VIA MEDICA

INVITED EDITORIAL

Piotr Adamski, Małgorzata Ostrowska

Department of Cardiology and Internal Medicine, *Collegium Medicum*, Nicolaus Copernicus University, Bydgoszcz, Poland

Bentracimab — a breakthrough for patients treated with antiplatelet agents?

Ticagrelor is a potent P2Y12 receptor inhibitor which reduces rates of major cardiovascular events in patients with the acute coronary syndrome (ACS) or previous myocardial infarction (MI) [1, 2]. It is recommended in both invasively and conservatively treated patients with ACS, and typically should be administered for 12 months after ACS [3]. Ticagrelor is also recommended in secondary prevention beyond one year after MI in patients without bleeding during the initial 12 months of dual antiplatelet therapy with aspirin [3]. According to data from registries use of ticagrelor in patients with ACS is continuously growing, although it is still prescribed less often than clopidogrel, an older P2Y12 receptor inhibitor with inferior recommendations in ACS [4].

The strong antiplatelet effect provided by ticagrelor limits thrombotic complications and improves prognosis in patients with coronary artery disease [1, 2]. On the other hand, ticagrelor increases the bleeding risk. In the PLATO study patients assigned to receive ticagrelor suffered from major and minor bleeding more often than those allocated to clopidogrel (16.1% *vs.* 14.6%, $p = 0.008$). Major bleeding not related to coronary-artery bypass grafting (CABG) (4.5% *vs.* 3.8%, $p = 0.03$), non-intracranial fatal bleeding (0.1% *vs.* 0.3%, $p = 0.03$) and fatal intracranial bleeding (0.1% *vs.* 0.01%, $p = 0.02$) also occurred more frequently in patients receiving ticagrelor than in clopidogrel group. Among patients treated with ticagrelor other bleeding events were also not uncommon: 5.8% suffered life-threatening or fatal bleeding, 8.9% had haemorrhage requiring red-cell transfusion, and 7.4% had CABG-related major bleeding [1]. Although the reduction of ticagrelor maintenance dose to 60 mg twice daily appears to slightly limit the bleeding complications compared with the standard dose (90 mg twice daily), haemorrhagic events on reduced dose are still more frequent compared with clopidogrel [2]. In the PEGASUS-TIMI 54 study patients receiving a reduced dose of ticagrelor suffered from TIMI major bleeding (2.3% *vs.* 1.0%, $p < 0.001$), TIMI minor bleeding (1.2% *vs.* 0.4%, $p < 0.001$), and bleeding requiring transfusion (2.1% *vs.* 0.7%, $p < 0.001$) more often than those in the clopidogrel arm. Importantly, as much as 6.2% of patients treated with reduced ticagrelor dose experienced bleeding leading to discontinuation of treatment as compared to 1.5% in patients on clopidogrel ($p < 0.001$). The TWILIGHT study showed that even though further de-escalation of antiplatelet treatment from ticagrelor-based dual antiplatelet therapy to monotherapy with standard dose ticagrelor reduced the bleeding rates substantially, haemorrhagic events still occurred in patients subjected to this step-down approach. In this study, 4.0% of patients who were randomized to receive ticagrelor 90 mg twice daily with placebo experienced the primary endpoint of BARC type 2, 3, or 5 bleeding, compared with 7.1% seen in the dual antiplatelet therapy arm. Identical proportions between the arms were seen when TIMI minor and major bleeding were compared [5].

As depicted above, bleeding events during treatment with ticagrelor are not infrequent. Various clinical scenarios exist when rapid reversal of its antiplatelet effect would be desired. Apart from active bleeding, a need for urgent surgery would have to be considered as a major indication for platelet function restoration in on-ticagrelor patients [6]. The antiaggregatory effect of oral P2Y12 receptor antagonists lasts for a few days after intake of the last dose. Clopidogrel and prasugrel provide irreversible blockade of platelet P2Y12 receptors,

Corresponding author: Piotr Adamski, Department of Cardiology and Internal Medicine, *Collegium Medicum,* Nicolaus Copernicus University, 9 Skłodowskiej-Curie Str., Bydgoszcz 85-094, Poland; e-mail: piotr.adamski@cm.umk.pl

Medical Research Journal 2023; Volume 8, Number 1, 5–7, 10.5603/MRJ.a2023.0011, Copyright © 2023 Via Medica, ISSN 2451-2591, e-ISSN 2451-4101

thus its action extends to the lifespan of platelets and lasts up to 7 days [7]. Despite the reversible nature of P2Y12 inhibition the antiplatelet effect of ticagrelor also persists for up to 5 days [8]. Therefore, the recommended time of P2Y12 receptor antagonist discontinuation before a non-emergent surgery is 3, 5 and 7 days for ticagrelor, clopidogrel and prasugrel, respectively [3].

Despite the very common use of P2Y12 receptor antagonists, no specific antidotes for these agents are commercially available at the moment. In the past several methods have been proposed to restore platelet function in patients treated with ticagrelor. The most promising of the tested strategies, among others, included platelet transfusion, human albumin supplementation, and haemadsorption [9–23]. However, none of these approaches was ticagrelor-specific or had clinical efficacy verified in a randomized study.

Due to the irreversible blockade of platelet P2Y12 receptors development of antidotes for clopidogrel or prasugrel currently is not very probable. On the other hand, because of ticagrelor's reversible mechanism of action, the recovery of platelet function in patients receiving this antiplatelet agent is more feasible. Bentracimab, the first specific antidote for ticagrelor, and in fact against any antiplatelet agent, is currently under clinical investigation.

Bentracimab, previously referred to as MEDI2452 or PB2452, is an antigen-binding fragment (Fab) characterized by a one-hundred-fold greater affinity for ticagrelor and its active metabolite than for platelet P2Y12 receptors [24]. It is specific for ticagrelor and its major metabolite, binding to both compounds equally. Simultaneously, it does not interact with molecules of similar structure, *i.e.* adenosine, adenosine di- or triphosphate. Reversal of ticagrelor's antiplatelet effect occurs in a concentration-dependent manner and is correlated with the reduction of free ticagrelor concentration [24]. In animal models bentracimab led to complete clearance of ticagrelor and its active metabolite after the first 5 minutes of infusion, which allowed restoration of ADP-mediated platelet aggregation within 60 minutes [25]. The first-in-human evaluation of bentracimab was performed by Bhatt et al. who conducted a single-centre, randomized, double-blind, placebo-controlled, phase 1 trial assessing the safety, efficacy, and pharmacokinetic profile of bentracimab in healthy volunteers [26]. All study participants (n = 64) were pre-treated with ticagrelor for 48 hours before bentracimab infusion. The trial explored various dosing regimens showing that the greater the bolus and duration of infusion were, the more rapid and sustained ticagrelor reversal was. Administration of a 6 g bolus of bentracimab allowed restoration of ticagrelor-inhibited platelet function within 5 minutes from the administration of the antidote. Further 12–16 hours of infusion up to a total dose of 18 g allowed to maintain this effect for 16–24 hours without any rebound effect in platelet reactivity after cessation of bentracimab infusion. Importantly, no dose-limiting toxic effects, infusion-related reactions, deaths, or adverse events leading to hospitalization or discontinuation of bentracimab were observed [26].

Although a full study report is not available yet, some insights from a phase 2b trial assessing the safety and efficacy of bentracimab in reversing the antiplatelet effect of ticagrelor were presented at the American College of Cardiology Annual Scientific Session 2022 [27]. This trial included 205 healthy volunteers pretreated with ticagrelor for 48 hours. The participants were randomized in a 3:1 ratio to receive either bentracimab (n = 154) or placebo (n = 51). In line with the previous study by Bhatt [26], ticagrelor-treated volunteers who received bentracimab had significantly higher platelet aggregation within the first 4 hours of the antidote infusion compared with volunteers receiving a placebo ($p < 0.0001$). Recovery of platelet function occurred in less than 10 minutes after the bolus administration, and like previously no rebound effect was observed after discontinuation of the infusion. This trial confirmed the acceptable safety profile of bentracimab, as no thrombotic events or deaths occurred during 48 hours of follow-up [27].

First data on the clinical efficacy of bentracimab should become available shortly upon completion of the Bentracimab in Ticagrelor-treated Patients with Uncontrolled Major or Life-Threatening Bleeding or Requiring Urgent Surgery or Invasive Procedure (REVERSE-IT) study. It is a currently ongoing phase 3, open-label, single-arm trial including on-ticagrelor patients with uncontrolled major or life-threatening bleeding or requiring urgent surgery or invasive procedure with an expected population of 200 participants. The study is anticipated to finish by the end of the year 2023 [28].

Since oral P2Y12 receptor antagonists have revolutionized the pharmacotherapy of coronary artery disease, clinicians have been struggling with increased haemorrhagic burden in patients receiving these agents. If proven to be effective in the restoration of haemostasis in on-ticagrelor patients with active bleeding or requiring urgent surgery, bentracimab may significantly facilitate the decision of which oral P2Y12 receptor antagonist should be prescribed in various clinical scenarios. The availability of an effective antidote for ticagrelor potentially may increase the number of patients who could benefit from thrombotic risk reduction offered by this agent, simultaneously offering a chance to successfully treat potential bleeding complications.

Conflict of interests: *None.*

Funding: *None.*

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