JACC: CARDIOVASCULAR INTERVENTIONS VOL. 5, NO. 3, 2012

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC. DOI: 10.1016/j.jcin.2012.01.006

Prasugrel Versus Tirofiban Bolus With or Without Short Post-Bolus Infusion With or Without Concomitant Prasugrel Administration in Patients With Myocardial Infarction Undergoing Coronary Stenting

The FABOLUS PRO (Facilitation through Aggrastat By drOpping or shortening Infusion Line in patients with ST-segment elevation myocardial infarction compared to or on top of PRasugrel given at loading dOse) Trial

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Objectives The authors sought to compare the effect on inhibition of platelet aggregation (IPA) of prasugrel therapy versus tirofiban bolus with or without a post-bolus short drug infusion in ST-segment elevation myocardial infarction (STEMI) patients.

Background The degree and rapidity of IPA after prasugrel alone with or without concomitant glycoprotein IIb/IIIa inhibition in STEMI patients is unknown.

Methods A total of 100 STEMI patients randomly received prasugrel 60 mg versus 25 μg/kg tirofiban bolus with or without post-bolus 2-h infusion of tirofiban, with or without concomitant prasugrel. IPA at light transmission aggregometry was performed throughout 24 h. The primary endpoint was IPA stimulated with 20 μmol/l adenosine diphosphate (ADP) at 30 min.

Results At 30 min, patients in the prasugrel group showed a significantly lower IPA to 20 μmol/l ADP stimulation as compared with tirofiban-treated patients (36 $\pm$ 35 vs. 87 $\pm$ 31, $p < 0.0001$). Similarly, patients taking prasugrel showed a suboptimal degree of platelet inhibition for at least 2 h compared with tirofiban patients. Post-bolus tirofiban infusion was necessary to maintain a high level of IPA beyond 1 h after bolus administration if concomitant clopidogrel was given, whereas the bolus-only tirofiban and concomitant prasugrel led to the higher and more consistent IPA levels after both ADP and thrombin receptor-activating peptide stimuli than either therapy alone.

Conclusions Our study shows that prasugrel administration leads to a suboptimal IPA for at least 2 h in STEMI patients. Yet, prasugrel, given in association with a bolus only of glycoprotein IIb/IIIa inhibitor, obviates the need of post-bolus infusion and almost completely abolishes residual variability of IPA after treatment. (Facilitation through Aggrastat By drOpping or shortening Infusion Line in patients with ST-segment elevation myocardial infarction compared to or on top of PRasugrel given at loading dOse [The FABOLUS PRO trial]; NCT01336348) (J Am Coll Cardiol Intv 2012;5:268–77) © 2012 by the American College of Cardiology Foundation

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Manuscript received September 10, 2011; revised manuscript received January 9, 2012, accepted January 11, 2012.

Given the pivotal role of the platelet in acute coronary syndromes (ACS), measures to inhibit platelet activity are paramount to its management (1). Over time, a growing recognition of the various pathways driving platelet activity has given rise to the need for multiple agents, which impart complimentary mechanisms of action.

Blocking simultaneous platelet upstream activation via aspirin and clopidogrel, a rather weak $P2Y_{12}$ receptor blocker, and downstream aggregation pathway with glycoprotein IIb/IIIa inhibitors (GPI) has been shown to be beneficial in preventing ischemic periprocedural complications in patients with ACS undergoing coronary intervention (2–5).

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Yet, the recent advent of potent and fast-acting oral $P2Y_{12}$ inhibitors, such as prasugrel or ticagrelor, which are able to almost completely suppress adenosine diphosphate (ADP)-induced platelet aggregation (PA) (6–8), is questioning the additional value of GPI in contemporary practice.

Pharmacokinetic data on the effect of prasugrel administration in ACS patients are limited, however (9,10), and there is no randomized comparison of GPI versus prasugrel measuring potency and rapidity of PA inhibition. This evaluation appears particularly critical for ST-segment elevation myocardial infarction (STEMI) patients, in whom the capability of clopidogrel to suppress ADP-induced platelet activation is largely inferior to what would be predicted based on assessments in stable patients (11).

We compared the degree of platelet inhibition after administration of prasugrel only versus a treatment strategy based on tirofiban bolus with or without a post-bolus short drug infusion, with or without concomitant prasugrel, in STEMI patients undergoing primary percutaneous coronary intervention (PCI).

Methods

Study design and patient population. The FABOLUS PRO (Facilitation through Aggrastat By drOpping or shortening Infusion Line in patients with ST-segment elevation myocardial infarction compared to or on top of PRasugrel given at loading dOse) study is a single-center, open-label, prospective randomized pharmacodynamic investigation of 2 main antiplatelet treatment strategies in patients undergoing coronary intervention for STEMI: oral administration of prasugrel alone at a loading dose of 60 mg or the administration of tirofiban 25 μg/kg bolus with or without a 0.15 μg/kg/min 2-h post-bolus infusion of tirofiban with concomitant or post-infusion administration of either 60 mg of prasugrel or 600 mg of clopidogrel (Fig. 1).

The study protocol was approved by the ethics committee and was conducted according to the principles of the Declaration of Helsinki. All patients provided written informed consent before enrollment.

Eligible subjects were those older than 18 years old, undergoing coronary intervention for symptoms of ischemia that were lasting at least 30 min with an electrocardiographic ST-segment elevation ≥1 mm in 2 or more contiguous electrocardiogram leads, or with a new left bundle-branch block, and admission either within 12 h of symptom onset or between 12 and 24 h after onset with evidence of continuing ischemia. The exclusion criteria included administration of fibrinolytics in the previous 30 days, major surgery within 15 days, current bleeding, or previous stroke in the last 6 months. All patients underwent primary angioplasty immediately after the start of the oral and/or intravenous treatment.

Randomization. An independent study nurse performed assignments of study treatments via a procedure employing sealed envelopes. A 3:1:1:1 computer-generated random sequence in blocks of 6, without stratification and supplied by an academic statistician was used to treat patients with the following 4 different treatment strategies: 1) prasugrel 60 mg only; 2) tirofiban 25 μg/kg bolus only and concomitant clopidogrel 600 mg; 3) tirofiban 25 μg/kg bolus only and concomitant prasugrel 60 mg; and 4) tirofiban 25 μg/kg bolus followed by 0.15 μg/kg/min 2-h tirofiban post-bolus infusion without any concomitant oral $P2Y_{12}$ inhibitors. At the time of discontinuation of the tirofiban infusion, this group of patients was subsequently randomly allocated to receive either prasugrel 60 mg or clopidogrel 600 mg according to a 1:1 computer-generated random sequence in blocks of 4.

Abbreviations and Acronyms

ADP = adenosine diphosphate
CI = confidence interval
GPI = glycoprotein IIb/IIIa inhibitors
IPA = inhibition of platelet aggregation
PA = platelet aggregation
PCI = percutaneous coronary intervention
STEMI = ST-segment elevation myocardial infarction
TRAP = thrombin receptor-activating peptide

Study medications and interventions. Upon presentation, patients received aspirin at 160 to 325 mg orally or 250 mg intravenously, followed by 100 mg orally indefinitely. Prasugrel was given at a 60-mg loading dose followed by 10 mg/day for at least 30 days, whereas clopidogrel was administered at a loading dose of 600 mg followed by 75 mg daily. Tirofiban was given as a bolus of 25 μg/kg with or without post-bolus infusion of 0.15 μg/kg/min for 2 h. In all patients, anticoagulation during the procedure was achieved via administration of unfractionated heparin given as a bolus of 100 U/kg, targeting an activated clotting time of at least 300 s.

Platelet function testing. PA was performed as previously reported (1,12) immediately before the administration of