Tailored antiplatelet therapy in a patient with ITP and clopidogrel resistance

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Dear Sirs,

Antiplatelet therapy is beneficial in acute myocardial infarction (AMI) (1) but interferes with haemostasis increasing bleeding risks (2); thus, it is generally withheld or given at reduced dosage in individuals with haemostatic defects such as idiopathic thrombocytopenic purpura (ITP) (3). Few cases of AMI in ITP have been reported, thus information on bleeding associated with antiplatelet drugs is limited (4).

We present here the case of a 60-year-old man with ST-elevation myocardial infarction (STEMI) and chronic ITP in whom resistance to clopidogrel (5) after percutaneous coronary intervention (PCI) was managed with ticagrelor (6) without bleeding complications.

The patient had a 12-year history of ITP diagnosed with STEMI complicated by cardiac shock secondary to refractory ventricular fibrillation. Circulatory support was achieved by amine infusion and intraaortic balloon pump insertion. A thrombotic occlusion of the right coronary artery was treated by percutaneous coronary intervention (PCI) with thrombectomy (Diver CE, Invatec, Brescia, Italy) and deployment of three zotarolimus-eluting stents; the platelet count at the time was 111 × 10¹²/l. Anticoagulant and antiplatelet therapy during angioplasty included bivalirudin (0.1 mg/kg i. v. bolus and 0.25 mg/kg/hour infusion), lysine acetylsalicylate (250 mg i. v. bolus) and clopidogrel (300 mg loading dose per os). After reperfusion, circulatory conditions improved and recurrent ventricular arrhythmia was treated with beta-blockers. Tropin-1 peak plasma concentration was 81 ng/ml. Echocardiography revealed akinesia of the inferior and posterior wall (proximal segments), with partial involvement of the posterolateral papillary muscle, but preserved left ventricular systolic function (EF 62%). Post-PCI therapy included daily oral aspirin (100 mg q.d.) and clopidogrel (75 mg q.d.).

Two months before the acute coronary event the patient had initiated treatment with a thrombopoietin receptor agonist (TPO-RA; eltrombopag), given in accordance with current guidelines because corticosteroids and splenectomy had failed to control the thrombocytopenia (7). With this therapy, the platelet count stabilised between 49–86 × 10¹²/l (the latter recorded a few days before the acute episode). After STEMI was diagnosed and PCI was performed, the platelet count increased to 127 × 10¹²/l and reached 146–× 10¹⁰/l when pneumonia was diagnosed 10 days later (►Figure 1A). At this time eltrombopag treatment was discontinued, considering that a) the platelet count had nearly normalised; b) TPO-RA treatment may increase the risk of thrombosis, although evidence in this regard is anecdotal and not definitive (8, 9) (of note, this patient developed AMI two months after initiating eltrombopag); and c) an enhanced risk of cardiovascular mortality has been observed in patients with pneumonia (10). Moreover, because resistance to clopidogrel increases the risk for ischaemic recurrences after an acute cardiovascular event (5, 11), we directly evaluated the level of P2Y12 ADP receptor inhibition in the patient platelets measuring P2Y12-mediated phosphorylation of VASP (vasodilator-stimulated phosphoprotein) by flow-cytometry (12). This test provides a platelet reactivity index (PRI) that is inversely related to the extent of P2Y12 receptor inhibition (13). Different methods have been used to monitor the antiplatelet effect of clopidogrel and the merits of each have been debated (14). Nonetheless, it is generally accepted that VASP-PRI results correlate well with ADP-induced aggregation in gauging clopidogrel antithrombotic activity (15) and are more selective than the latter as a specific measure of P2Y12 target effect (16). A VASP-PRI value <69–48% has been associated with a better clinical outcome post-PCI (17, 18). In the propositus, the PRI was 85% after 10 days of clopidogrel treatment, signalling resistance to the drug; this was confirmed by presence of the CYP2C19*2 genotype associated with poor cardiovascular outcomes (19, 20). Considering the severity of the ischaemic attack, complicated by cardiac arrest, and the heightened thrombotic risk associated with ITP (21, 22), the patient – who at the time had a normal platelet count (143 × 10¹²/l) - was switched from clopidogrel to ticagrelor (90 mg b.i.d.) (6).

After nine days the PRI dropped to 2%, indicating a profound P2Y12 functional inhibition, but the platelet count decreased from 104 × 10¹²/l to 23 × 10¹²/l, a level at which serious bleeding may occur. Thus, ticagrelor was stopped for one day and corticosteroids were tapered in with the goal of increasing the platelet count to at least 50 × 10¹²/l. When platelets were below this limit, rather than risking stent thrombosis after stopping full antiplatelet therapy, we opted for halving ticagrelor daily dose to 45 mg b.i.d.; nonetheless, as confirmed by re-
peated measurements, the VASP PRI value remained below the more stringent 48% target cut-off value (17, 18), as desired (Figure 1A). The inhibitory effect observed with low-dose ticagrelor was not surprising, based on the results of earlier pharmacokinetics studies in healthy volunteers that showed inhibition of platelet aggregation with single daily doses of 100–400 mg; moreover, with a dose of 50 mg b.i.d. (essentially the same we used) ticagrelor has been shown to inhibit aggregation not less than the standard 75 mg q.d. of clopidogrel (23). This notwithstanding, evaluation in other suitable patients and in relation to clinical outcome is necessary before recommending for more general use the antiplatelet treatment we adopted in this case – i.e. decreasing the ticagrelor dose to half that suggested by guidelines when a bleeding risk such as thrombocytopenia develops. During treatment with ASA plus ticagrelor, platelet inhibition was monitored with additional tests including ADP-induced platelet aggregation (Figure 1B) and thrombus volume measurement in flowing blood exposed to fibrillar collagen type I (24). The results of these tests were all consistent with...
significant inhibition of platelet function (►Figure 1C).

Twelve months after discharge the patient suffered one episode of epistaxis; on the occasion, the platelet count was 19 × 10^9/L. At this time, one year after PCI, ticagrelor was discontinued according to guidelines (25) and antiplatelet treatment continued with ASA alone. To date, 17 months after discharge, the patient remains free of complications.

Conclusions

Despite the thrombocytopenia, ITP patients have a greater risk of venous (22) and arterial (21) thrombosis than the general population, increasing with age, after splenectomy (26) and coexisting risk factors such as family history, diabetes, hypertension and dyslipidaemia (all present in our patient). Coronary artery thrombosis has been reported in ITP not only after platelet count increase following intravenous IgG (27), corticosteroids or TPO-RA (28) treatment, but also in patients with platelets as low as 2 × 10^9/L (29, 30). Thus, acute coronary events in ITP should be treated according to standards of care (4), but in most reported cases antiplatelet drugs have been administered only for a short duration and typically after PCI with bare-metal stents (4, 30). However, because of multiple thrombosis risk factors – including use of TPO-RA at the time of AMI and a platelet count of 111 × 10^9/L in subsequent days – we opted for treating our patient with drug-eluting stents (DES) (4) and 12-month dual antiplatelet therapy. Laboratory support proved crucial in this case, quickly evidencing the lack of response to clopidogrel and providing relevant information on platelet number and function during administration of the potent anti-P2Y12 drug, ticagrelor, in alternative to clopidogrel. In this regard, whenever the platelet count fell below 50 × 10^9/L, which happened repeatedly over the first 100 days of treatment, the dose of ticagrelor was halved (►Figure 1A). Nonetheless, the VASP PRI consistently remained below the stringent limit (48%) associated with significant reduction of stent thrombosis (17). Admittedly, no definitive recommendations can be drawn from a single case, but the lack of thrombotic and bleeding complications in the patient presented here indicate that ticagrelor may be a valid anti-thrombotic treatment option in ITP patients. Half the recommended 90 mg twice daily seems adequate for antithrombotic protection when platelet counts are severely reduced (< 50 × 10^9/L), with the advantage over thienopyridines of a more rapid reversibility of anti-platelet action in case of severe haemorrhagic complications. In conclusion, with the support of frequent platelet count and function monitoring, it is possible to balance antithrombotic efficacy and bleeding risk in critical ITP patients benefiting from full antithrombotic treatment.

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Conflicts of interest

None declared.

References


