

Ticagrelor: An emerging oral antiplatelet agent

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INTRODUCTION

Acute coronary syndrome (ACS) is a leading cause of myocardial infarction in the world. It is one of the major cause of mortality in the present lifestyle scenario and a main reason for hospital admissions. A critical role in atherothrombosis is played by platelets.^[1] Antiplatelet agents are of great therapeutic value in thromboembolic diseases.^[2] Potent inhibitors of platelet function have been developed in recent years, resulting in lowered rates of restenosis and thrombosis after angioplasty and vascular stenting procedures.^[1]

Aspirin has been the gold standard antiplatelet agent for the prophylaxis of myocardial infarction and other thromboembolic events.^[3] The thienopyridenes (clopidogrel, ticlopidine and prasugrel) are another class of antiplatelet agents that inhibit adenosine diphosphate induced platelet aggregation irreversibly via P2Y₁₂ receptor located on the surface of platelets.^[4,5]

It has been seen that 1 in 3 ACS patient dies due to repeat MI despite intensive monitoring and prompt treatment of cardiac instability, thrombolytic activity, acute invasive interventions and dual antiplatelet therapy with aspirin and thienopyridines.^[6] In patients with ACS, the most commonly used thienopyridine is clopidogrel.^[6] However, it has some limitations. It causes irreversible inhibition of platelets and thus may increase the risk of bleeding in patients who may require surgery/intervention. Moreover, it requires hepatic conversion to an active metabolite resulting in delayed onset of action and there is an interindividual

variation in conversion rate due to pharmacogenomic differences. The mean levels of inhibition of ADP-induced platelet aggregation with clopidogrel are modest.^[7] So, there is a need to have a new antiplatelet agent without all these drawbacks. Ticagrelor is expected to confer better antiplatelet effects to patients with ACS while being devoid of these demerits.

CHEMICAL STRUCTURE AND MECHANISM OF ACTION

Ticagrelor (formerly AZD140), a novel non-thienopyridine platelet P2Y₁₂ receptor antagonist, is the first oral agent in a new chemical class of cyclopentyl-triazolo-pyrimidines (CPTP). Exploration of structure-activity relationships showed affinity-increasing property of substituents in the 2nd position of the ATP adenine ring and stability-increasing properties of β, γ-methylene substitutions in the triphosphate. The drug development program with ATP analogs led to the identification of several potent selective P2Y₁₂ antagonists with short half-life and requiring intravenous (IV) administration like cangrelor. Subsequent modifications by elimination of phosphate group and changes in the core purine and sugar moiety resulted in identification of the first selective and stable non-phosphate P2Y₁₂ antagonist AR-C109318XX. Further refinement to improve oral bioavailability resulted in development of ticagrelor, the first CPTP to be developed clinically.^[7]

Ticagrelor selectively blocks the platelet P2Y₁₂ receptor by interacting with a binding site different from ADP (non-competitive inhibition) and thus, inhibits the prothrombotic effects of ADP. Unlike thienopyridines, the binding of ticagrelor to P2Y₁₂ receptor is reversible.^[8,9]

PHARMACOKINETICS AND DOSAGE

Ticagrelor is absorbed quickly from the gut, with a

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bioavailability of 36%. The peak plasma levels are reached in 1.5-3.0 hours. Its half-life is approximately 12 hours. The antiplatelet effect is low at 48 hours after the last dose.^[9,10] Ticagrelor is predominantly metabolized by CYP3A4 and to some extent by CYP3A5. ARC124910XX is an active metabolite of ticagrelor, but the parent compound is responsible for the majority of the antiplatelet effect.^[9,11] Elimination is through hepatic metabolism. No dose adjustment is required in patients with renal impairment.

The recommended oral dose of ticagrelor is 180 mg (loading dose) followed by a dose of 90 mg twice daily.^[12,13] A number of trials have been conducted to study the clinical efficacy of ticagrelor in preventing thrombotic events in patients with ACS.

CLINICAL TRIALS

Onset/Offset trial

The ONSET/OFFSET trial, a phase II study, evaluated the timing of the antiplatelet effect of ticagrelor versus clopidogrel in patients with stable coronary artery disease. A total of 123 patients were randomized to receive ticagrelor 180 mg loading dose followed by 90 mg twice daily or clopidogrel 600 mg loading dose followed by 75 mg daily for 6 weeks. Aspirin 75-100 mg daily was given to all patients. At all time points 0.5, 1, 2, 4, 8 and 24 hours after loading dose and at 6 weeks, ticagrelor had a significantly greater inhibition of platelet aggregation (IPA). The offset of ticagrelor action was also faster as evidenced by a comparable IPA result for ticagrelor at day 3 to that of clopidogrel at day 5. This study demonstrates that ticagrelor has faster onset and offset action compared to clopidogrel due to its reversible nature.^[11,12]

Disperse trial

In DISPERSE study, a phase II trial, 200 patients with atherosclerosis were randomized to receive either ticagrelor (doses of 50, 100 or 200 mg twice daily or 400 mg once daily) or clopidogrel (75 mg once daily) for 28 days in addition to 75-100 mg of aspirin once daily.^[8] This trial demonstrated nearly complete inhibition of ADP-induced platelet aggregation with ticagrelor 100 mg, 200 mg twice daily and 400 mg once daily doses as compared to clopidogrel.^[8,9] This trial was followed by a metacentric DISPERSE-2 trial to analyze the safety and efficacy of ticagrelor in 990 patients with non-ST elevation ACS. The patients in this trial were randomized to receive ticagrelor 90 mg or 180 mg twice daily or clopidogrel 300 mg loading dose plus 75 mg once daily for up to 2 weeks. It is to be noted that the 90 mg and 180 mg doses of ticagrelor used in DISPERSE-2 were reformulations of the 100 mg and 200 mg doses used in DISPERSE. This study demonstrated that 90 mg ticagrelor twice daily possess similar safety and efficacy compared to clopidogrel but ticagrelor 180 mg twice daily have poorer safety compared with clopidogrel.^[8,9,11]

Respond trial

This was a randomized, double-blind, double-dummy, crossover trial, which was conducted on 98 patients with stable coronary artery disease. This study included both clopidogrel responders and non-responders. The RESPOND trial revealed the mean IPA increase of 26% in clopidogrel responders switching from clopidogrel to ticagrelor but 24% mean IPA decrease switching from ticagrelor to clopidogrel. Thus, it was concluded that clopidogrel non-responders and responders exhibit superior platelet inhibition with ticagrelor therapy.^[8,9]

Plato trial

The PLATO study is the largest phase III trial, which started in October, 2006 and ended in March, 2009. It was a multicentered or multicentric, double-blind, randomized trial in patients with ACS comparing 2 treatment strategies: ticagrelor (180 mg loading dose, 90 mg twice daily thereafter) and clopidogrel (300 to 600 mg loading dose, 75 mg daily thereafter) with a goal to evaluate the impact of a more potent platelet inhibitor for the prevention of cardiovascular events. In this study, 18,624 patients admitted to the hospital with ST elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI) were evaluated. At 12 months, the primary end point, that is, a composite of death from vascular causes, MI or stroke had occurred in 9.8% of patients receiving ticagrelor compared with 11.7% of those receiving clopidogrel. PLATO showed that treatment with ticagrelor as compared with clopidogrel in patients with ACS significantly reduced the mortality from vascular causes, myocardial infarction and stroke.^[4,10]

Pegasus-timi 54 trial

It is an ongoing trial that aims to compare long-term treatment with ticagrelor plus acetylsalicylic acid (ASA) to ASA alone in reducing the composite end point of cardiovascular death, non-fatal MI and non-fatal stroke.^[6,11,12]

INDICATIONS

Ticagrelor co-administered with aspirin is indicated in ACS (unstable angina, both NSTEMI and STEMI) and in the patients who are to be managed with percutaneous coronary intervention (PCI) or coronary artery by-pass graft (CABG) for the secondary prevention of thrombotic events (cardiovascular death, myocardial infarction and stroke).^[6,14]

ADVERSE EFFECTS

Ticagrelor is generally well tolerated.^[9] Headache, hypotension, epistaxis, bradyarrhythmias, ventricular pauses (not associated with clinical symptoms), elevated liver enzymes, raised serum creatinine and elevated uric acid levels have been reported with ticagrelor in some patients.^[6,7] Dyspnea was reported in some

of the patients, which was mild to moderate in nature. Bleeding is the most common adverse effect seen with ticagrelor. The bleeding events have been reported in the form of subcutaneous/dermal bleeding, gastrointestinal hemorrhages and urinary tract bleeding.^[6,11,13,14] The monitoring of hemoglobin concentration and renal function is recommended with ticagrelor therapy.^[6]

CONTRAINDICATIONS^[11,14]

- Hypersensitivity to ticagrelor.
- Active pathological bleeding such as peptic ulcer.
- History of intracranial hemorrhage.
- Moderate to severe hepatic impairment.

DRUG INTERACTIONS

Ticagrelor is a moderate inhibitor of CYP3A4, CYP2C9, CYP3A5 and CYP2D6.^[6] Ticagrelor and its major metabolite are weak p-glycoprotein substrates and inhibitors. Digoxin levels need to be monitored when given along with ticagrelor, the latter being a p-glycoprotein inhibitor.^[6,14] Antiplatelet drugs and statins are commonly administered together in patients with cardiovascular diseases. Ticagrelor when given with simvastatin and lovastatin increases their serum concentration as they are metabolized by CYP3A4. So, simvastatin and lovastatin in doses >40 mg should be avoided with ticagrelor.^[14,15] Ticagrelor should be avoided in patients on CYP3A4 inhibitors (ketoconazole, clarithromycin, nefazodone, ritonavir and atazanavir) and CYP3A4 inducers (rifampicin, dexamethasone, phenytoin, carbamazepine and phenobarbital).^[14]

SUMMARY

Ticagrelor possesses many desirable characteristics as compared to the thienopyridines and was approved by European Union in December, 2010.^[15] Ticagrelor got FDA approval in July, 2011 for clinical use in ACS. It is not available in India yet. As compared to clopidogrel, ticagrelor has a faster and stronger antiplatelet effect along with a greater clinical efficacy with a comparable rate of bleeding. It has been indicated to be used with low dose aspirin (aspirin dose not exceeding 100 mg) as it loses its efficacy when administered with high dose aspirin.

Ticagrelor at present is in use for ACS but may also offer promising results in broader clinical scenarios, like stroke, in the future, based on ongoing trials.

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