

EDITORIAL COMMENT

Cutaneous Clopidogrel Hypersensitivity

Give Steroids and Do Not Stop the Clopidogrel*

Paul A. Gurbel, MD,
Young-Hoon Jeong, MD, PhD,
Udaya S. Tantry, PhD
Baltimore, Maryland

Dual antiplatelet therapy (DAPT) with clopidogrel and aspirin is widely used as a secondary prevention strategy in patients with acute coronary syndrome and following stent implantation. Ideally, at least 1 year of uninterrupted DAPT is recommended for patients with acute coronary syndrome and for patients treated with drug-eluting stents (1,2). In this issue of the *Journal*, the work of Cheema et al. (3) highlights a difficult clinical problem associated with clopidogrel therapy—cutaneous hypersensitivity. Attending physicians are all aware of the major concern of jeopardizing patient safety by early discontinuation of therapy to alleviate

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the troublesome skin rash symptoms. Discontinuation of either aspirin or clopidogrel, particularly early after stent implantation, is associated with a heightened risk of stent thrombosis (4). Unfortunately, cutaneous hypersensitivity most often begins within 5 to 6 days of the initiation of DAPT (5). Moreover, there are no definitive guidelines instructing the clinician on the proper management of this side effect. Often antihistamines and/or a course of steroids will be administered in an attempt to carry on with the current antiplatelet regimen (5). Concomitant therapies associated with potential hypersensitivity may be selectively discontinued. If these measures fail, the physician is confronted with the decision to switch thienopyridine therapy

despite the lack of significant data to support the efficacy of this strategy. Thus far, no standardized assays are available to confirm clopidogrel-related allergic reactions. In light of our limitation of not knowing the optimal method to diagnose and treat the patient with a rash on clopidogrel therapy, the contribution of Cheema et al. (3) is welcomed. To the best of our knowledge, this report is the single most comprehensive assessment of the mechanisms underlying clopidogrel hypersensitivity and its treatment. The data of Cheema et al. (3) provide the clinician with reassurance that a simple treatment is safe and highly effective and that interruption of clopidogrel therapy is not required.

Clopidogrel therapy has been increasing, and it accounted for approximately \$10 billion in worldwide sales in 2009 (6). Moreover, the patent for clopidogrel will soon expire in the United States, and usage will likely remain high with less expensive generic agents on the horizon. Therefore, even a low overall prevalence of hypersensitivity reactions will affect the clinical impact in a substantial number of patients. There are numerous publications describing desensitization protocols for clopidogrel hypersensitivity that are similar to those employed for aspirin allergy (5,7,8). The latter protocols have included intensive care unit observation periods and multiday outpatient regimens; a 90% success rate has been reported. However, these protocols require a drug washout period, which is undesirable particularly early after stenting, when the rash arises (8).

Cheema et al. (3) evaluated 62 patients who underwent percutaneous revascularization at a single medical center and developed a probable or definite hypersensitivity reaction attributable to clopidogrel therapy. The prevalence of the reaction was 62 in 3,877 (1.6%). These patients were treated with a 3-week tapering course of prednisone beginning with 30 mg twice daily; they also received diphenhydramine 25 to 50 mg every 6 to 8 h as needed. The latter strategy was successful in 95% of patients; rash resolved at a median of 5 ± 2 days, and clopidogrel therapy did not have to be interrupted in a single patient. Only 1 patient with angioedema required hospitalization (3).

It is important to note that the paper by Cheema et al. (3) only addressed cutaneous reactions. Other clinical manifestations of hypersensitivity to clopidogrel include fever, abdominal pain, neutropenia, and thrombocytopenia. Very rarely thrombotic thrombocytopenia purpura (4 cases per million patients) has also been associated with clopidogrel therapy (9). In a study by Lokhandwala et al. (10) of 76 patients with a hypersensitivity reaction to clopidogrel, 93% had a rash, 5% had angioedema, 4% had thrombocytopenia, and 3% had neutropenia. In another report of 24 cases of clopidogrel allergy, the most common presentation was a pruritic, erythematous, macular, and confluent rash that began on the face or trunk and spread to the extremities (7). In the CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events) trial, approximately 6% of patients suffered from a pruritic rash, which accounted for 1.5% of clopidogrel discontinuation (11). In the TRITON-TIMI 38 (Trial to Assess Improvement in Thera-

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peutic Outcomes by Optimizing Platelet Inhibition With Prasugrel–Thrombolysis in Myocardial Infarction 38) study, approximately 4% of patients treated with clopidogrel or prasugrel suffered allergic reactions, such as anaphylactic reaction, rash, pruritus, and urticaria (12). Notably, the prevalence of hypersensitivity to clopidogrel in the Cheema et al. study (3) was lower and may reflect underreporting. In the PLATO (Platelet Inhibition and Patient Outcomes) trial, clopidogrel and ticagrelor treatments were associated with a 1.7% and 1.6% prevalence of allergy and hypersensitivity, respectively (13).

In the study by Cheema et al. (3), generalized exanthema occurred in 79%, localized skin reaction in 16%, and angioedema or urticaria in 5% of patients. The rash findings observed by Cheema et al. (3) and the timing of onset are largely consistent with prior reports (5,7). Recently, in a review of medical records, Campbell et al. (14) reported the resolution of hypersensitivity symptoms without interrupting clopidogrel therapy among 25 patients treated with stenting (64% drug-eluting stents). In the Campbell et al. study (14), drug sensitivity was observed 6 ± 2 days after clopidogrel initiation. The patients were treated with corticosteroids and antihistamines (corticosteroids or antihistamines in 5 patients each and both drugs in 15 patients) for a mean of 10 ± 8 days, and clopidogrel therapy was continued without interruption. The latter therapy was effective in 22 of 25 patients (88%), and there were no incidences of adverse clinical events in the long-term follow-up of up to 1,138 days (14).

The study by Cheema et al. (3) stands out from previous studies in many aspects. In addition to evaluating therapy, the investigators performed hematologic measurements, skin testing, and histological analyses to elucidate the mechanism of clopidogrel hypersensitivity; they also assessed cross-reactivity with other thienopyridines. The results of skin prick and intradermal testing was rarely positive. However, patch testing was frequently abnormal (81%). These latter findings, in combination with the timing of rash onset and histological analysis of punch biopsies performed in a minority of patients, point to a lymphocyte-mediated delayed hypersensitivity reaction (type IV) as the responsible mechanism in the majority of patients; only 7% of patients had immediate hypersensitivity reactions with angioedema or urticaria. In addition, the investigators performed cross-reactivity testing and found a significant rate of positive reactions: 24% to ticlopidine, 17% to prasugrel, and 7% to both ticlopidine and prasugrel (3). The latter observations indicated that switching to other thienopyridines may not necessarily be an effective remedy to overcome clopidogrel hypersensitivity. Clinical experience is less frequent with prasugrel—as compared with clopidogrel-treated patients—and the prevalence of hypersensitivity is less certain. Recently, based on case reports, the European Medicines Agency requested that Daiichi Sankyo Inc. and Eli Lilly inform physicians of the potential risk of hypersensitivity reactions to prasugrel (15). The use of a nonthienopyridine P2Y₁₂ inhibitor such as ticagrelor may be particularly effective in a patient with clopidogrel hypersensitivity. However, the study by Cheema et al. (3) strongly suggests that treatment with a course of prednisone is a safe, moderately rapid, and highly effective strategy for patients suffering from

cutaneous clopidogrel hypersensitivity. DAPT can continue without interruption, and no switching is necessary. This is very good news for the troubled patient and worried physician.

Reprint requests and correspondence: Dr. Paul A. Gurbel, Sinai Center for Thrombosis Research, Cardiac Catheterization Laboratory, 2401 West Belvedere Avenue, Baltimore, Maryland 21215. E-mail: pgurbel@lifebridgehealth.org.

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