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NEW DRUGS

Ticagrelor: a Novel P2Y12 Platelet Receptor Antagonist - A Review of its Properties, Pharmacology and Clinical Usefulness

Hector Anninos, MD, Spyridon Koulouris, MD
and Antonis S. Manolis, MD

First Department of Cardiology, Evagelismos Hospital, Athens

ABSTRACT

Blockade of platelet adenosine-diphosphate (ADP) receptors has been established as a key therapeutic strategy in cardiovascular disease. Among the thienopyridines, clopidogrel decreases ischemic outcome in patients who present with acute coronary syndromes and the more potent prasugrel has been demonstrated to be superior to clopidogrel in patients who are scheduled to undergo percutaneous coronary intervention. However, the antiplatelet potency is also associated with an increased risk of bleeding complications, and the irreversible ADP receptor antagonism has potential implications especially in the setting of coronary by-pass operation. Ticagrelor is a new reversible antagonist of the P2Y12 receptor, which seems to be more effective and at the same time equally safe to the so far established antiplatelet regimens. This article reviews the current data on this novel compound focusing on its advantageous pharmacology and the clinical results provided by the first phase IIb and III trials.

KEY WORDS: *antiplatelet medication, acute coronary syndrome, ADP receptors*

Abbreviations
ACS= acute coronary syndromes
ADP= adenosine diphosphate
CABG= coronary artery bypass grafting
IPA= inhibition of platelet activation
PCI= percutaneous coronary intervention

Correspondence to:
Spyridon Koulouris, MD
Kekropos 64
151 25, Marousi, Athens
Tel. 210 6148740
e-mail:
Spyridon.koulouris@gmail.com

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INTRODUCTION

Oral antiplatelet therapy with platelet P2Y12 antagonists, primarily the thienopyridine clopidogrel, is a major strategy for preventing cardiovascular events in patients with acute coronary syndromes (ACS) and those undergoing percutaneous coronary intervention. Nevertheless, limitations of clopidogrel include the requirement for metabolic conversion to its active metabolite, leading to slow onset of its effect, and irreversible binding of the active metabolite to the P2Y12 receptor, which precludes recovery of platelet function as well as generally low and variable levels of platelet inhibition that may be associated with the risk of adverse clinical events. [1-3] The new thienopyridine, prasugrel, is metabolized to its active form more efficiently than clopidogrel and produces higher levels of platelet inhibition but this benefit has been accompanied by an increased risk of major bleeding. [4] Thus, despite the active research on platelet inhibition, the need for more potent and safer antiplatelet agents is still present. Ticagrelor is a new reversible P2Y12 antagonist with favourable pharmacologic characteristics. The results from the first phase III trial evaluating its efficacy and safety are encouraging.

PHARMACOKINETICS-PHARMACODYNAMICS

Ticagrelor (AZD6140) is a member of a new chemical class of antiplatelet agents termed cyclopentyl-triazolopyrimidines (Fig. 1). It is the first oral agent which binds P2Y12 receptor reversibly[5]. Unlike thienopyridines, ticagrelor does not require metabolic conversion to an active form (Table 1).

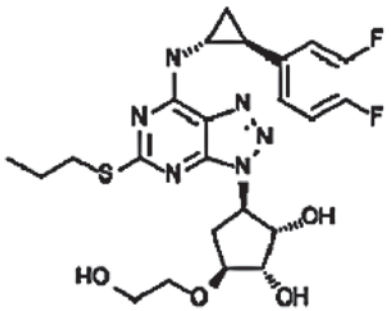

FIGURE 1. Chemical structure of ticagrelor.

The metabolite AR-C124910XX has a similar potency with the parent compound in inhibiting the P2Y12 receptor [6]. AR-124910XX is rapidly formed [time to peak plasma concentration (tmax) 1.3–2 h] by cytochrome P4503A. Both ticagrelor and ARC124910XX are mainly excreted in faeces and renal clearance is of minor importance.[7] Ticagrelor binds rapidly to the P2Y12 receptor[8,9] and notably, this binding was shown to be reversible, with the offset of effect following declining plasma concentrations. In detail, ticagrelor binds to the P2Y12 receptor at a site distinct from the ADP binding site, inhibits ADP-induced receptor signalling in a non-competitive manner with ADP and has greater affinity for the receptor and greater potency in platelet inhibition than thienopyridines such as clopidogrel and prasugrel. Within 30 min, a ticagrelor loading dose of 180 mg resulted in roughly the same level of inhibition of platelet aggregation as that achieved 8 h after a clopidogrel loading dose of 600 mg.[10-12]

Following the administration of 1.0, 3.0, 10, 30, 100, 200, 300 and 400 mg ticagrelor, absorption of the drug was rapid, with the median t_{max} ranging from 1.3 to 2.0 h. The formation of the active metabolite, AR-C124910XX, was also rapid (median

TABLE 1. Basic characteristics of P2Y12 inhibitors

	Ticagrelor	Prasugrel	Clopidogrel
Drug nature	The first of a new class of orally active non-thienopyridine antiplatelet agents: cyclopentyltriazolopyrimidines	3rd generation thienopyridine	2nd generation thienopyridine
Mechanism of action	Reversible inhibitor of the adenosine diphosphate (ADP) P2Y12 receptor	Irreversible inhibitor of the adenosine diphosphate (ADP) P2Y12 receptor	Irreversible inhibitor of the adenosine diphosphate (ADP) P2Y12 receptor
Active substance drug/metabolite	Both drug and its metabolite are active	Drug is inactive and needs to be metabolized to active metabolites	Drug is inactive and needs to be metabolized to active metabolites
Time to achieve maximum platelet inhibition or maximum plasma concentration	After loading dose 180 mg the maximum plasma concentrations and maximum platelet inhibition are reached in 1–3 h	After loading dose 60 mg the maximum 60-70% platelet inhibition is usually achieved 2-4 h, maximum plasma concentrations of active metabolite is reached within 0.5 h	After loading dose 600 mg the maximum plasma concentrations is achieved in 1 h and maximum platelet inhibition is within 2–3 h
The mean elimination half-life	The mean elimination half-life is 6 to 13 h (dose independent)	The mean elimination half-life of active metabolite is 3.7 h	After a single of 75 mg dose half-life is approximately 6 h. The elimination half-life of the inactive acid metabolite is 8 h after single and repeated dose
Elimination	No specific data	Approximately 70% of prasugrel metabolites are eliminated by the kidney	Approximately 40% of a 75 mg dose is excreted in urine and 35–60% is excreted in faeces

t_{max} 1.5–3.0 h) At doses ≥30 mg, the mean t½ was 7.1–8.5 h for ticagrelor and 8.5–10.1 h for AR-C124910XX. The inhibition of ADP-induced platelet aggregation, as assessed by optical aggregometry, was found to be dose-related following a single oral dose of ticagrelor demonstrated a rapid (by 2 h), dose-related (up to 100 mg ticagrelor) and almost complete final-extent inhibition of platelet activation [IPA] (at doses of ≥100 mg); the IPA did not increase further at doses >100 mg due to near complete inhibition). No marked inhibition of platelet aggregation was observed at ticagrelor doses <30 mg. The ticagrelor-mediated IPA was reversible, since a lessening of inhibition, based on observed decreases in IPA from peak levels, was evident by 12 and 24 h after dosing as active moiety concentrations were reduced in the plasma. Following a single oral dose of ticagrelor, the pharmacokinetics of ticagrelor and its metabolite were linear.[13]

In animal models, ticagrelor was compared with a chemical compound indistinguishable from the active metabolite of prasugrel, and it exhibited greater affinity for the P2Y12 receptor and greater potency in inhibiting ADP-induced receptor signaling/aggregatory response. The difference in pharmacodynamics in terms of binding irreversibility indicates a greater separation between antithrombotic effect and bleeding effect for the reversible inhibition.[14]

The ONSET/OFFSET Study was designed to determine the onset and offset of the antiplatelet effect of ticagrelor with the PLATO trial dose compared with high-loading-dose clopidogrel and placebo in stable patients with coronary heart disease given background aspirin therapy. A total of 23 patients were randomized in a double-blind fashion to clopidogrel (600 mg loading dose, 75 mg/day maintenance dose), ticagrelor (180 mg loading dose, 90 mg twice a day maintenance dose), or placebo for six weeks. A 10-day drug-offset period followed. Several platelet aggregation parameters were assessed such as: platelet aggregation induced by ADP (20 and 5 μmol/L), collagen 2 μg/mL, and arachidonic acid 2 mmol/L in platelet-rich plasma, platelet aggregation in whole blood, ADP-stimulated (5 μmol/L, final concentration) expression of glycoprotein, IIb/IIIa receptors and P-selectin. Moreover, measurement of vasodilator-stimulated phosphoprotein phosphorylation (VASP-P) was performed which is a method of quantifying P2Y12 receptor reactivity and reflects the extent of P2Y12 receptor blockade.

The primary end point for onset was IPA (20 μmol/L ADP, final extent) at 2 hours after the first dose; for offset, it was the slope of IPA between 4 and 72 hours after the last dose of study drug. Secondary pharmacodynamic end points were IPA (final and maximal extent), measured by 5- and 20-μmol/L ADP– and 2μg/mL collagen–induced light-transmittance aggregometry, ADP induced glycoprotein IIb/IIIa and P-selectin expression along with other sophisticated aggregation indices. The primary end point for onset, IPA at 2 hours after loading was greater for ticagrelor than for clopidogrel (88% vs 38%, p=0.0001). In fact, within 1 hour of ticagrelor loading, IPA was greater than the maximum IPA achieved after clopidogrel loading. The mean time to maximum IPA in the ticagrelor group was 5.8 hours less than that required for clopidogrel. The rate of onset (slope) of the antiplatelet effect curve from 0 to 2 hours after the loading dose was also greater in the ticagrelor group (43.57 versus 19.45 IPA %/h, p=0.0001). By 2 hours after loading, a greater proportion of patients receiving ticagrelor achieved >50% IPA (98% vs 31%, p=0.0001) and >70% IPA (90% vs 16%, p=0.0001).

At the end of the 6 weeks of treatment, IPA was significantly higher in the ticagrelor group. The ticagrelor group had significantly lower IPA at 72 and 120 hours after the last dose (p<0.05), and the IPA did not differ thereafter between the groups. The rate of offset (slope) of the antiplatelet effect curve from 4 to 72 hours after the last dose, which was the primary end point for offset, was greater in the ticagrelor than in the clopidogrel group (-1.04 vs -0.48 IPA %/h, p<0.0001). IPA for ticagrelor on day 3 after the last dose was comparable to that for clopidogrel at day 5 and IPA on day 5 for ticagrelor were similar to clopidogrel on day 7 and did not differ from placebo. Bleeding rates were greater with ticagrelor administration (28% vs 13%) but no major haemorrhages were noted in the study. [12]

CLINICAL STUDIES

The DISPERSE (Dose confirmation Study assessing anti-Platelet Effects of AZD6140 vs clopidogrel in non–ST segment Elevation myocardial infarction)-2 trial was a randomized, double-blind, double-dummy trial conducted to assess the safety, tolerability, and initial efficacy of AZD6140 plus aspirin in comparison with clopidogrel plus aspirin in patients with non–ST-segment elevation ACS. A number of 990 eligible patients were randomized to receive AZD6140 90 mg or180 mg twice daily, subrandomized to receive or not an initial loading dose of 270 mg, or clopidogrel 300 mg followed by 75 mg once daily for up to 3 months, in a 1:1:1 double-blind manner.

The primary end-point, major or minor bleeding at 4 weeks, was not different among the 3 groups (9.8% vs 8.0% vs 8.1%, p=0.43 and p= 0.96 vs. clopidogrel, respectively). No statistical significance was noted in the differences of the rates of "major - fatal/life-threatening" bleeding or "major - other" bleeding. Major bleeding in the first 48 hours, reflecting the effect of the loading doses, was also not statistically significant among all groups. Moreover, the rates of death and cardiovascular death were similar between clopidogrel and ticagrelor treated patients although the small number of clinical events did not allow reliable conclusions regarding the efficacy of AZD6140 versus clopidogrel to be extracted. Notably, a numerically lower rate of bleeding in ticagrelor receiving patients undergoing CABG between 1 and 5 days after stopping study

drug was observed, which could be attributed to a recovery of platelet function due to the reversible binding of AZD6140 to the P2Y12 receptor.[15]

The PLATelet inhibition and patient Outcomes (PLATO) trial was a phase III multicenter, double-blind, randomized trial comparing ticagrelor with clopidogrel on top of aspirin treatment, in patients admitted to the hospital due to an ACS with or without ST segment elevation. Ticagrelor was given at a loading dose of 180 mg followed by a dose of 90 mg twice daily. Clopidogrel was administered at a 300-mg loading dose followed by a dose of 75 mg daily. Patients undergoing PCI after randomization received, in a blind fashion, an additional dose of their study drug at the time of PCI, i.e. 300 mg of clopidogrel, at the investigator's discretion, or 90 mg of ticagrelor for patients who were undergoing PCI more than 24 hours after randomization. In patients undergoing CABG, it was recommended that the study drug be withheld — in the clopidogrel group, for 5 days, and in the ticagrelor group, for 24 to 72 hours. Treatment continued for up to 12 months and the patients were followed at 1, 3, 6, 9 and 12 months.

These medications were compared over the primary efficacy end point of time to first occurrence of death from vascular causes, myocardial infarction, or stroke. The principal secondary efficacy end point was the primary efficacy variable studied in the subgroup of patients for whom invasive management was planned at randomization while other composite end points served as additional secondary end points evaluated in the whole study population. The primary safety variable was major bleeding as defined in the study protocol. Over 18000 patients were enrolled and the primary efficacy end point incidence was significantly lower in the ticagrelor than in the clopidogrel group (9.8% vs. 11.7% at 12 months $p<0.001$). This difference was apparent within the first 30 days of therapy and persisted throughout the study period. The secondary efficacy variables also occurred less often in the ticagrelor treated patients, as did the individual components of death from vascular causes and myocardial infarction, but not of stroke. These beneficial effects were seen in both ST elevation and non-ST elevation ACS group of patients and they were independent of the invasive or non-invasive strategy planned. However, in the small cohort of patients from North America (n = 1,814) ticagrelor was not found superior to clopidogrel, a finding likely being related to the small sample size.

No statistically significant differences were noted in terms of major, life-threatening or fatal bleeding. Hemorrhagic complications related to by-pass surgery were similar in frequency, but those not related to by-pass surgery were higher in rate in the ticagrelor group, estimated either according to the study criteria (4.5% vs. 3.8%, p = 0.03) or the TIMI criteria (2.8% vs. 2.2%, p = 0.03). Ticagrelor was also associated with more episodes of intracranial bleeding (26 [0.3%] vs. 14 [0.2%], p = 0.06), including fatal intracranial bleeding (11 [0.1%] vs. 1 [0.01%], p = 0.02) although with fewer episodes of other types of fatal bleeding (9 [0.1%], vs. 21 [0.3%]; p = 0.03). [16]

In 13408 of the patients recruited in the PLATO trial, an invasive therapeutic approach was chosen. In this particular group, in accordance with the whole study population, the primary and secondary composite endpoints occurred in a smaller proportion of patients randomized on ticagrelor than clopidogrel (primary end point: 9% vs 10.7%, p=0.0025). Rates of death resulting from cardiovascular causes and of myocardial infarction were lower in the ticagrelor group, whereas rates of stroke did not differ between the groups. Total mortality rate was significantly reduced in the ticagrelor versus the clopidogrel group (3.9% vs 5.0%, p=0.0103). As far as safety endpoints are concerned, non by-pass surgery-related major or minor bleeding was the only significantly different variable, with ticagrelor associated with more haemorrhagic complications (8.9%7.1%, p=0.0004). [17]

NON-BLEEDING ADVERSE EFFECTS

Non-bleeding side effects were only seldom observed in all clinical trials. Interestingly, dyspnea was quite frequent. In ONSET/OFFSET trial dyspnoic phenomena attributed to the drug occurred in 25%, 4%, and 0% of patients in the ticagrelor, clopidogrel, and placebo groups, respectively (ticagrelor versus clopidogrel p=0.01). Three patients in the ticagrelor group stopped the study drug due to dyspnea. In the DISPERSE trial nonspecific symptoms, such as headache, were common. Nausea, dyspepsia, and hypotension seemed more common among ticagrelor recipients as was dyspnea (Table 2). Of those who reported dyspnea, 27% of the patients had resolution of this symptom within 24 h, 25% had resolution of the dyspnea after 24 h and 48% experienced persistent symptoms during treatment (>15 days). As expected, PLATO trial confirmed this observation. Dyspnea was more common in the ticagrelor group than in the clopidogrel group (13.8% vs 7.8%). An immune-mediated mechanism has been proposed to explain this adverse reaction. Although this suggestion has been contradicted, it seems that the immune conflict between the hostile platelet receptors subjected to the reversible blockade by the antiplatelet agent may lead to mild episodes of thrombotic thrombocytopenic purpura and consequent fluid retention contributing to dyspnea. Furthermore, as an ATP modified molecule, AZD 6140 can be metabolized to adenosine and cause bradycardia or trigger dyspnea especially in cases of airway hyper-reactivity.[18]

In the same study, there was also a higher incidence of ventricular pauses in the ticagrelor group in the first week, but not at day 30. Pauses were rarely associated with symptoms and the two treatment groups were not significantly different in terms of the incidence of syncope or the pacemaker implantation rate. Ticagrelor intake was associated with a mild increase in creatinine and uric acid levels.[18,19]

Table 2. Non-hemorrhagic adverse effects (data from the ADVERSE trial)

	Clopidogrel n=327	Ticagrelor 90 mg bid n=334	P value vs clopidogrel	Ticagrelor 180 mg bid n=323	P value vs clopidogrel
Dyspnea	21 (6.4%)	35 (10.5%)	0.07	51 (15.8%)	<0.0002
Chest pain	29 (8.9%)	25 (7.5%)	0.57	24 (7.4%)	0.57
Headache	28 (8.6%)	32 (9.6%)	0.69	21 (6.5%)	0.37
Nausea	11 (3.4%)	22 (6.6%)	0.07	21 (6.5%)	0.07
Dyspepsia	9 (2.8%)	16 (4.8%)	0.22	10 (3.1%)	0.82
Insomnia	9 (2.8%)	18 (5.4%)	0.12	15 (4.6%)	0.22
Diarrhea	11 (3.4%)	10 (3.0%)	0.83	24 (7.4%)	0.02
Hypotension	2 (0.6%)	14 (4.2%)	0.004	12 (3.7%)	0.01
Dizziness	10 (3.1%)	14 (4.2%)	0.53	11 (3.4%)	0.83
Syncope	2 (0.6%)	4 (1.2%)	0.69	5 (1.5%)	0.28
Rash	2 (0.6%)	3 (0.9%)	1.00	6 (1.9%)	0.17

CONCLUSION

Ticagrelor is a novel non-thienopyridine inhibitor of the P2Y12 ADP platelet receptor, which binds reversibly to its ligand allowing platelets to almost fully regain their activity within 3 days after therapy discontinuation. It also achieves rapid onset of action due to its rapid absorption and pharmacokinetics and is a powerful antiplatelet agent, more potent than the well-established thienopyridine clopidogrel. Initial studies as well as the large phase III PLATO trial have shown that ticagrelor use in acute coronary syndromes is associated with better outcomes with respect to all cause mortality, cardiovascular death and myocardial infarction, without a concomitant increase in major bleeding complications with the exception of intracranial hemorrhage which was more frequent although the absolute numbers were small. The relatively rapid cessation of ticagrelor's action after its withdrawal would make it suitable in cases where an open-heart surgery is anticipated. However, by-pass surgery related bleeding showed only a trend towards reduction with ticagrelor compared to clopidogrel, which did not reach statistical significance. Moreover, extrapolation of the results from PLATO trial to other indications for clopidogrel monotherapy, such as stroke, or peripheral arterial disease, is premature. Ticagrelor's usefulness in patients undergoing elective stenting is also undetermined so far and finally, concomitant use of fibrinolytic agents is another issue that needs to be addressed particularly in view of the associated increase in intracranial bleeding and taking into account that patients undergoing fibrinolysis were excluded from PLATO. Thus, although the results from the initial trials are encouraging, further analyses of the PLATO data may offer more insight into the efficiency of this antiplatelet agent in specific subgroups of patients. More studies both in pharmacogenomics and in of ticagrelor will be necessary before this drug establishes its role in modern antiplatelet therapy.

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