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Original article

Effects of CYP2C19 allelic variants on inhibition of platelet aggregation and major adverse cardiovascular events in Japanese patients with acute coronary syndrome: The PRASFIT-ACS study☆

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ABSTRACT

Background: We examined the effects of cytochrome P450 2C19 (CYP2C19) polymorphisms on the efficacy and safety of prasugrel and clopidogrel in a post hoc analysis of the PRASugrel compared with clopidogrel For Japanese patIenTs with acute coronary syndrome (ACS) undergoing percutaneous coronary intervention (PCI) (PRASFIT-ACS) study.

Methods: Japanese ACS patients undergoing PCI were randomized (double-blind) to receive prasugrel (loading/maintenance dose: 20/3.75 mg) or clopidogrel (300/75 mg) plus aspirin for 24–48 weeks. Pharmacogenomic analyses were conducted in 773/1363 patients. $P2Y_{12}$ reaction units (PRU) were determined using the VerifyNow® $P2Y_{12}$ assay (Accumetrics, San Diego, CA, USA). CYP2C19 genotypes were classified as extensive metabolizers (EM), intermediate metabolizers (IM), and poor metabolizers (PM).

Results: Overall, 39.2% and 60.8% of patients in the prasugrel group and 35.2% and 64.8% of patients in the clopidogrel group were classified as EM and IM + PM, respectively. Among EM patients, PRU was significantly lower in the prasugrel group than in the clopidogrel group at 2–4 and 5–12 h after the loading dose, but was similar in both groups from week 4 onwards. Among IM + PM patients, PRU was significantly lower in the prasugrel group than in the clopidogrel group throughout the study. Among EM patients, the incidence of major adverse cardiovascular events (MACE) at 24 weeks was 11.8% in the prasugrel group and 11.9% in the clopidogrel group [hazard ratio (HR): 0.99, 95% confidence interval (CI): 0.50–1.96]. Among IM + PM patients, the incidence of MACE was 9.3% in the prasugrel group and 12.5% in the clopidogrel group (HR: 0.78, 95% CI: 0.45–1.35). The incidences of major, minor, and clinically relevant bleeding were similar between the two groups for each genotype.

☆ Clinical trial registration: JapicCTI-101339 (Japan Pharmaceutical Information Center).

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Conclusions: Prasugrel showed more consistent antiplatelet effects than clopidogrel in Japanese ACS patients irrespective of the CYP2C19 phenotype.

Introduction

The 2009 Japanese Guidelines for the Management of Anticoagulant and Antiplatelet Therapy in Cardiovascular Disease recommend the use of antiplatelet agents for preventing reinfarction following percutaneous coronary intervention (PCI) in patients with acute coronary syndrome (ACS) [1]. Clopidogrel, an irreversible inhibitor of the platelet $P2Y_{12}$ adenosine diphosphate receptor, has become the standard therapeutic drug in this setting and is often administered in combination with or instead of aspirin to prevent thrombosis. Because clopidogrel is a prodrug that is biotransformed into its active moiety by cytochrome P450 enzymes, particularly CYP2C19, genetic variants of CYP2C19 were reported to interfere with the metabolic activation and extent of platelet inhibition during treatment with clopidogrel [2–9]. Moreover, the presence of at least one reduced-function CYP2C19 allele was associated with increased risk of major adverse cardiovascular events (MACE), particularly stent thrombosis, in clopidogrel-treated patients [10]. For these reasons, CYP2C19 genetic testing [11–15] has been proposed before starting clopidogrel therapy to identify patients likely to show reduced antiplatelet activity.

Prasugrel is a newer thienopyridine antiplatelet agent that also irreversibly inhibits platelet $P2Y_{12}$ receptors. Like clopidogrel, prasugrel is a prodrug that is biotransformed in vivo by members of the cytochrome P450 system, although CYP3A4 and CYP2B6 seem to be the predominant activators of prasugrel [16,17]. In vivo studies have demonstrated that the antiplatelet activity (i.e. inhibition of platelet aggregation) of prasugrel is greater than that of both clopidogrel and ticlopidine when either drug was administered alone or in combination with aspirin [18].

The large-scale Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38) subsequently confirmed that prasugrel [loading dose/maintenance dose (LD/MD): 60/10 mg] significantly reduced the incidence of ischemic events, especially stent thrombosis, but had a higher incidence of bleeding than clopidogrel (LD/MD: 300/75 mg) in ACS patients [19]. More recently, the PRASugrel compared with clopidogrel For Japanese patIenTs with ACS undergoing PCI (PRASFIT-ACS) study revealed that a prasugrel dosing regimen (LD/MD: 20/3.75 mg) that was adjusted for Japanese patients was associated with a low incidence of MACE and with a low risk of clinically serious bleeding [20]. These results suggest that prasugrel may represent an effective and safe alternative to clopidogrel in Japanese ACS patients undergoing PCI.

In Japan, the prevalence of patients with genetic variants of CYP2C19 that are responsible for poor metabolism of clopidogrel is much higher (18–23%) than that in Western countries (e.g. 2–3% in the USA and ~3.5% in Europe) [21–23]. In a study of Japanese ACS patients [6], about three-quarters had CYP2C19 variant alleles and the majority of patients classified as intermediate metabolizers (IM) or poor metabolizers (PM) displayed increased platelet reactivity. However, the incidence of adverse outcomes was not apparently affected by the CYP2C19 status [6]. In another study of Japanese patients, platelet reactivity was significantly greater in patients with CYP2C19 variant alleles among patients with ACS or stable angina [24]. It was also noted that cardiovascular events in patients with CYP2C19 variant alleles were more frequent in those patients with ACS than in those with stable angina [24]. Although genetic variants of CYP2C19 are not thought to influence prasugrel metabolism because of the minor contribution of this isoform to the activation of prasugrel, it is important to verify that CYP2C19 genetic variants do not reduce platelet inhibition or increase the risk of MACE in Japanese ACS patients. To examine this issue, 773/1363 patients in the PRASFIT-ACS study underwent genetic testing to determine the influence of CYP2C19 polymorphisms on the efficacy and safety of prasugrel and clopidogrel.

Materials and methods

Study design

PRASFIT-ACS was a randomized, double-blind, double-dummy, parallel-group study conducted at 162 centers in Japan between December 2010 and June 2012 [20]. The study consisted of a 24–48-week treatment period followed by a 14-day follow-up period. Patients were randomly allocated to prasugrel (LD/MD: 20/3.75 mg) or clopidogrel (300/75 mg). The LD was to be administered before PCI, except in urgent cases, when it could be administered up to 1 h after leaving the cardiac catheterization laboratory. The MD was administered once daily after breakfast, starting on the day after the LD, and was continued for the remainder of the treatment period. All patients received aspirin (81–330 mg for the first dose and 81–100 mg/day thereafter) throughout the treatment period. The concomitant use of other antiplatelet drugs, anticoagulant drugs, thrombolytic drugs, or chronic administration of oral, non-steroidal anti-inflammatory drugs was prohibited.

Clinical visits were scheduled every 2–4 weeks for the first 12 weeks, and every 12 weeks thereafter. Although 48 weeks was the recommended duration of study drug administration, the investigators could complete drug administration at week 24 taking into account stent type and the recommended duration of antiplatelet therapy as stated in the package inserts.

The study was conducted according to the Declaration of Helsinki and Good Clinical Practice and was approved by institutional review boards at all participating institutions. The study was registered on the Japan Pharmaceutical Information Center database (identifier: JapicCTI-101339).

Patients

As previously described [20], this study involved Japanese ACS patients who were scheduled for coronary artery stenting and who satisfied the following major eligibility criteria: males/females; age $\geq$20 years; presence of chest discomfort or ischemic symptoms lasting $\geq$10 min within 72 h before randomization; and ST-segment deviation of $\geq$1 mm, or T-wave inversion of $\geq$3 mm, or elevated levels of cardiac biomarkers for necrosis. The main exclusion criteria included the following: pancytopenia or aplastic anemia; history of intracranial bleeding; history of ischemic stroke/transient ischemic attack; history of or predisposition to hemorrhagic disease; poorly controlled hypertension; severe hepatic or renal impairment; New York Heart Association grade IV heart failure; and administration of thienopyridine or thrombolytic drugs within 5 days before starting the study drug or a thrombolytic drug within 24 h before starting the study drug. All of the patients provided informed consent before enrolment.