Ticagrelor – out with the old, in with the new?

Ticagrelor (Brilinta) is a new oral antiplatelet medicine, which has been available, fully subsidised, with Special Authority, since 1 July, 2013. Ticagrelor, co-administered with low dose aspirin, is an alternative to clopidogrel for the prevention of atherothrombotic events in patients with acute coronary syndromes. In most cases, ticagrelor will be initiated in hospital and continued for 12 months after discharge.

Ticagrelor (pronounced *tie-kag-re-lore*), co-administered with aspirin as dual antiplatelet treatment, is indicated for the prevention of atherothrombotic events in adult patients with acute coronary syndromes, such as ST elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (NSTEMI). It is anticipated that for the majority of patients, ticagrelor will be initiated in hospital and then continued in the community after discharge. Patients will qualify under the Special Authority criteria (for the subsidised prescription of ticagrelor) whether they are treated with medical management or revascularisation (e.g. percutaneous coronary intervention or coronary artery bypass grafting) for their acute coronary syndrome.[1, 2]

Special Authority criteria for ticagrelor

The Special Authority criteria for ticagrelor are the same for both an initial application for use in a patient with an acute coronary syndrome (valid for 12 months) and for a second application for a subsequent acute coronary syndrome. Applications are able to be made by any relevant practitioner. Both the initial approval and renewal are valid for 12 months.

Prerequisites:

1. Patient has recently* been diagnosed with an ST elevation or non-ST elevation acute coronary syndrome **AND**
2. Fibrinolytic therapy has not been given in the last 24 hours and is not planned

* "Recently" in the context of this Special Authority is acute coronary syndrome diagnosed within a few days or weeks rather than months.

N.B. Some patients in New Zealand have been taking ticagrelor as part of an AstraZeneca product familiarisation programme, and will continue on this programme.

Evidence of the effectiveness of ticagrelor

Evidence of the effectiveness of ticagrelor comes largely from the PLATO trial.[3] This multicentre, randomised, double-blind trial compared ticagrelor with clopidogrel, both used in combination with aspirin, as dual antiplatelet treatment in 18 624 patients with acute coronary syndromes.

Results from the PLATO trial showed that compared to patients taking clopidogrel, those patients taking ticagrelor, had an absolute risk reduction of 1.9% (relative risk reduction of 16% or an NNT of 54) for the combined primary endpoints of myocardial infarction, stroke and death from vascular causes.[3, 5] This further breakdown of the results showed that patients taking ticagrelor and aspirin, compared with patients taking clopidogrel and aspirin, had a significantly lower incidence of:

- Myocardial infarction (5.8% versus 6.9%)
- Death from vascular causes (4.0% versus 5.1%)
- Deaths from any cause (4.5% versus 5.9%)
- Stent thrombosis (in patients receiving a stent during the study period) (1.3% versus 1.9%)

There was no significant difference in the overall incidence of stroke between the two treatment groups. However, there were more haemorrhagic strokes in patients taking ticagrelor than in those taking clopidogrel (23 [0.2%] versus 13 [0.1%]).[3]

The beneficial effects of ticagrelor compared to clopidogrel were detected within the first month of the study and persisted for the length of the trial.[3] There was no significant difference between the treatment groups in the rate of major bleeding (as defined by the study criteria), and in the rate of fatal or life-threatening bleeding. However, there was an increase in major non-CABG related bleeding in the ticagrelor group and a significant increase in the small number of patients who experienced fatal intracranial haemorrhage, compared with patients in the clopidogrel group.[3]

A change in practice for patients with acute coronary syndromes

Until now, the majority of patients with acute coronary syndromes have been prescribed clopidogrel and aspirin. There is evidence, however, from the Platelet Inhibition and Patient Outcomes (PLATO) trial that patients prescribed dual antiplatelet treatment with ticagrelor and aspirin may be at lower risk of ischaemic events and death when compared to patients taking clopidogrel and aspirin (See: "Evidence for ticagrelor").[3] The 2012 New Zealand guidelines for the management of non-ST elevation acute coronary syndromes recommend ticagrelor, rather than clopidogrel, as the preferred antiplatelet medicine.[4]

How does ticagrelor work?

Ticagrelor reversibly inhibits the platelet adenosine diphosphate (ADP) P2Y12 receptors which results in rapid inhibition of platelet activation and aggregation. Clopidogrel also acts on these receptors, however, because it is a "prodrug", the transformation to the active metabolite tends to result in slower and less consistent inhibition of platelets than with ticagrelor.[3, 5] The transformation of clopidogrel to its active metabolite requires the enzyme CYP2C19. Approximately 30–40% of people of Māori, Pacific and Asian ethnicity have reduced function CYP2C19 polymorphisms, compared to 15% of Europeans.[6] Although it is not yet proven, ticagrelor may be of particular benefit, compared with clopidogrel, for people in these ethnic groups (Māori, Pacific and Asian).

Prescribing ticagrelor

Twice daily dosing is required

Treatment with ticagrelor is initiated with a loading dose of 180 mg (two 90 mg tablets), followed by one 90 mg tablet, twice daily, with or without food. The twice daily dosing may mean that ticagrelor is less preferred for patients who have poor compliance with medicines; clopidogrel is dosed once daily.

Ticagrelor should be co-administered with low dose aspirin, e.g. 100 mg daily (see: "Black box warning", opposite). Treatment with ticagrelor is usually continued for 12 months.[2, 4]

No dose reduction is required for older patients or patients with renal or mild hepatic impairment. If a patient requires elective surgery, it is recommended that ticagrelor be stopped five days prior.[7]

FDA black box warning re: ticagrelor and high dose aspirin

The United States Food and Drug Administration (FDA) released a black box warning stating that ticagrelor should not be used concurrently with doses of aspirin of more than 100 mg daily.[8] This warning was placed because sub-group analysis from the PLATO trial suggested that ticagrelor was of less benefit when used with higher doses of aspirin (> 100 mg daily). However, higher aspirin doses are uncommonly used outside of the United States, and the scientific basis for the warning has been challenged recently in the literature.[8, 9]

Contraindications

Ticagrelor is contraindicated in patients with:[2]

- Active bleeding
- History of intracranial haemorrhage
- Moderate to severe hepatic impairment (due to an absence of data)

There is currently no data on the safety of ticagrelor for patients who have had fibrinolytic therapy within the last 24 hours for a STEMI, as these patients were excluded from the PLATO trial. There is also no clinical data on the safety of ticagrelor in patients on renal dialysis, those with moderate or severe hepatic impairment or in children aged under 18 years.

Cautious use is required in selected patients

Ticagrelor should be used with caution in patients who have an increased risk of bleeding, e.g. after recent surgery or trauma, recent gastrointestinal tract bleeding and coagulation disorders.[2] It should also be used with caution in patients taking medicines that may increase their bleeding risk such as NSAIDs,[2] or patients who have asthma or chronic obstructive pulmonary disease (see: "Adverse effects").

Patients with an increased risk of bradycardia were excluded from the PLATO trial because an earlier study had identified an increase in this type of event.[2, 3] Ticagrelor should therefore be used with caution in patients at risk of bradycardia (e.g. patients with sick sinus syndrome, second or third degree AV block) unless a pacemaker is fitted.

Interactions with other medicines

Ticagrelor is metabolised in the liver primarily by the enzyme CYP3A4, a member of the cytochrome P450 group of isoenzymes. Ticagrelor is also a weak inhibitor of CYP3A4 which has implications for patients who are taking other medicines metabolised by CYP3A4, such as simvastatin. It is recommended that patients taking ticagrelor should not be prescribed more than 40 mg of simvastatin daily as ticagrelor has the potential to increase the serum concentration of simvastatin, which may increase the likelihood of adverse effects from the statin.[2, 10] Smaller increases in plasma concentrations of atorvastatin have been found when taken with ticagrelor, however, these increases are not thought to be clinically significant.[2]

Ticagrelor should not be prescribed if the patient is already taking a CYP3A4 inhibitor such as ketoconazole or clarithromycin. Medicines that induce CYP3A4 enzymes, such as carbamazepine, phenytoin and rifampicin should also be avoided.

Ticagrelor also inhibits a transporter protein, p-glycoprotein (P-gp), which can result in an increase in serum concentration of P-gp substrates such as digoxin and ciclosporin.[11] Because digoxin has a narrow therapeutic range, if ticagrelor is initiated plasma digoxin levels should be monitored.

Limited clinical evidence suggests there is no significant clinical interaction between ticagrelor and proton pump inhibitors (PPIs). In contrast, clopidogrel may be less effective when used in combination with some PPIs, e.g. omeprazole.[6, 12]

Adverse effects

Bleeding – As with all antiplatelet medicines, ticagrelor is associated with an increased risk of bleeding. Overall, ticagrelor is not associated with an increased risk of bleeding when compared to clopidogrel although in the PLATO trial there were higher numbers of non-CABG related major bleeds and, although the numbers were small, a significantly higher number of fatal intracranial bleeds.[3]

Dyspnoea – Patients taking ticagrelor have been found to have an increased risk of dyspnoea compared to patients taking clopidogrel. In the PLATO trial, however, only approximately 1% of patients who developed dyspnoea had to discontinue the medicine for this reason.[3, 13] Most episodes of dyspnoea have been reported to be mild or moderate, transient, self-limiting and likely to occur in first month of treatment.[13] The mechanism underlying the development of dyspnoea is currently unknown, however, it does not appear to be due to aggravation of a pre-existing respiratory or cardiac condition. Although a subgroup analysis of the PLATO study did not find a higher risk of worsened dyspnoea in patients with pre-existing dyspnoea or those at increased risk of dyspnoea, e.g. patients with asthma, COPD or congestive heart failure, ticagrelor should be used with caution in these patients.[2]

Elevations in creatinine and urate – Levels of creatinine and urate were significantly increased in patients taking ticagrelor compared to patients taking clopidogrel in the PLATO trial.[3]

Creatinine – It is recommended that renal function is checked after one month of treatment with ticagrelor and as clinically indicated after that. Patients aged over 75 years, those who have moderate or severe renal impairment and those taking an angiotensin receptor blocker (ARB) may be more at risk of an increase in creatinine levels.[2]

Urate – It is recommended that ticagrelor is used cautiously in patients who have a history of hyperuricaemia or gout. The use of ticagrelor in patients who have uric acid nephropathy is not recommended.[2]

Other adverse effects reported include gastrointestinal disturbances (e.g. nausea, vomiting, diarrhoea, dyspepsia, abdominal pain), dizziness, headache, rash and pruritus.[7]

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