results of SEPIA-ACS1 TIMI 42

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Acute coronary syndromes (ACS) are frequently mediated by the formation of intracoronary thrombus at the rupture site of atherosclerotic plaque. Plaque rupture leads to exposure of tissue factors and the consequent activation of factor X. Factor Xa is a major component of the prothrombinase complex that drives the final common pathway of the coagulation cascade, generating thrombin, which then converts fibrinogen to insoluble fibrin. Therefore, inhibiting thrombin generation and/or activity is a logical strategy in the treatment of ACS. Otamixaban is a novel, intravenous, direct, selective inhibitor of factor Xa. The Study Program to Evaluate the Prevention of Ischemia with direct Anti-Xa inhibition in Acute Coronary Syndromes 1 – Thrombolysis In Myocardial Infarction (SEPIA-ACS1 TIMI) 42[1] is a randomized, double-blind, active-controlled, Phase II trial designed to assess the efficacy and safety of otamixaban in non-ST-elevation (NSTE) ACS and to identify the optimum dose range for future Phase III studies. The primary results of this trial have just been published; they were presented in a Hotline session of the 2009 Congress of the European Congress of Cardiology and are reviewed in this issue of *Cardiology Scientific Update*.

Bursts of thrombin production are often observed in patients with ACS.[2] In these patients, a decrease in the generation of thrombin markers during anticoagulant therapy has been related to improved clinical outcomes.[3] Factor Xa plays a pivotal role in thrombin generation because of its position at the convergence of the intrinsic and extrinsic clotting pathways and therefore is a logical target for treatment of arterial thrombosis. Until recently, unfractionated heparin (UFH) had been the standard anticoagulant therapy for patients presenting with an NSTE ACS.[4] However, the use of UFH has limitations: it is an indirect, non-selective inhibitor of coagulation factors; it cannot inhibit clot-bound thrombin; it can cause heparin-induced thrombocytopenia; and it has somewhat unpredictable pharmacodynamic activity.[5] Otamixaban is a novel, intravenous, direct, selective inhibitor of factor Xa.[6-8] This novel agent directly inhibits free and proteinase-bound factor Xa, and is independent of platelet function or antithrombin III. Otamixaban has not been approved by Health Canada.

In the SEPIA-PCI (Study to Evaluate the Pharmacodynamics, the Safety and Tolerability, and the Pharmacokinetics of Several Intravenous Regimens of the Factor Xa Inhibitor Otamixaban [XRP0673], in Comparison to Intravenous Unfractionated Heparin in Subjects Undergoing Non-Urgent Percutaneous Coronary Intervention) trial,[9] a dose-ranging Phase II study of otamixaban compared with unfractionated heparin in 947 patients undergoing non-urgent PCI, the highest dose of otamixaban was better than UFH in reducing thrombin generation. Although not designed to detect differences in clinical events, in patients given intermediate doses of otamixaban (0.120 mg/kg/hr and 0.160 mg/kg/hr) in SEPIA-PCI, the rates of the composite endpoint of death, myocardial infarction (MI), or the need for urgent target vessel revascularization tended to be lower than the rate in the UFH group, and the rates of TIMI major or minor bleeding were similar. In part encouraged by these promising results, the SEPIA-ACS1 TIMI 42 trial[1] was designed to assess the efficacy and safety of several different doses of otamixaban compared with UFH plus eptifibatide in patients with high-risk NSTE ACS, and to identify the optimum doses for further assessment in a Phase III study.

Study design

SEPIA-ACS1 TIMI 42 was a randomized, double-blind, Phase II, parallel group, dose-ranging, active-controlled study that recruited 3241 patients from 196 sites in 36 countries. The trial enrolled patients, aged ≥18 years, who were within 24 hours of having at-rest symptoms suggestive of an ACS of at least

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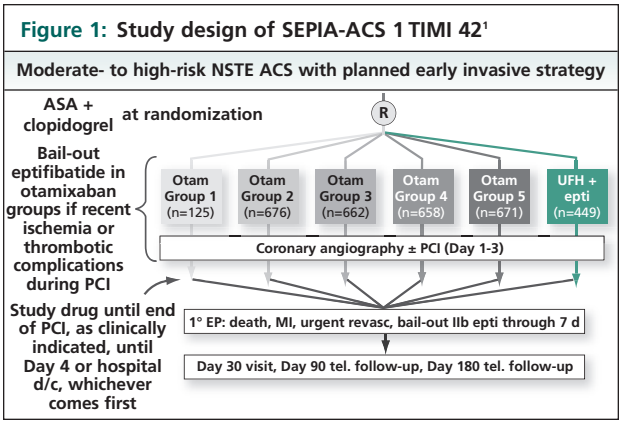
Figure 1: Study design of SEPIA-ACS 1 TIMI 42[1]



NSTE = non-ST-elevation; ACS = acute coronary syndrome; ASA = acetylsalicylic acid; otam = otamixaban; epti = eptifibatide; PCI = percutaneous coronary intervention; MI = myocardial infarction; EP = endpoint; tel. = telephone; d/c = discharge.

10 minutes' duration and with high-risk features. These features consisted of either new or presumably new ST-segment deviation (depression or transient elevation) ≥0.1 mV in ≥2 contiguous electrocardiographic leads, or a cardiac biomarker of necrosis above the upper limit of normal, and being scheduled for treatment with an early invasive strategy. The key exclusion criteria were: ACS anticoagulant treatment for >24 hours before randomization; requirements for treatment with an oral anticoagulant; severe hypertension defined as systolic blood pressure (BP) >200 mm Hg and/or diastolic BP >110 mm Hg; major surgery or trauma in the past 6 weeks; history of stroke in the past 30 days or any history of hemorrhagic stroke; or creatinine clearance <30 mL/ min, a platelet count <100 000 per L, PCI within 30 days, or cardiogenic shock. The protocol recommended that participants receive acetylsalicylic acid (ASA) and clopidogrel according to practice guidelines at randomization (if not already administered) and that both drugs be continued for the duration of the study. Anticoagulants started before enrollment were discontinued, and study drugs were begun either 90-150 minutes after discontinuation of a UFH infusion or 8-12 hours after the last dose of low-molecular-weight heparin.

The overall study design is illustrated in Figure 1. Recruited patients were randomized to receive double-blinded treatment with 1 of 5 doses of otamixaban (0.08 mg/kg bolus followed by infusions ranging from 0.035 to 0.175 mg/kg/hr) or UFH (60 IU/kg intravenous bolus [maximum 4000 IU], followed by an infusion of 12 IU/kg/h [initial maximum 1000 IU/h]) + the glycoprotein IIb/IIIa inhibitor (GPI), eptifibatide (180 µg/kg intravenous bolus [maximum 22.6 mg] followed by an infusion of 2.0 µg/kg/min [maximum 15 mg/h] or 1.0 µg/kg/min in patients with a creatinine clearance <50 mL/min). Otamixaban (or matching placebo) and UFH (or matching placebo) were to be administered until the end of the PCI. Eptifibatide (or matching placebo) was to be administered until 18–24 hours after the end of the PCI. If no PCI was performed, study drugs could be discontinued after diagnostic angiography or continued as long as clinically indicated up until Day 4 of hospital admission. Study drug was to be discontinued at least 3 hours before coronary artery bypass graft (CABG) surgery. At the discretion of the investigator, a patient could receive bailout GPI, which was provided as a masked bolus of eptifibatide (or matching placebo for patients already on eptifibatide), to be followed by an infusion of open-label eptifibatide.

The primary efficacy endpoint was the composite of all-cause death, new MI, severe recurrent ischemia requiring urgent revascularization, or bailout use of a GPI through day 7. The primary safety endpoint was TIMI major or minor bleeding unrelated to CABG up to 7 days. Dose arm 1 (lowest dose) was stopped early at the recommendation of the Data Safety Monitoring Committee due to inadequate anticoagulation; the remaining dose arms enrolled to scheduled completion.

Results

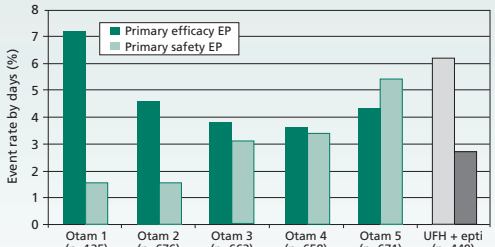
The primary results of SEPIA-ACS1 TIMI 42 have recently been presented and published simultaneously.[9] Baseline characteristics are shown in Table 1; the mean age of subjects was 61 years and 31% were female. A total of 99% of subjects underwent angiography, 63% underwent PCI, and 4% underwent CABG; in addition, 98% were treated with ASA and 98% with

Table 1: Baseline characteristics[1]

	Otamixaban (mg/kg/h)					UFH + eptifibatide (n=449)
	0.035 (n=125)	0.070 (n=676)	0.105 (n=662)	0.140 (n=658)	0.175 (n=671)	
General characteristics						
Age (years)	60.0 (13.1)	61.6 (11.3)	61.7 (11.3)	61.5 (11.3)	61.3 (11.6)	61.0 (11.5)
Men	92.0 (73.6%)	456 (67.5%)	477 (72.1%)	459 (69.8%)	466 (69.4%)	299 (66.6%)
Weight (kg)	78.9 (18.0)	79.2 (17.1)	78.7 (15.5)	78.6 (16.0)	79.3 (15.4)	78.2 (15.4)
Creatinine clearance (mL/min)	103.1 (43.9)	94.6 (37.5)	94.4 (34.4)	93.5 (35.5)	95.2 (34.8)	95.0 (33.9)
Creatinine clearance <50 mL/min	9 (7.7%)	56 (8.9%)	46 (7.5%)	50 (8.1%)	51 (8.2%)	34 (8.1%)
Medical history						
Hypertension	85 (69.1%)	465 (69.7%)	457 (70.7%)	467 (72.2%)	466 (70.8%)	297 (67.2%)
Dyslipidemia requiring therapy	56 (45.5%)	341 (51.1%)	318 (49.2%)	320 (49.5%)	327 (49.7%)	217 (49.1%)
Current smoker	40 (32.5%)	212 (31.8%)	200 (31.0%)	208 (32.1%)	209 (31.8%)	152 (34.4%)
Diabetes mellitus	31 (25.2%)	190 (28.5%)	177 (27.4%)	201 (31.1%)	189 (28.7%)	125 (28.3%)
Previous MI	22 (17.9%)	123 (18.4%)	132 (20.4%)	169 (26.1%)	146 (22.2%)	90 (20.4%)
Index presentation						
ST deviation ≥0.1 mV	61 (48.8%)	366 (54.1%)	389 (58.8%)	367 (55.8%)	394 (58.7%)	254 (56.6%)
Elevated troponin or CK MB	106 (84.8%)	508 (75.1%)	509 (76.9%)	518 (78.7%)	508 (75.7%)	353 (78.6%)

Data are mean (SD) or number (%). ST deviation includes depression or transient elevation. Percentages based on available data for every variable. UFH = unfractionated heparin; CK = creatine kinase.

Figure 2: Primary efficacy and safety endpoints[1]



	Otam 1 (n=125)	Otam 2 (n=676)	Otam 3 (n=662)	Otam 4 (n=658)	Otam 5 (n=671)	UFH + epti (n=449)
Otamixaban bolus (mg/kg)	0.08	0.08	0.08	0.08	0.08	n/a
Otamixaban infusion (mg/kg)	0.035	0.070	0.105	0.140	0.175	n/a

RR (95% CI) for otamixaban vs UFH + eptifibatide

Primary efficacy EP	1.16 (0.56-2.38)	0.74 (0.45-1.21)	0.61 (0.36-1.02)	0.58 (0.34-0.996)	0.69 (0.42-1.15)	Reference
Primary safety EP	0.61 (0.14-2.70)	0.61 (0.27-1.38)	1.15 (0.57-2.32)	1.26 (0.63-2.52)	2.02 (1.06-3.85)	Reference

RR = relative risk; CI = confidence interval.
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clopidogrel. Vascular access was obtained through the femoral approach in 2518 patients (79%), the radial approach in 662 (21%), and the brachial approach in 16 (1%). The median duration of treatment with otamixaban or UFH was roughly 5 hours and with eptifibatide or placebo, 21 hours.

Data on the primary efficacy and safety endpoints are summarized in Figure 2. There was no statistically significant difference in the rate of the primary efficacy endpoint across all of the otamixaban arms; however, in all except dose arm 1, the point estimate for the primary efficacy endpoint favoured otamixaban over UFH + GPI. At intermediate doses (dose arm 3 [0.105 mg/kg/hr] and dose arm 4 [0.140 mg/kg/hr]), treatment with otamixaban resulted in approximately 40% reductions in the primary efficacy endpoint (relative risk [RR] 0.61; 95% confidence interval [CI], 0.36-1.02 and RR 0.58; 95% CI, 0.34-0.996, respectively), these differences in the composite endpoint were driven by an approximate 45% reduction in death or MI (RR 0.52; 95% CI, 0.28-0.98 and RR 0.56; 95% CI, 0.30-1.03, respectively) when compared with UFH + GPI. The differences in the rates of the primary endpoint seen by 7 days persisted during 180 days of follow-up. There was a significant dose response in terms of the primary safety endpoint among the 5 otamixaban arms (P= 0.0003), but the rate in otamixaban dose arms 3 and 4 (3.1%-3.4%) were not significantly higher than the rate with UFH + GPI (2.7%).

Data on individual efficacy endpoints up to 7 days are shown in Table 2. Patients given low doses of otamixaban (0.035 and 0.070 mg/kg/h) tended to have higher rates of bailout GPI use for recurrent ischemia or for a thrombotic complication than did those given UFH plus eptifibatide (RR 2.87; 95% CI, 0.78-10.54 for otamixaban 0.035 mg/kg/h; RR 1.99; 95% CI, 0.73-5.44 for otamixaban 0.070 mg/kg/h; RR 2.13; 95% CI, 0.80-5.47; P=0.12 for doses combined). On the other hand, patients given otamixaban at doses >0.105 mg/kg/h had bailout rates of GPI use similar to those noted with UFH + eptifibatide.

In patients who underwent PCI, TIMI flow Grade 3 and procedural success (residual stenosis <50% and TIMI flow Grade 3) were each achieved in >90% of cases across all treatment groups. Patients given low doses of otamixaban (0.035 and 0.070 mg/kg/h) tended to have higher rates of procedural thrombotic complications than those given UFH + eptifibatide (Figure 2). Patients given otamixaban at doses >0.105 mg/kg/h had rates of thrombotic complications similar to those noted with UFH + eptifibatide.

As shown in Figure 2, there was a significant dose response in the primary safety endpoint across the 5-otamixaban groups (P=0.0001 for trend). Patients given low doses of otamixaban (0.035 and 0.070 mg/kg/h) tended to have lower rates of the primary safety endpoint, those given intermediate doses (0·105 and 0·140 mg/kg/h) had similar rates, whereas those given the highest dose (0.175 mg/kg/h) had a significantly higher risk (P=0.0273) than those given UFH + eptifibatide.

Discussion and clinical implications

The principal findings of SEPIA-ACS-1 TIMI 42 demonstrate that otamixaban at intermediate doses is associated with a lower risk of ischemic events and a comparable risk of bleeding compared with UFH + GPI in patients with NSTE ACS. Otamixaban is a novel, selective, and direct inhibitor of factor Xa[7] and unlike other anticoagulants, such as UFH, enoxaparin, or fondaparinux, does not require antithrombin as a cofactor. Both *in vitro* and *ex vivo* studies indicate that otamixaban reduces thrombin

Table 2: Individual efficacy endpoints up to 7 days[1]

	Otamixaban (mg/kg/h)					UFH + eptifibatide (n=449)
	0.035 (n=125)	0.070 (n=676)	0.105 (n=662)	0.140 (n=658)	0.175 (n=671)	
Primary efficacy endpoint	9 (7.2%)	31 (4.6%)	25 (3.8%)	24 (3.6%)	29 (4.3%)	28 (6.2%)
Death, MI, or urgent revascularization	7 (5.6%)	29 (2.8%)	21 (3.2%)	20 (3.0%)	23 (3.4%)	25 (5.6%)
Death, MI	6 (4.8%)	19 (2.8%)	17 (2.6%)	18 (2.7%)	19 (2.8%)	22 (4.9%)
Death	1 (0.8%)	9 (1.3%)	8 (1.2%)	8 (1.2%)	8 (1.2%)	8 (1.8%)
MI*	5 (4.0%)	11 (1.6%)	9 (1.4%)	13 (2.0%)	12 (1.8%)	14 (3.1%)
Spontaneous	3 (2.4%)	5 (0.7%)	6 (0.9%)	6 (0.9%)	6 (0.9%)	6 (1.3%)
Peri-PCI	3 (2.4%)	4 (0.6%)	3 (0.5%)	6 (0.9%)	5 (0.8%)	7 (1.6%)
Urgent revascularization	1 (0.8%)	2 (0.3%)	5 (0.8%)	2 (0.3%)	4 (0.6%)	3 (0.7%)
Protocol-defined bailout GP IIb/IIIa inhibitor us	4 (3.2%)	15 (2.2%)	9 (1.4%)	5 (0.8%)	8 (1.2%)	5 (1.2%)

Data are number (%) of patients. UFH = unfractionated heparin. MI = myocardial infarction. GP = glycoprotein. * Patients could have had both a spontaneous and a peri-PCI MI.
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generation by inhibiting fluid-phase and clot-bound factor Xa without effects on platelet aggregation.[7] The effective half-life of otamixaban in humans is short (ie, 30 minutes),[8,10] and when administered intravenously, it presents a rapid "on and off" of anticoagulant activity related to the short initial elimination of the drug upon cessation of the dose.

In the current study, doses of otamixaban ≤0.070 mg/kg/h appear to be associated with an increased need for bailout GPI therapy and in thrombotic complications during PCI. On the other hand, the dose of 0.175 mg/kg/h may be associated with more TIMI major bleeding or minor bleeding. Otamixaban doses of 0.105 and 0.140 mg/kg/h are associated with non-significant excesses of TIMI major bleeding and TIMI major or minor bleeding. The results of SEPIA-ACS1 TIMI 42 are consistent with those of the earlier SEPIA-PCI trial[9] in patients undergoing elective PCI. In SEPIA-PCI, otamixaban doses in the range of 0.120 mg/kg/h to 0.160 mg/kg/h were associated with 30%-55% lower rates of death or ischemic complications, and similar rates of TIMI major or minor bleeding when compared with UFH.

Although the choice of UFH + eptifibatide on background dual antiplatelet therapy as the comparator is appropriate and appears supported by ACS treatment guidelines,[11,12] alternative anticoagulants and potent antiplatelet agents have been studied and are currently under development for the treatment of NSTE ACS. These agents include low-molecular-weight heparin;[13,14] the direct thrombin inhibitor, bivalirudin;[15] fondaparinux, an indirect factor Xa inhibitor;[16] oral factor Xa inhibitors, such as apixaban[17] and rivaroxaban;[18] as well as the newer and more potent antiplatelet agents, including prasugrel[19] and ticagrelor.[20] When some of these agents are incorporated into clinical practice, the efficacy and safety profile of otamixaban will need to be assessed in conjunction with them. Furthermore, the single bolus dose of one of the comparators, epitifibatide, employed in the control arm may not necessarily reflect current practice, since double bolus doses have been employed in the Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT)[21] and the Platelet aggregation and Receptor occupancy with Integrilin – a Dynamic Evaluation (PRIDE) study.[22]

Conclusion

The preliminary efficacy and safety data of SEPIA-ACS1 TIMI 42 are encouraging and provide a strong rationale for the planning of additional Phase III studies of otamixaban in the management of patients with NSTE ACS. The optimal doses to be employed in these studies will require a careful examination of the dose responses to arrive at a balance of ischemic, thrombotic, and bleeding endpoints.

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