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Case Report

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Hypersensitivity to ticagrelor and low response to clopidogrel: a case report

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Ticagrelor is widely used to treat acute coronary syndrome. Hypersensitivity reaction of ticagrelor is rarely recognized. A low response to clopidogrel, which occurs in up to 23% of patients, is an independent risk factor for stent thrombosis. Management of patients with a low response to clopidogrel and ticagrelor hypersensitivity who are undergoing antithrombotic therapy remains to be a challenge. Herein, we report a patient with low response to clopidogrel and ticagrelor hypersensitivity, who was successfully managed using aspirin and warfarin.

Key words: Antiplatelet therapy; Hypersensitivity; Low response; Ticagrelor; Clopidogrel; Warfarin

INTRODUCTION

Ticagrelor is generally tolerated in most patients with acute coronary syndrome. It is, in most cases, recommended, especially in those with a low response to clopidogrel. A low response to clopidogrel is an independent risk factor for stent thrombosis [1]. Management of antithrombotic therapy in patients with low response to clopidogrel and ticagrelor hypersensitivity remains to be a challenge. Herein, we report such a patient who was successfully managed with aspirin and warfarin.

CASE REPORT

A 68-year-old male developed pruritic and exanthematous eruptions over a 24-hour period. He had a history of angina for the past 6 months, and he underwent elective percutaneous coronary intervention in the left anterior descending artery and left circumflex artery on June 24, 2015. Three drug-eluting stents were inserted (2 paclitaxel eluting stents, YINYI Biomedical Materials R&D Center Co., Ltd., Liaoning, China; and 1 sirolimus eluting stent, Lepu Medical Technology Co., Ltd., Beijing, China). All 3 stents were made of 316L stainless steel. Moreover, he also had a previous history of hypertension and hypercholesterolaemia. He had no history of prior drug allergy.

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Drugs included aspirin, ticagrelor, bisoprolol, and rosuvastatin. He has taken aspirin, bisoprolol, and rosuvastatin for the last 5 months, showing a good tolerance. After taking ticagrelor for 2 days, he developed pruritic and maculopapular rash on his bilateral costal margin, which was then generalized to the trunk (predominantly affected the chest and abdomen). His extremities were not affected, with no angioedema, no fever, and no arthralgia.

The laboratory test result showed an elevation in the leukocyte count (11.4 $\times 10^9$/L) and in the neutrophil count (8.21 $\times 10^9$/L). The lymphocyte count was 1.72 $\times 10^9$/L and the eosinophil count was 0.58 $\times 10^9$/L. The liver function test results were as follows: alanine aminotransferase, 14 U/L; aspartate aminotransferase, 27 U/L; total protein, 61.9 g/L; albumin, 40.2 g/L; total bilirubin, 36.8 μmol/L; direct bilirubin, 5.59 μmol/L; γ-glutamyltranspetidase, 61 U/L; total bile acid, 0.9 μmol/L; and lactate dehydrogenase, 380 U/L.

He showed to have a hypersensitive reaction to ticagrelor, and he was treated with antihistamines. Ticagrelor was switched to clopidogrel. Soon thereafter, his rash was gradually improved.

However, 10 days later, he developed severe chest pain and received emergency coronary angiogram. Subacute definite stent thrombosis was confirmed, and thrombectomy was performed. After the procedure, a platelet function test was conducted, revealing a low response to clopidogrel.

To achieve therapeutic platelet aggregation inhibition, ticagrelor was reused under close supervision. Within approximately 2 hours, he developed generalized maculopapular rash in the whole trunk, which was resolved with intravenous corticosteroids. Ticagrelor was discontinued to avoid further hypersensitive reaction. Our patient showed delayed-type hypersensitivity reaction from the use of ticagrelor, represented in the form of generalized maculopapular rashes. Ticagrelor desensitization might not be appropriate for this patient.

Switching to other kinds of P2Y12 receptor antagonist antiplatelet drug was considered. Drugs that are structurally different from ticagrelor may be a good substitute for those with ticagrelor hypersensitivity. The chemical class of ticagrelor is cyclopentyl-triazolo-pyrimidine, and the other chemical class consists of thienopyridines (clopidogrel, prasugrel, ticlopidine) [2]. This patient presented a low response to clopidogrel and had suffered subacute in-stent thrombosis. Currently, prasugrel has not been approved for use in China. Ticlopidine has been associated with toxic side effects, such as rash, severe neutropenia, diarrhea, and thrombocytopenic purpura. Therefore, antithrombotic therapy was significantly difficult in this patient.

The patient ultimately received aspirin and warfarin as an antithrombotic treatment. He was given subcutaneous injection of low molecular weight heparin for 7 days. The regulated dose of warfarin was maintained in between 2 and 3 of the international normalized ratio (INR). During the follow-up period, our patient did not report any discomfort.

DISCUSSION

According to the drug description of ticagrelor, hypersensitive reaction, in the form of rashes, is relatively rare (≥1/1,000, <1/100). According to the Drug Information Portal (U.S. National Library of Medicine), a side effect of rash from ticagrelor was reported in 34 cases by the U.S. Food and Drug Administration. Quinn and Connelly [3] reported the first case of hypersensitive reaction to ticagrelor.

In the present case, the patient suffered pruritus and exanthema rash after taking ticagrelor for 2 days. The rash was improved after discontinuation, with a recurrence upon resumption of ticagrelor. This pattern suggests that our patient was hypersensitive and intolerant to ticagrelor.

Ticagrelor and clopidogrel are both P2Y12 receptor antagonists; however, the chemical structures of these two differ. For patients with ticagrelor hypersensitivity, cross-reactive hypersensitivity might be less likely susceptible to thienopyridines antiplatelet drugs (clopidogrel, prasugrel, and ticlopidine). Ticagrelor is a novel, direct and reversible P2Y12 receptor antagonist. The effectiveness of clopidogrel depends on the activation of an active metabolite by the cytochrome P450 (CYP) system [4]. The effectiveness might be diminished in poor metabolizers [5]. This patient showed a low response to clopidogrel and had suffered stent thrombosis. Continued antiplatelet treatment with clopidogrel is not recommended. Prasugrel is a thienopyridine analogue of clopidogrel. It is a prodrug, which is rapidly metabolized, and is effective in most individuals [6]. Prasugrel might be a substitute for ticagrelor, but currently in the Chinese market, it is unobtainable. Ticlopidine, however, has many side effects, and thus, it has been withdrawn from the market.

Desensitization has been reported as a potential method for allergy treatment [7]. Ticagrelor desensitization can be an alternative therapy for patients with an immediate-type of hypersensitivity. This patient suffered generalized maculopapular

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rashes after taking ticagrelor, showing a delayed-type of hypersensitivity reaction, which is not the usual indication of ticagrelor desensitization.

In this case, the problem was successfully resolved using aspirin and warfarin. Warfarin, as an anticoagulant drug, helps to prevent blood clot formation, and has normally been used to prevent thrombosis and thromboembolism. Since the process of blood coagulation consists of a complex system, clotting factors may play an important role in thrombus formation. Warfarin has been used in antithrombotic treatment for cardia intervention therapy, especially before the development of ticlopidine. Warfarin is now known to be less effective in the prevention of new thromboses in coronary arteries; antiplatelet drugs have commonly been used to prevent clotting in arteries [8]. However, for patients who are intolerant to antiplatelet drugs, warfarin might be an alternative substitute choice. Warfarin has several shortcomings: multi-interactions with commonly used medications and some daily foods; the need to regularly monitor the blood for INR; the possibility of increased ischemia or bleeding risks, among others, due to labile INR [9].

In conclusion, for patients with ticagrelor hypersensitivity and a low response to clopidogrel, warfarin might be a good alternative solution.

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