Maintenance of platelet inhiBition with cangreloR after dIscontinuation of thienopyriDines in patients undergoing surGEry: The BRIDGE trial

Published: 01-04-2010
Last updated: 03-05-2024

The primary hypotheses in this study is that a cangrelor infusion will maintain target levels of platelet inhibition (> 60% inhibition) after discontinuation of a thienopyridine (clopidogrel or ticlopidine) in patients waiting for surgery.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Coronary artery disorders
Study type	Interventional

Summary

ID

NL-OMON34815

Source
ToetsingOnline

Brief title
BRIDGE

Condition

- Coronary artery disorders

Synonym
platelet inhibition

Research involving
Human

Sponsors and support

Primary sponsor: Medicines Company

Source(s) of monetary or material Support: financiering op basis van contract met industrie

Intervention

Keyword: acute coronary syndrome, CABG, platelet inhibition, thienopyridine

Outcome measures

Primary outcome

The primary endpoint for this trial is maintenance of platelet inhibition in 80% of patient samples above 60% as determined by VerifyNowTM P2Y12 point of care assay measured during cangrelor infusion prior to surgery.

Secondary outcome

The main safety endpoint of the trial is the absence of excessive CABG-related bleeding. Excessive CABG-related bleeding is defined as the ccurrence of the combination of any one of the following 3 components during the CABG procedure through hospital discharge:

• Surgical re-exploration

• 24 hour CT output of >1.5 liters

• Incidence of PRBC transfusions > 4 units

Additional secondary endpoints of this trial are:

• Difference between cangrelor and placebo treatment in term of percentage of total patient samples which maintains at least 60% platelet inhibition as determined by VerifyNowTM P2Y12 point of care assay

• Percentage of patients who maintains at least 60% platelet inhibition in their last ontreatment sample before the surgery.

• CABG-related bleeding (TIMI, GUSTO, ACUITY) up to 7 days post CABG or discharge whichever occurs first.

• All blood product transfusions up to 7 days post CABG or discharge, whichever is sooner.

Additional safety observations will include:

• Incidence of bleeding from randomization until discontinuation of study drug (TIMI, GUSTO, ACUITY)

• Incidence of the combination of the combined ischemic endpoint of death, MI, stroke or need for urgent revascularization within 30 days following surgery

• Incidence of the combined ischemic endpoint of death, MI, stroke or need for urgent revascularization from the time of randomization until discontinuation of study drug.

• Incidence of adverse events and serious adverse events up to 7 days post CABG or discharge whichever occurs first.

Study description

Background summary

Dual antiplatelet therapy with clopidogrel and aspirin reduces clinical ischemic events and improves outcomes for patients with acute coronary syndromes (ACS). However, as both aspirin and clopidogrel are irreversible platelet antagonists that inhibit platelet function for the live of the platelet concerns about bleeding for patients who might require coronary artery bypass grafting (CABG) have limited adoption of upstream dual anti-platelet therapy. Also, as current ACC/AHA and Society of Thoracic Surgeons (STS) guidelines recommend cessation of clopidogrel before non-emergent cardiac surgical procedures in order to minimize bleeding risks length of stay is also potentially impacted by the choice of initiating clopidogrel at presentation.

On the other hand, while there are risks associated with early initiation of irreversible antiplatelet therapy in ACS patient requiring surgical revascularization suggest that there is also a benefit of P2Y12 inhibition in terms of decreased thrombotic events prior to CABG. Therefore, even though clopidogrel treatment prior to CABG does increase bleeding to its irreversibility, platelet P2Y12 inhibition does appear to prevent ischemic events in patients requiring CABG.

There are other clinical situations in which the ability to maintain adequate P2Y12 inhibition with rapid reversibility would be desirable. For instance, patients with indwelling drugeluting stents are maintained on aspirin and clopidogrel to prevent stent thrombosis. Should these patients require a surgical procedure, cessation of clopidogrel increases the risk for ischemic events or stent thrombosis, while maintaining irreversible platelet inhibition with aspirin and a thienopyridine leads to unacceptable operative bleeding risk. Additionally, cessation of clopidogrel may increase the incidence of ischemic events in the short-term due to a *rebound* effect of platelet activation. Currently, no short-acting platelet inhibitors are available which allow maintenance of platelet inhibition before surgery without increasing bleeding complications at the time of surgery. Potentially, effective platelet inhibition with an ultra short-acting platelet inhibitor during the period of clopidogrel withdrawal may protect patients from ischemic events and cangrelor also preserve normal hemostasis at the time of surgery. We hypothesize that the reversible, ultra short-acting P2Y12 platelet inhibitor cangrelor may be a safe and effective drug to bridge patients from the irreversible platelet inhibitors clopidogrel or ticlopidine to the time of surgery.

Study objective

The primary hypotheses in this study is that a cangrelor infusion will maintain target levels of platelet inhibition (> 60% inhibition) after discontinuation of a thienopyridine (clopidogrel or ticlopidine) in patients waiting for surgery.

Study design

This study will be a Phase II, prospective, randomized, double-blind, multi-center trial in patients who discontinue thienopyridine and are undergoing non-emergent coronary artery bypass grafting (CABG). The trial will consist of two stages.

Stage I: Open label lead-in period:
Cangrelor IV infusion, will be administered to cohort of 5 patients at a time in a step-wise fashion at pre-determined doses (0.5 µg/kg/min, 0.75 µg/kg/min, 1.0 µg/kg/min and 1.5 µg/kg/min) until percent platelet inhibition as measured by VerifyNowTM P2Y12 is > 60% in 80% of samples or a dose of 2.0 µg/kg/min is

reached.
The first set of patients will receive an infusion of 0.5 µg/kg/min. If platelet inhibition as measured by VerifyNowTM P2Y12 is not > 60%, in greater than 80% of patient samples the second set of 5 patients will be administered a 0.75 µg/kg/min IV infusion. If platelet inhibition as measured by VerifyNowTM P2Y12 is again not consistently > 60%, the third set of 5 patients will be administered a 1.0 µg/kg/minute infusion, followed by a fourth set of 5 patients who will receive a 1.5 µg/kg/minute infusion, if needed. If platelet inhibition as measured by VerifyNowTM P2Y12 is still <= 60% the decision will be made to use a 2.0 µg/kg/min.

Stage II: Blinded, randomized period:
A single infusion dose of cangrelor or matching placebo ranging from 0.5 µg/kg/min to 2.0 µg/kg/min IV infusion (depending on the results of the Stage I evaluation) or matching placebo.
Up to 200 patients will be randomized at approximately 30 centers globally. Informed consent will be obtained from patients meeting the inclusion criteria before the initiation of any study specific procedures. Eligible patients will be randomized to receive cangrelor plus standard of care (SOC) versus placebo plus SOC in a 1:1 ratio.
Patients will be randomized into two arms, to enroll concurrently. In the first arm, patients will receive only standard of care, in which the thienopyridine is discontinued after the need for surgery has been determined and a placebo infusion is administered. In the second arm, a cangrelor infusion will be started in addition to SOC when the thienopyridine has been discontinued after the need for surgery has been determined. The infusions (cangrelor or matching placebo) will continue throughout the pre-operative period. It is recommended that patients wait 5 days after discontinuation of clopidogrel before undergoing surgery (in accordance with ACC/AHA and STS guidelines), but the timing of surgery will be left to the discretion of the investigator with an allowed maximum of 7 days of infusion. The Data Safety Monitoring Board (DSMB) chairman will perform a dose confirmation analysis following enrollment of the first 20 patients in Stage II.

Intervention

not applicable

Study burden and risks

Seven Phase I, five Phase II and two Phase III studies have been completed to date, in which approximately 7600 subjects were exposed to cangrelor. The main risk associated with anti-platelet therapy is bleeding. Preclinical studies demonstrated renal toxicity in rats when administered by IV infusion at a dose of 25 µg/kg/min for 1 month or in dogs administered at the dose of 60 µg/kg/min

for 1 week. The histopathological changes were, however, completely reversible in animals one-month after cessation of similar cangrelor infusions. The early signs of renal toxicity can be monitored (increase in plasma serum creatinine levels) before histopathological changes are observed. Relevant risks and benefits of cangrelor are fully described in the cangrelor Investigator Brochure (cangrelor Investigator*s Brochure, 2010).

Contacts

Public
Medicines Company

8 Sylvan Way
NJ 07054 Parsippany
US
Scientific
Medicines Company

8 Sylvan Way
NJ 07054 Parsippany
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Provide written informed consent before initiation of any study related procedures.
2. Be at least 18 years of age.
3. Anticipate non-emergent coronary artery bypass graft (CABG) surgery, either *onpump* or *off-pump,* no sooner than 48 hours from randomization but no longer than 7 days from

randomization, with patient to remain hospitalized until planned CABG.
4. Have received a thienopyridine (at least 75 mg of clopidogrel or 500 mg ticlopidine) within 48 hours prior to enrollment in the study for the treatment of an acute coronary syndrome or as long-term preventative therapy following drug-eluting stent treatment.

Exclusion criteria

1. Confirmed of suspected pregnancy (if woman of child-bearing potential) or lactating females
2. Cerebrovascular accident within one year
3. Intracranial neoplasm or history of intracranial surgery
4. History of bleeding diathesis
5. Thrombocytopenia (platelet count of less than 100,000/µL)
6. Known International Normalized Ratio (INR) greater than 1.5 at screening.
7. Requirement for dialysis treatment (hemodialysis or peritoneal)
8. Estimated Glomeular filtration rate eGFR <30 ml/min
9. Administration of abciximab within 24 hours of randomization or administration of eptifibitide or tirofiban within 12 hours of randomization.
10. Plans to continue oral anticoagulant, thienopyridine or GPIIb/IIIa antagonist therapy in the pre-operative period.
11. Need of planned concomitant valvular heart surgery
12. Refusal to receive blood transfusion
13. Receipt of fibrinolytic therapy in the 12 hours preceding randomization
14. Allergy, hypersensitivity, or contraindication to cangrelor, mannitol, sorbitol, or microcrystalline cellulose
15. High likelihood of being unavailable for follow-up
16. Participation in other clinical research studies involving the evaluation of other investigational drugs or devices within 30 days of randomization
17. Any disease or condition which, in the judgment of the investigator, would place the patient at undue risk by being enrolled in the trial

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)

Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-12-2010
Enrollment:	50
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cangrelor for injection
Generic name:	Cangrelor

Ethics review

Approved WMO Date:	01-04-2010
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	20-09-2010
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-10-2010
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-01-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United

(Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2008-001135-35-NL
CCMO	NL31843.100.10