Review Article
ISSN: 0974-6943

Somsuvra B. Ghatak et al. / Journal of Pharmacy Research 2010, 3(6),1271-1273

Available online through
www.jpronline.info

Ticagrelor: A Novel Player in the field of Anti-Platelet Therapy

Somsuvra B. Ghatak*, Shital J. Panchal

Department of Pharmacology, Institute of Pharmacy, Nirma University, Sarkhej-Gandhinagar Highway, Ahmedabad-382 481, Gujarat, India

Received on: 15-02-2010; Revised on: 14-04-2010; Accepted on:16-05-2010

ABSTRACT

Anti-platelet therapy has long been proven to be of clinical benefit for both the treatment and prevention of acute coronary syndromes (ACS). Although clopidogrel has continued to dominate the field as a potent anti-platelet agent, several new oral and intravenous P2Y12 inhibitors are under development to overcome the current limitations of clopidogrel therapy (slow onset, low level of inhibition, interindividual variability). Ticagrelor (Brilinta) is a novel, selective, orally active, reversible P2Y12 purinoceptor antagonist that belongs to a novel class of compounds called cyclopentyltriazolopyrimidine inhibitors. Unlike thienopyridines, ticagrelor does not require conversion to an active metabolite. Compared with clopidogrel, ticagrelor produces a greater and more consistent inhibition of ADP-induced platelet aggregation. Its rapid onset of action has the potential to improve outcomes for patients with acute coronary syndromes, and its reversibility may offer advantages to patients needing surgery after initiating anti-platelet therapy. Preliminary investigations in early-phase clinical trials have demonstrated ticagrelor to be characterized by a rapid, greater and consistent anti-platelet effect with a favorable safety profile. Recently concluded pivotal phase III (PLATO) trial have shown ticagrelor to be more effective in preventing ischemic events in acute coronary syndrome patients without an increased risk of protocol-defined major bleeding, but with an increase in the rate of non procedure-related bleeding, compared with currently recommended treatment regimens. This contribution provides a comprehensive review of ticagrelor, as a valuable option for the prevention of ischemic events, with the results from large-scale, randomized trials as its vivid backdrop.

Keywords: Ticagrelor, clopidogrel, anti-platelet, clinical trials

INTRODUCTION

Acute coronary syndrome (ACS) is a clinical syndrome characterized by unstable angina (UA) and both non–ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI). In most of the cases, the primary mechanism of development of ACS is reduced myocardial perfusion that results from coronary artery narrowing caused by the formation of nonocclusive thrombi in response to rupture of atherosclerotic plaques on the vessel wall.[1,2] ACS is the most common cause of cardiovascular disability and death in the United States, affecting approximately 1.8 million Americans annually.[3]

Platelets, being the major players in arterial thrombosis and the progression of atherosclerotic lesions, surmount interest has been generated in the development of anti-platelet drugs in the field of pharmaceutical research.[4-6] Activation of the platelets can occur at the rupture of atherosclerotic plaques, or at the implantation of stent material in coronary arteries, thereby involving the production of several platelet agonists including thromboxane A2, thrombin, and adenosine diphosphate (ADP), which further stimulate platelet aggregation.[7-9] ADP, in turn, stimulates platelet activation via 2 G-protein coupled receptors, P2Y1 and P2Y12. Hence, the P2Y12 receptor has been a potential target for anti-thrombotic agents, including both active metabolites of the thienopyridine prodrugs (ticlopidine, clopidogrel and prasugrel).

The thienopyridine clopidogrel, which irreversibly blocks the adenosine diphosphate (ADP) receptor P2Y12 on platelets, has become an integral component of therapy in patients with ACS, because it significantly improves the clinical outcomes.[10] However, clopidogrel has at least three significant drawbacks: delayed onset of action, large inter-individual variability in platelet response, and irreversibility of its inhibitory effect on platelets.

Published reports have shown that approximately one fourth of clopidogrel-treated patients carry a common reduced-function variant allele of the gene CYP2C19 that encodes the hepatic cytochrome P-450 isoenzyme involved in the transformation of the prodrug. These subjects are hardly able to form the active metabolite responsible for the platelet-inhibiting effect of clopidogrel, so that poor metabolizers have inadequate inhibition of platelet aggregation that results in a high rate of recurrent cardiovascular events like coronary thrombosis.[11, 12] Even though insufficient generation of the active metabolite remains the underlying fact for poor clopidogrel responsiveness, other factors may also play their respective roles, such as limited intestinal absorption and interactions with such frequently used drugs as omeprazole, lipophilic statins and calcium channel blockers.[13] Another problem with clopidogrel is its delayed inhibition of platelet aggregation after intake, that renders this prodrug less suitable when the anti-platelet effect is needed early and quickly in ACS. In the light of the above, the prolonged and irreversible platelet inhibitory effect induced by clopidogrel is of major concern when ACS patients need non-deferrable surgery such as urgent coronary-artery bypass grafting (CABG), because the intake of this drug before the procedure is associated with increased blood loss and reoperation for bleeding.[14]

In context of the above limitations, a number of promising anti-platelet drugs, currently under evaluation in clinical trials, have been developed.[15] This review focuses exclusively on the major pharmacological features of ticagrelor (Brilinta or formerly AZD6140), the novel oral, reversible P2Y12 receptor antagonist, along with its results obtained in the most advanced phases of clinical development, thereby attempting to critically appraise the potential limits of this new agent.

Ticagrelor: Mechanism of Action

Ticagrelor, the first of the cyclopentyltriazolopyrimidines, blocks the ADP receptors of subtype P2Y12 to inhibit ADP's prothrombotic effects, similar to that of clopidogrel and ticlopidine. However, in contrast to the other anti-platelet drugs, the blockage is reversible and it nearly completely inhibits ADP-induced platelet aggregation *ex vivo*. Moreover, as described earlier, unlike the thienopyridines, ticagrelor is orally active without the need of metabolic activation, which could substantially reduce the risk of drug interactions.[16] An active metabolite of ticagrelor, identified as AR-C124910XX, has been identi-

***Corresponding author.**
Somsuvra B. Ghatak
Department of Pharmacology,
Institute of Pharmacy, Nirma University,
Sarkhej-Gandhinagar Highway, Ahmedabad-382481, Gujarat, India
Tel.: + 91-(79) (2717) (241900)-05
Telefax: +91-(79) (2717) (241917)
E-mail: ghataksom16@gmail.com

fied in the circulation; it is about as potent as the parent molecule with respect to blocking the P2Y12 receptor and is thought to contribute to the anti-platelet effect of the parent molecule. [17]

Ticagrelor (formerly AZD6140): Pharmacokinetics

Peak plasma levels of ticagrelor are reached between 1.5 and 3 hours after treatment, with steady state reached after 2 to 3 days. The mean elimination half-life is 6 to 12 hours, independent of dose and accordingly the treatment is given twice daily. [17] Concentrations of ticagrelor and its active metabolite increase in plasma in a dose-dependent manner, irrespective of sex or age.

Ticagrelor (formerly AZD6140): Human Clinical Data

Phase I:

Phase I dose-dependency studies in healthy volunteers showed that single oral doses of AZD6140 100 to 400 mg were rapidly absorbed with linear and dose-dependent pharmacokinetics. Complete platelet inhibition was achieved 2 hours after dosing. Inhibition close to 100% was seen with 300- and 400-mg/d doses, and approximately 90% inhibition was maintained with these doses over a 24-hour period. However, at 4, 12, and 24 hours, inhibition of platelet aggregation (IPA) was 99%, 89%, and 57%, respectively, signifying a lessening of effect over 24 hours with AZD6140 100 mg/d. [18]

Phase II:

In the double-blind phase IIa Dose-finding Investigative Study to assess the Pharmacodynamic Effects of AZD6140 versus clopidogrel in non-ST Elevation myocardial infarction (DISPERSE), 200 stable outpatients with atherosclerotic disease were randomised to receive ticagrelor (50 mg, 100 mg and 200 mg twice daily or 400 mg once daily) or clopidogrel 75 mg daily for 28 days on top of aspirin, 75–100 mg once daily.[19] The final and maximal extent inhibition of platelet aggregation was more pronounced and consistent in patients receiving ticagrelor at doses higher than 100 mg twice daily than that of clopidogrel. The primary tolerability measure was the incidence of adverse events, defined as any untoward medical occurrence developing or worsening after study drug administration. However, the incidence of bleeding was higher with the three largest doses of ticagrelor compared with that observed with the standard dose of clopidogrel.

In the subsequent phase II dose confirmatory DISPERSE-2 trial, 990 patients with non-ST segment elevation myocardial infarction were randomised to ticagrelor 90 or 180 mg twice daily or clopidgrel 75 mg once daily for 12 weeks. [20] Half of the patients receiving AZD6140 were sub-randomized to receive a loading dose of 270 mg, whereas the other half started therapy with the maintenance dose. All patients also received aspirin 75 to 100 mg daily. Both doses of ticagrelor provided greater level of platelet inhibition than clopidogrel. During the study period, total bleeding rates (primary endpoint) for the two ticagrelor groups did not differ significantly from that in the clopidogrel group. Also, no significant difference was found in the number of ischemic events. However, a post hoc analysis of continuous electrocardiograms showed the prevalence of several adverse events, particularly the prevalence of dyspnea (15.8% in patients receiving ticagrelor 180 mg twice daily, 10.5% in patients receiving ticagrelor 90 mg twice daily, and 6.4% in patients receiving clopidogrel 75 mg once daily) and bradycardia with ventricular pauses>2.5 seconds.

Phase III

Based on the lack of increased major bleeding and the encouraging trends in efficacy seen in DISPERSE-2, ticagrelor was being studied in the Platelet Inhibition and Patient Outcomes (PLATO) trial, which provided the most valuable information regarding the clinical use of ticagrelor. [21–24] This phase III trial was designed to test the hypothesis that ticagrelor compared with clopidogrel would result in a lower risk of recurrent thrombotic events. PLATO was an international, randomized, double-blind, event-driven trial that compared treatment with ticagrelor (180 mg loading dose followed by 90 mg twice a day) to treatment with clopidogrel (300-600 mg loading dose followed by 75 mg once a day) for the prevention of cardiovascular events. A total of 18,624 patients, who had been admitted for ST-segment elevation acute coronary syndrome (STEACS) referred to primary PCI (38%) or with non-ST-segment elevation acute coronary syndrome (NSTEACS) referred to an invasive or medical strategy (62%) were included in the study. Before randomization, 94% were treated with aspirin and 46% with clopidogrel. Patients were treated for an average of 278 days (6 months minimum and 12 months maximum). 99.97% of the patients completed follow-up, while only 5 patients were lost to follow-up.

The primary endpoint of death from cardiovascular causes, myocardial infarction (MI), and stroke was reduced from 11.7% to 9.8% (hazard ratio [HR] =0.84; 95% confidence interval [CI], 0.77-0.92;p<0.001). In the predefined hierarchical testing of secondary endpoints, reductions were observed in the composite endpoint of death, MI, and stroke from 12.3% to 10.2% (p=0.0001) and in CV, MI, stroke, severe recurrent ischemia, transient ischemic accident (TIA) and other arterial thrombotic events from 16.7% to 14.6% (p<0.001); death from MI alone was reduced from 6.9% to 5.8% (p=0.005), and CV death was reduced from 5.1% to 4% (p=0.001). Total mortality was reduced from 5.9% to 4.5% (p<0.001). There was no difference in total severe bleeding (11.6% vs 11.2% [p=0.434]), but there was a greater incidence of severe bleeding unrelated to coronary artery bypass surgery (CABG) (4.5% vs 3.8% [p=0.026]). Dyspnea episodes were more frequent with ticagrelor (14.2%) than with clopidogrel (9.2%), which led to the treatment being interrupted in 1% and 0.3% of patients, respectively. There were no differences in other relevant side effects.

The superiority of ticagrelor over clopidogrel has been proved in the PLATO study both in terms of the primary and secondary end points since treatment with ticagrelor instead of clopidogrel in a wide spectrum of patients with ACS provides a clinically important reduction in mortality and myocardial infarction without an increase in total severe bleeding, although it does involve an increase in the rate of non–procedure related bleeding.

Although PLATO was meticulously designed and conducted, it did have some drawbacks. Published reports suggest that the trial would have been stronger if the study drug had been administered for least 1 year, if clopidogrel loading (preferably in a 600-mg dose) had been used for all patients in the clopidogrel group irrespective of whether they had been treated previously with clopidogrel, and if proton-pump inhibitors had been used less frequently after randomization in order to reduce any potentially negative interference with clopidogrel efficacy. [25] The proton-pump inhibitors were used in approximately 54% of the patients in both the treatment groups from randomization till the end of the study.

Another multicenter, randomized, double-blind assessment, popularly known as the ONSET/OFFSET study of platelet inhibition (IPA) with ticagrelor using the PLATO (PLATelet inhibition and patient Outcomes) trial loading dose (180 mg) with a high loading dose (600 mg) of clopidogrel also comprehensively clarified that ticagrelor's anti-platelet effects take effect more swiftly and can also be attenuated, or "turned off," more quickly, than clopidogrel's effects. [26]

Ticagrelor (formerly AZD6140): Future Prospects

The development of anti-platelet drugs has evolved greatly, not only because of the improvement of our understanding of the mechanisms underlying platelet-mediated thrombogenesis but also owing to our awareness of the clinical limitations of available agents, particularly clopidogrel. Accordingly, based on the comprehensive data obtained from the PLATO study, AstraZeneca has submitted a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for ticagrelor in November 2009, for the reduction of major adverse cardiac events in patients with ACS. [27] The proposed trade

name for ticagrelor is BRILINTA(TM), pending approval from the FDA.

It is evident from the conducted clinical trials that ticagrelor, the first reversible oral P2Y12 receptor antagonist, provides faster, greater, and more consistent platelets inhibition than clopidogrel. In particular, ticagrelor therapy may be preferred in patients whose coronary anatomy is unknown and for whom a Coronary Artery Bypass Graft Surgery (CABG) is deemed probable. If patients who are receiving clopidogrel or prasugrel need elective surgery, it is reasonable to switch them to ticagrelor 5 to 7 days before surgery. However, clopidogrel might still be appropriate for selected patients who are at relatively low risk of myocardial infarction or stent thrombosis and/or high risk of major bleeding, and/or for whom non-compliance with ticagrelor because of cost or twice daily dosing regime is a concern. Ticagrelor therapy should also be discouraged in patients who have chronic obstructive pulmonary disease (COPD), hyperuricemia, moderate or severe renal failure, bradyarrhythmias unprotected by pacemakers, a history of syncope, or a need for treatment with an ADP-receptor antagonist for more than 1 year. Moreover, the rapidly reversible effect of ticagrelor makes careful surveillance of patients' compliance with the drug mandatory. Nonetheless, the introduction of ticagrelor, a more potent and effective agent which is as safe as its predecessor, is a benchmark event that should re-define the care of patients with ACS. The pharmacology and clinical profiles of this emerging platelet inhibition therapy suggest that it indeed has the potential to provide more consistent, more rapid, and more potent anti-platelet effects than do anti-platelet agents currently used in clinical practice. However, further extensive as well as rigorous clinical studies on new anti-platelet agents are needed to establish a new "gold standard" anti-platelet therapy. [28-30]

Last but not the least, efforts to develop novel effective and safe anti-thrombotic drug regimens should be persistent and not be discouraged on account of the perception that an increase in anti-thrombotic efficacy is necessarily associated with a higher risk of bleeding episode.

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Source of support: Nil, Conflict of interest: None Declared