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Abstract: The anti-IgE Omalizumab may be helpful to treat clopidogrel hypersensitivity without stopping thienopyridine administration in patients requiring continuous antiplatelet therapy after coronary stent placement.

Keywords: Clopidogrel, omalizumab, prasugrel, thienopyridines, ticagrelor, urticaria.

1. INTRODUCTION

Dual antiplatelet therapy (DAPT), usually represented by a thienopyridine (THP) plus aspirin, is a key association in the treatment of acute coronary syndromes and after coronary intra-arterial stent placement [1]. Actually, the family of thienopyridines is composed by three drugs: ticlopidine, clopidogrel and prasugrel. They are powerful inhibitors of adenosine diphosphate (ADP)-induced platelet aggregation because they irreversibly block the ADP-receptor P2Y12 on the surface of platelets [1]. Ideally, in a patient undergone coronary stent placement, the DAPT should be continued for a whole year and more, because the premature withdrawal of DAPT may lead to 3-fold increased risk of thrombotic events, such as stent thrombosis and recurrent myocardial infarction [1]. However, the onset of a hypersensitivity reaction to thienopyridines makes highly problematic the management of these cardiologic patients. Cheema et al. identified 3 different cutaneous patterns of hypersensitivity to clopidogrel, which is the most used thienopyridine in DAPT worldwide [2]. Firstly, there was a major group of patients who have developed a generalized pruritic maculopapular exanthema predominantly affecting the trunk, abdomen and shoulders, then a second group of patients exhibiting a rash limited to localized areas such as neck, face, back, axilla, palm of the hands or soles of the feet and developing in a
focal and symmetrical manner. The last group was a minority of patients who showed widespread urticaria and/or isolated angioedema. Interestingly, all the patterns of cutaneous hypersensitivity, including urticaria, were delayed-type reactions [2], although skin tests may be positive at the immediate reading [2]. Sometimes, hypersensitivity symptoms are so severe that THPs administration needs to be interrupted in 1.5% of patients [3]. The strategies to overcome THP hypersensitivity are mainly three: 1) pharmacological treatment with anti-reactive drugs without stopping clopidogrel administration; 2) drug desensitization; 3) switching thienopyridine, usually clopidogrel, with another thienopyridine or another antiplatelet agent as cilostazol, although the latter is not as efficient as a thienopyridine [3]. Hereby we describe a case of a 72-year-old female patient who had developed severe urticaria following the completion of clopidogrel after a coronary stent placement.

2. CASE REPORT

The patient was a nonsmoker 72-year-old obese diabetic woman with hypertensive, ischemic cardiopathy and hyperuricemia. Because of recurrent episodes of myocardial ischemia, in December 2017, a coronary angiography revealed a 47% stenosis at the middle left anterior descending artery and a 61% stenosis at the distal right coronary artery with sufficient left ventricular performance, so the patient underwent coronary stent placement with medicated sirolimus-eluting stents and started a dual antiplatelet therapy (DAPT) with aspirin 100 mg and clopidogrel 75 mg. After a month of DAPT, she developed an urticarial rash all over her trunk and extremities. In that period, she also consumed allopurinol 300 mg daily, metformin 850 mg at the main lunches, simvastatin 10 mg, furosemide 25 mg daily and a beta-blocker, carvedilol 25 mg daily too. She had already taken aspirin with no side effect, so cardiologists focussed their attention on clopidogrel. They stopped clopidogrel for three days with a slight improvement of urticarial symptoms. They started a pharmacological treatment of urticaria with anti-reactive drugs such as corticosteroids, antihistamines and montelukast as suggested by the Jefferson protocol [4] without stopping clopidogrel administration. According to their ideators, the Jefferson protocol should be conducted for 13-18 days and should induce a pharmacological tolerance to clopidogrel without stopping oral antiplatelet treatment [4] and it has been successfully used by other authors [2]. However, in that patient, after the 5th day, although urticaria seemed to improve, diabetes worsened and the patient started to show psychotic aspects of behavior, being aggressive and refusing any kind of medicine. Therefore, cardiologists switched clopidogrel with prasugrel without any washout period as suggested by other similar experiences in the cardiologic field [5]. The patient did not show any improvement or resolution of urticaria, probably for the cross-reactivity between clopidogrel and prasugrel, due to the similarity of their chemical structures, although cross-sensitivity between clopidogrel and prasugrel seems to occur rarely [2, 5]. Lastly, cardiologists decided to have an allergist consult for starting a desensitization protocol to clopidogrel. As patient needed a 15 days washout period from clopidogrel before desensitization and cardiologists reputed such a recommendation highly hazardous for the patient, so, given our experience about omalizumab use in elderly patients with chronic spontaneous urticaria [6], we suggested cardiologists to administer subcutaneous omalizumab 300 mg once monthly as to treat a chronic spontaneous urticaria in that patient. Previously, omalizumab has been used in drug hypersensitivity to treat insulin allergy [7], which is a true IgE mediated hypersensitivity. Again cardiologists were highly worried by the potential cardiovascular risks linked to the omalizumab administration [8], above all in a cardiopathic patient, and because its use would have been off-label. The US Food and Drug Administration (FDA), after having collected the reported adverse events for omalizumab since January 2004 to January 2011, observed that most of the omalizumab users who have experienced arterial thrombotic events were females aged over 45 years [8]. For that reason, written consent was prepared and the patient accepted to receive omalizumab at the aforementioned dosage. Three days later, the first administration of Omalizumab, the urticarial rash had greatly improved and cutaneous symptoms could be managed with cetirizine 10 mg daily without stopping clopidogrel intake. Omalizumab was continued for 6 months and the patient had completely
interrupted antihistamines compnsuntion because she obtained a good control of urticaria. After 6 months with omalizumab, cardiologists who were still worried for omalizumab cardiovascular side effects suggested to switch clopidogrel with ticagrelor 90 mg, a new antiplatelet agent, to stop omalizumab administration.

Ticagrelor is the first member of a new chemical class of antiplatelet agents called cyclopentyltriazolo-pyrimidines and it can bind reversibly and directly the P2Y12 receptor [9]. Moreover, it shows a chemical structure different from THPs and it has been successfully used as alternative molecule in case of clopidogrel hypersensitivity [3, 10]. A graded challenge test with ticagrelor was performed the day after having interrupted clopidogrel, and ticagrelor was introduced every 24 hours at the increasing dose of 10 mg, 30 mg, 60 mg and 90 mg until the therapeutic dose of 90 mg bis in die without eliciting no urticaria. Although the ticagrelor loading dose is 180 mg, according to cardiologists, because of the immediate stop of clopidogrel, there was an overlap action between the two drugs. Patient started a cardiological and allergological follow-up, being visited weekly to control hives occurrence. After a month from clopidogrel and omalizumab interruption, she had no cutaneous symptoms. Although omalizumab was initially efficacious to overcome clopidogrel hypersensitivity in that patient, pathomechanisms of the allergic reaction remained unclear, so we asked patient to perform skin test (skin prick tests, patch tests and intradermal tests) with the same THPs concentrations suggested by Cheema et al. [2]. The patient declined any further investigations and actually she is still assuming ticagrelor in DAPT regimen without having any cutaneous reactions.

3. DISCUSSION

Most of the patients with urticaria/angioedema display these symptoms hours after clopidogrel exposure [3], however the delayed onset may be dependent on two different reasons. Firstly, THPs are pro-drugs which require hepatic metabolism to be converted in their pharmaceutically active form, although the metabolic pathway is different for every THPs [3]. Furthermore, it has been showed that approximately 85% of a THP as clopidogrel’s initial dose is metabolized to an inactive thiolactone derivative, being only 15% therapeutically active [3]. Actually no specific IgE antibody to THPs has been isolated in vitro, probably because a specific serum IgE recognizes a clopidogrel metabolite and not the commercial naive formulation.

Alternatively, urticaria, showing a delayed type onset, is a T-cell mediated reaction too. Cheema et al. [2] investigated THPs hypersensitivity through intradermal tests and patch tests with clopidogrel (20% in petrolatum alba and 30% in water), ticlopidine (75% in water), and prasugrel (5% in water) with immediate and delayed reading 48 and 72 hours after applicating patch tests or carrying out intradermal tests in 62 patients [2]. In his study, patch testing was positive in 81% of tested patients with clopidogrel hypersensitivity and only 3 patients (5%) with urticaria/angioedema showed positive immediate reading intradermal tests, thus suggesting the IgE mediated pathomechanism is rarely involved in thienopyridine hypersensitivity and actually only skin tests may help us to distinguish reaginic reaction from a T cell-mediated one. Scala et al. demonstrated in a patient with a double drug-induced hypersensitivity, exanthema caused by penicillin-G and delayed-type urticaria to betamethasone, the T cell-mediated response showed different patterns of T lymphocyte subsets: CD8+ in the exanthema and CD4+ in urticaria [11]. Interestingly, Sanchez-Machin has shown omalizumab in spontaneous chronic urticaria may increase the activity of CD4+ T cells through measurement of ATP released by CD4* T lymphocytes and suggested that such a T cell subset has regulatory activity in spontaneous chronic urticaria [12]. This is the reason why omalizumab was efficacious even in clopidogrel induced T cell-mediated urticaria.

Previously omalizumab has been used to overcome an aspirin-exacerbated urticaria in cardiological patients with chronic idiopathic urticaria requiring acetylsalicylic acid as antiplatelet agent [13]. In that case, omalizumab was given to control chronic urticaria, but it was observed that biological agent induced even a tolerance towards NSAIDs [13]. Such side effect has been reported even in patients with NSAIDs exacerbated asthma, but the induction of NSAIDs tolerability seems to
be strictly related to the monthly administration of omalizumab [14]. However, omalizumab induced NSAIDs tolerance was due to the ability of the drug to downregulate eicosanoids metabolism and pro-inflammatory cysteinyl-leukotrienes production such as Leukotriene D4 and E4 Prostaglandin F2, whose urinary levels resulted reduced in 11 subjects treated with omalizumab [15].

CONCLUSION

To our knowledge, ours is the first case report in which omalizumab was used to treat a thienopyridine induced urticaria in a patient undergone coronary stent placement and as alternative treatment when steroids fail their pharmacological induction of THPs tolerance. Actually, cardiologic patients treated with thienopyridines represent a hard challenge for allergist and cardiologist when they develop a THP hypersensitivity, because the necessity to continue antiplatelet therapy wished by cardiologist contrasts the need for a washout period claimed by allergist to perform an allergic work up or a drug desensitization, so, in our opinion and experience, the right management of these patients requires the active collaboration of both the specialists.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No animals/humans were used for studies that are base of this research.

CONSENT FOR PUBLICATION

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The authors declare no conflict of interest, financial or otherwise.

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