TICAGRELOR - A Novel Antiplatelet Agent

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ABSTRACT

Cardiovascular (CV) deaths are one of the leading cause of death, both in developed and developing countries, with acute coronary syndrome (ACS) accounting for about 50 % of CV deaths. Atherothrombosis formation is the prime reason behind ACS and platelets play a central role in formation of thrombus. Antiplatelet drugs, particularly dual antiplatelet therapy (DAPT) with Aspirin and Clopidogrel play a vital role and are widely used in the management of ACS for the past decade. However in spite of currently available options for antiplatelet therapy there remains a significant risk of arterial thrombosis and post ACS mortality grows over a period of time. Thus there is need for novel antiplatelet agents which can overcome some limitations of current antiplatelet therapies.

TICAGRELOR is a novel antiplatelet agent which has a faster onset of action, produces high level of platelet inhibition with minimum inter patient variability. This review summerises the pharmacokinetics, pharmacodynamics characteristics and clinical evidence of TICAGLELOR in the management of ACS.

1. Acute Coronary Syndrome - Global and Indian perspective

Cardiovascular death (CVD) is one of the leading causes in the non-communicable disease (NCD) deaths. According to WHO estimates around 17 million people die of CVD each year,[1] out of which coronary heart disease (CHD) accounts for 7.1 million deaths. Developing countries like India are witnessing economic transition, urbanization and industrialization resulting in major lifestyle changes like increase tobacco use, physical inactivity and unhealthy diet, that has lead to a dramatic increase in CVD and CHD.[2]

In the Indian context, there are many challenges in managing patients of ACS. ACS patients in India die younger and sicker with average age at 57 years, almost 10-15 years younger than in west. Moreover, they carry high risk factor profile that includes Diabetes, Hypertension, Smoking, and Dyslipidemia and close to 20 % patients suffer from a 2nd heart attack in India.[3] As per CREATE registry 60% of patients in India were of STEMI whereas as per global registray data 40% patients were of STEMI. This implies that Indian patients admitted for ACS are likely to have worse prognosis and those in developed countries. In spite of being at high risk, in India, <10% ACS patients are managed through PCI with less than 15% receiving DAPT.[3]

Experience in the developed world has shown that significant reductions in CAD prevalence and mortality can be achieved via timely intervention and medical therapy. In spite of increasing burden of CVD, there are no definite guidelines in India to combat this serious problem. Hence there is need to develop proper infrasturcture in India to overcome this problem.

2. Role of platelets in ACS and importance of antiplatelet therapy

Platelets protect vascular integrity and play an important role in hemostasis.

However, rupture of an atherosclerotic plaque causes a platelet – dependent thrombus formation leading to occlusion of a coronary artery resulting in acute myocardial infarction. Thus platelets play a central role in pathogensis of acute myocardial infarction. Strong evidence which suggest that AMI is platelet related disease is the capability of antiplatelet therapy to reduce morbidity and mortality in this clinical setting[4].

Many landmark trials of aspirin and thienopyridines have established the role of anti-platelet agents in the management of ACS. Aspirin is the oldest of anti-platelet drugs and has stood the test of time as an integral part of management of ACS.[5-8] The use of thienopyridines, which act by blocking the P2Y12 receptor on the platelet surface, has shown benefit when added to aspirin in this setting.[9-12] Thus DAPT is the current standard of care for patients of ACS which is currently recommended for period of at least 1 year. However, inspite of currently available anti-platelet therapy, there remains a significant risk of arterial thrombosis and post ACS mortality grows over a period of time. Thus there is need for novel anti-platelet agents which can overcome limitations of current anti-platelet therapies like slow onset of action, low level of platelet inhibition, high interpatient variability at the cost of clinically acceptable bleeding events.

3. Ticagrelor: Molecular Discovery

Adenosine triphosphate (ATP) competitively antagonize ADP induced platelet aggregation. However unfavourable properties of ATP, such as low potency and poor stability does not allow its use as P2Y12 receptor antagonist. Efforts were directed toward formulating ATP analogues with high potency and more stability. However because of retention of triphosphate group these agents had very short plasma half life and they need to be given intravenously. Subsequent modification of these compounds lead to discovery of selective and stable non-phosphate P2Y12 receptor antagonist AZD6140 (ticagrelor) belonging to a new chemical class Cyclo Pentyl Triazolo Pyrimidine (CPTD). Although ATP structure was used as basis for designing of ticagrelor, it does not contain an adenosine group and therefore is distinct from true ATP analogues such as Cangrelor.[13]

4. Ticagrelor : Mechanism of action

It is an oral, reversible and directly acting inhibitor of P2Y12 receptor. Like thienopyridines, ticagrelor inhibit prothrombotic effects of ADP by blocking the platelet P2Y12 receptor. However, unlike thienopyridines, the binding and effect is reversible and it does not require metabolic activation before its action. It has rapid onset of action, produces high and consistent inhibition of platelet aggregation with minimal inter patient variability.[14] It binds at the site distinct from ADP binding site, causing locking of the receptor in an inactive state thereby inhibiting ADP signaling and receptor conformational changes. Unlike other thenopyridines, ticagrelor is a non-competitive antagonist of P2Y12 receptor resulting in no receptor activation in spite of increase ADP concentration.

5. Ticagrelor : Pharmacological aspects

Ticagrelor is rapidly absorbed on oral administration without interference of food intake on absorption. The T max is 1.3-2 h and plasma half life (t ½) is 7-12 h [15-16]. It is metabolized in liver by CYP3A4 enzyme to produce active metabolite AR-C12490XX. Elimination of ticagrelor and active metabolite occurs primarily via hepatic metabolism and biliary secretion, respectively. Therefore, no dose adjustment is required for renal patients.

6. Ticagrelor : Clinical development

Safety and tolerability of ticagrelor was tested in various phase I and phase II trials. Inhibition of platelet activity (IPA) was better sustained at high levels with twice daily doses than once daily regimens.[17] **DISPERSE II** was dose confirmation study[18]. Based on safety and efficacy profile 90 mg bd was selected for phase III study.[19] Just 30 min post loading (ticagrelor 180 mg and clopidogrel 600 mg) IPA with ticagrelor was 41% versus 8% in clopidogrel group. At the end of 2 h IPA with ticagrelor was 88% versus 38% in clopidogrel group. At 2 h post –loading, 90% patients in ticagrelor group achieved greater than 70% IPA versus 16 % in clopidogrel group. Higher levels of IPA achieved with ticagrelor was maintained throughout 6 weeks of study period. This indicates sustained and consistant antiplatelet action of ticagrelor. After last dose, antiplatelet effect of ticagrelor declined very rapidly as compared to clopidogrel. 24 h after last dose, IPA with ticagrelor was similar to clopidogrel. This means patients who miss 1 dose of ticagrelor will still have IPA at 24 h equivalent to patients on clopidogrel therapy. IPA at day 3 and 5 with ticagrelor were comparable to IPA at day 5 and 7 with clopidogrel respectively.[20]

Effect of ticagrelor in clopidogrel non-responders was studied in **RESPOND** study which showed that ticagrelor treatment result in consistently higher IPA in patients irrespective of responder status. Ticagrelor was

found to be effective in overcoming high platelet reactivity below the ischemic cut off points in both responders and non-responders to clopidogrel therapy. This study also showed that switching patients from clopidogrel to ticagrelor result in rapid, higher and consistant IPA [21]

7. Ticagrelor evidence in ACS: PLATO study

Platelet Inhibition and patient outcome (PLATO) trial was deisgned to test the hypothesis that ticagrelor is superior to clopidogrel for prevention of recurrent thrombotic events in broad ACS population and this would be achieved with clinically acceptable bleeding rate and overall safety profile. This study was conducted across the world in 43 countries with 862 sites and 18,624 patients. India was also a part of this international trial.

PLATO was designed to reflect real world clinical practice by enrolling full spectrum of ACS (UA, NSTEMI, STEMI) patients within 24 h of their index event based on initial presentation and ECG, irrespective of whether they are managed medically or undergoing invasive management. All patients received baseline aspirin therapy at std doses as per local practice. In ticagrelor group, patients received 180 mg loading dose followed by 90 mg bd as maintenance dose. In clopidogrel arm, those patients who were on clopidogrel, received 300 mg as loading dose and 75 mg as maintenance dose while in clopidogrel pretreated patients loading dose of clopidogrel was not given. Additional 300 mg of clopidogrel was allowed pre-PCI based on physician's discretion. Randomised treatment continued from a minimum of 6 months to maximum of 12 months. Important highlight of PLATO trial design was inclusion of broad ACS population, inclusion of patients previously treated with clopidogrel and allowing clopidogrel loading doses greater than 300 mg[22]

Key inclusion criteria for NSTMI were two of the three, ST segment changes indicating ischemia; positive biomarkaers, or one of several risk factors. For STEMI patient two criterias should be met. Persistant ST-segment elevation and the intension to perform primary PCI. Key exclusion were fibrinolytic therapy within 24 h before randomization, a need for oral an anticoagulation therapy, an increased risk of bradycardia, and concomitant therapy with strong CYP3A4 inhibitor or inducer. [22]

Baseline characteristics were well balanced between two groups. Female population respresented 28 % in both groups and 15.5% patients randomized aged 75 year or above. In PLATO study, for every 54 ACS patients treated with ticogrelor instead of clopidogrel one athrothrmbotic event was prevented. Primary endpoint was mainly driven by reduction in MI and cardiovascular death with no difference in stroke.[23]

The incidence of definite stent thrombosis was also reduced with ticagrelor as compared to clopidogrel (1.3% vs 1.9%). There was no significant difference in the rate of major threatening bleeding between two groups. There was increased fatal intracranial bleeding, no difference in CABG related major bleeding in ticagrelor group. However higher rate of non-CABG related bleeding was observed. [24,25]

Dyspnoea occurred more frequently in ticagrelor group than clop gp. (13.8% vs 7.8%). However this dyspnea was usually mild to moderate and resolved spontaneously in majority. Mortality benefits were maintained irrespective of dyspnea status. Dysponea is thought to be due to increase in adenosine levels in blood due to inhibition of re-uptake of adenosine in RBC by ticagrelor.

Higher incidence of **ventricular pauses** of >3 s during first week of treatment was seen and resolved spontaneously. Ventricular pauses were sinoatrial in origin, asymptomatic and did not correlate with any adverse events. **Creatinine and uric acid** levels increased slightly more in ticagrelor group which was non-progressive and without significant adverse events.[26-27]

In diabetics, cardiovascular events are more due to multiple factors. The primary endpoint benefit was seen in ticagrelor gp in PLATO trial and no interaction between diabetic status and treatment was found.[26]

To summerise, PLATO was designed to reflect current medical practice by enrolling the full spectrum of ACS (UA, NSTEMI or STEMI) patients and following them whether they were medically managed or undergoing an

invasive management. Result demonstrated that ticagrelor achieved greater efficacy in the primary endpoint (composite of CV death, MI and stroke) over clopidogrel without increase in major bleeding.

8. ESC guidelines for management of NSTE-ACS (2011)

The ESC guidelines recommend using aspirin in all patients of ACS at loading dose of 150-300 mg, and at maintainance dose of 75-100 mg daily long term (Class IA). P2Y12 inhibitor should be added to aspirin for the duration of 12 months (Class IA). Among the different P2Y12 inhibitors **TICAGRELOR** is recommended to all patients of ACS at moderate to high risk of ischemic events regardless of initial treatment strategy including those pre-treated with clopidogrel (Class I B). The guidelines recommends the use of Prasugrel in patients who are planned for PCI and whose coronary anatomy is known (Class I B). Clopidogrel is recommended only in patients who cannot receive ticagrelor or Prasugrel (Class I A). In patients undergoing CABG or any other major surgery the guideline recommends stopping clopidogrel or ticagrelor 5 days before and Prasugrel 7 days before the surgery (Class IIa C).[28]

9. ESC guidelines for the management of STE-ACS (2012)

Recently published ESC guidelines for STEMI recommends aspirin loading dose of 150-300 mg followed by maintenance dose of 75-100 mg daily term (Class I B). ADP receptor blocker should be added to aspirin for duration of 12 months (Class I A). For patients undergoing primary PCI options include ticagrelor 180 mg loading dose, 90 mg bd maintenance dose (Class I B); Prasugrel 60 mg loading dose, 10 mg od maintenance dose in clopidogrel-native patients with no h/o prior stroke/TIA and age <75 years (Class I B); clopidogrel 600 mg loading dose, 75 mg maintenance dose preferably when Prasugrel or ticagrelor are either nor available or contraindicated (Class I C).

For patients receiving fibrinolytic therapy, clopidogrel LD 300 mg followed by MD 75 mg daily should be given along with aspirin.[29]

10. American college of cardiology foundation (ACCF) / American heart association (AHA) guidelines for management of UA/NSEMI (2012)

ACCF/AHA guidelines recommend the use of aspirin to UA/NSTEMI patients as soon as possible after hospital presentation and continued indefinitely in patients who tolerate it (Class I A). In patients in whom an initial conservative management is selected clopidogrel or ticagrelor (LD followed by MD) should be added to aspirin and anticoagulant therapy as soon as possible after admission and continued for 12 months. (Class I B).

In those with initial invasive strategy is selected, either ticagrelor or clopidogrel or IV GP IIB/IIIa inhibitor before PCI is recommended, or ticagrelor or prasugrel or clopidogrel is recommended at the time of PCI (Class I B). In patients who are intolerant to aspirin use of clopidogrel or ticagrelor (in all UA/NSTEMI) or Prasugrel (in PCI patients) [30]

11. ACC/AHA – PCI 2011

Patients already on aspirin therapy should take 81 mg-325 mg aspirin before PCI (Class I B). Loading Dose of P2Y12 Receptor inhibitors should be given to patients undergoing PCI, options include clopidogrl 600 mg, Prasugrel 60 mg, ticagrelor 180 mg (Class I B). In patients receiving stent (BMS or DES) during PCI for ACS, P2Y12 inhibitors therapy should be given for atleast a year. Options include clopidogrel 75 mg od, prasugrel 10 mg od or ticagrelor 90 mg bd (Class I B) [31]

12. Conclusion

Considering dramatic increase in incidence of and mortality form ACS, there is dire need for optimizing management strategy of ACS. Platelet play a central role in pathogenesis of ACS and DAPT is an important cornerstone of ACS therapy. There remains a significant incidence of arterial thrombosis in patients patients treated with currently available anti-platelet therapy. Novel P2T12 antagonist TICAGRELOR represents advancement over currently available oral anti-platelet agents. Its advantage include rapid onset of action, high and consistent platelet inhibition, lack of need for metabolic conversion, an acceptable safety profile and documented evidence in reducing cardiovascular events and mortality in broad-spectrum ACS patients.

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