



A joint allergist/cardiologist classification for thienopyridines hypersensitivity reactions based on their symptomatic patterns and its impact on the management strategies

G.F. Calogiuri ^{a,c,*}, S. Al-Sowaidi ^b, E. Nettis ^c, G. Cortellini ^d, L. Macchia ^c, A. Vacca ^e, N.G. Kounis ^f

^a Pneumology Department Civil Hospital "NinottoMelli" S. Pietro Vernotico, Brindisi, Italy

^b Department of Internal Medicine, UAE University, Al-Ain, United Arab Emirates

^c Section of Allergy and Clinical Immunology, Department of Internal Medicine, Immunology and Infectious Diseases, University of Bari Medical School, Bari, Italy

^d Internal Medicine Allergy and Rheumatology Unit, Rimini Hospital, Rimini, Italy

^e Department of Biomedical Science and Human Oncology, Section of Internal Medicine and Clinical Oncology University of Bari Medical School, Bari, Italy

^f Department of Cardiology, University of Patras Medical School, Patras, Achaia, Greece

ARTICLE INFO

Article history:

Received 11 May 2016

Accepted 8 July 2016

Available online 16 July 2016

Keywords:

Thienopyridines
Hypersensitivity
Ticlopidine
Clopidogrel
Prasugrel
Urticaria
Arthritis
Exanthema

ABSTRACT

The role and importance of thienopyridines such as ticlopidine, clopidogrel, and prasugrel is well-established for several indications, ranging from prevention of acute coronary syndromes to percutaneous coronary interventions, where the dual antiplatelet therapy represents the gold standard to avoid *de novo* coronary stenosis. However, there is a significant cohort of patients with coronary artery disease who may manifest hypersensitivity reactions to thienopyridines. The examination of the various case reports from medical literature leads to identify mainly four clinical patterns of hypersensitivity to thienopyridines which involves more frequently cutaneous, hematologic, and articular tissues, therefore the kind and predominance of clinical symptoms may determine a different clinical approach to overcome or neutralize thienopyridines hypersensitivity.

© 2016 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Thienopyridines (THPs) are powerful inhibitors of platelet aggregation induced by adenosine diphosphate (ADP). ADP is a platelet activator released by red blood cells, activated platelets, and damaged endothelial cells. ADP is able to induce platelets activations and aggregation through its binding to two P2 receptors, which show two separate subtypes, the P2X1 and the P2Y1 [1]. THPs exert their antiplatelet effect by irreversibly binding with trans-membrane protein P2Y, so inhibiting ADP-mediated platelet activation for the life of the platelet [1].

THPs are currently used and highly recommended in patients undergone to coronary stents implantation to avoid stent thrombosis, indeed dual antiplatelet therapy with aspirin and a thienopyridine is the gold standard used in the neuroendovascular setting of intra-arterial stent placement [2].

The family of thienopyridines (THPs) includes essentially three molecules: the first-generation ticlopidine, the second-generation clopidogrel, and the third-generation prasugrel. THPs are pro-drugs which require

hepatic metabolism to be converted in their pharmaceutically active form, although the metabolic pathway is different for every THP [3,4]. The active metabolite of ticlopidine and clopidogrel contains a thiol group able to bind irreversibly to free cysteine on P2Y1 receptor, inhibiting permanently the receptor activity [3]. Moreover, such metabolites bind also to other proteins such as glutathione and hepatic cytochrome P450 [3].

All the three THPs are quite similar in their chemical structures, being clopidogrel different from ticlopidine for a carboxymethyl side group. Interestingly, all the metabolites of clopidogrel maintains the carboxymethyl ester group or have a carbocyclic acid group, so they are structurally different from ticlopidine metabolites. In the same way, prasugrel contains a cyclopropyl group and a fluorine atom conjugated to the phenyl group instead of chlorine atom as in clopidogrel and ticlopidine. Similarly to the clopidogrel, the cyclophenyl group is maintained by prasugrel metabolites, too. Prasugrel has been developed because clopidogrel has shown some limitations, such as interpatient variability in antiplatelet response and delayed onset of action [4]. Prasugrel is more active and powerful of clopidogrel and its activation is less dependent from cytochrome P450 enzyme than clopidogrel [5], but several important differences exist in the pharmacokinetic and pharmacodynamic profiles of the THPs.

* Corresponding author at: Pneumology Department Civil Hospital "NinottoMelli" S. Pietro Vernotico, Brindisi, Italy.

E-mail address: gf.calogiuri@libero.it (G.F. Calogiuri).

THPs may induce hypersensitivity reactions which make harder the treatment of patients undergone to a recent placement of coronary stents because the cessation of these drugs is associated to a very high risk of stents thrombosis; for that reason, it is fundamental to recognize and treat properly a THP hypersensitivity.

2. Clinical pictures of thienopyridines hypersensitivity

From a careful review of literature, it has been observed that THPs may induce different hypersensitivity reactions which can be essentially distinguished in:

- Type H (hematologic)
- Type E (epidermal)
- Type R (rheumatologic)
- Overlap type SHORES (systemic/hematologic/organ-related/epidermal symptoms)

2.1. Hypersensitivity Type H (hematologic)

Hematologic reactions are represented mainly by leucopenia [6,7], isolated thrombocytopenia [8], aplastic anemia [9,10], that eventually may have a fatal outcome [10,11], or idiopathic immune thrombocytopenia. Although such side effects may have a hypersensitivity pathogenesis, a toxic component cannot be excluded [8].

Sometimes the hematologic adverse reaction may result in a pancytopenia involving platelets, leucocytes, and red blood cells [11,12].

The severity of these cytopenias is not dose-dependent, the lapsing time to the onset is about 4–10 weeks, and the marrow failure is reversible, but it is usually complicated by infectious episodes, sometimes life threatening or fatal.

The most reported and dangerous hematologic hypersensitivity syndrome is represented by thrombotic thrombocytopenic purpura (TTP), a life-threatening multisystem disease characterized by thrombocytopenia, microangiopathic hemolytic anemia, fever, neurologic manifestations as fluctuating mental status, and acute renal deficiency. Although it may be idiopathic, many drugs have been associated with such syndrome. Its cause seems to be related to autoantibodies against a vital metalloproteinase enzyme referred as ADAMTS13 (A Disintegrin And Metalloproteinase with Thrombo-Spondin motifs 13) that degrades von Willebrand factor. Impaired proteolysis of von Willebrand factor (vWF) leads to the binding of unusually large multimers to platelets so resulting in platelet microthrombi. Drug-associated TTP represents about 12% of all cases and drugs may cause TTP via two mechanisms: a dose-related toxicity and/or an immune-mediated reaction [13].

Thienopyridine-associated TTP is characterized by two clinical syndromes. Most cases of ticlopidine-associated TTP and a minority of clopidogrel-associated TTP cases present with severe thrombocytopenia, microangiopathic hemolytic anemia, markedly elevated serum levels of lactate dehydrogenase, and normal renal function, and they occur between 2 and 12 weeks after initiation of thienopyridine therapy, while most cases of clopidogrel-associated TTP and a minority of ticlopidine-associated TTP cases present with mild thrombocytopenia, microangiopathic hemolytic anemia, mildly elevated serum levels of lactate dehydrogenase, and marked renal insufficiency. Onset usually occurs within 2 weeks of thienopyridine initiation [14].

Two mechanistic pathways for thienopyridine-associated TTP have been suggested: an immunologic pathway associated with more than 2 weeks of thienopyridine use and a non-immunologic pathway associated with 2 weeks or less of thienopyridine use [14].

It has been evidenced that ticlopidine-related TTP is more likely to occur after at least 2 weeks of therapy, to be associated with low ADAMTS13 levels with demonstrable autoantibodies, and it may benefit from plasma exchange therapy. Clopidogrel-induced TTP tends to occur within the first 2 weeks of treatment, is less likely to be associated with

low ADAMTS13 levels and autoantibodies, and is less likely to benefit from plasma exchange [15].

Although patients with ticlopidine- and clopidogrel-associated TTP are similar in age and sex, they differ significantly in duration of thienopyridine exposure prior to the onset of TTP: patients with ticlopidine-associated TTP are more prone to have assumed more than 2 weeks of a thienopyridine before TTP and they show a more severe thrombocytopenia (platelet count <20% from baseline) but less likely to have renal insufficiency [15].

The presence of IgG autoantibodies against ADAMTS13 distinguishes TTP from related syndrome, including hemolytic-uremic syndrome [16] and these inhibitory antibodies are found in 44% to 93% of patients with acquired TTP so they are reputed to be deeply involved in its pathogenesis [17].

2.2. Hypersensitivity Type E (epidermal)

On the contrary, cutaneous allergic reactions are more common and they show a great range of clinical aspects, but usually they are not so serious and life-threatening as hematologic reactions, although they may cause interruption of THPs therapy.

Various studies have investigated the clinical patterns of THPs cutaneous allergy. One of the studies was performed retrospectively on 136 patients underwent coronary or saphenous graft stent implantation receiving 250 mg ticlopidine twice daily [18]. Authors identified surely 16 patients with a cutaneous rash, induced by ticlopidine, 6 patients showed an urticarial-like eruption, 8 patients had an erythematous maculopapular rash, 1 patient had a fixed drug eruption, and the last patient showed a mixed rash, both maculopapular and urticarial [18].

Another study performed on 24 patients who had developed an allergic reaction to clopidogrel showed that the most common dermatologic eruption was a pruritic maculopapular erythematous confluent rash starting on the trunk or face and subsequently spreading to the extremities while urticaria was observed in 17% of patients [19]. Allergic symptoms generally manifest 6 days after exposure to clopidogrel, but they can occur within 24 h. [19].

Then Lohkawala et al. examined 76 patients with an allergic or hematologic adverse reaction to a THP. They observed that 93% had a rash, 5% had angioedema, 4% had thrombocytopenia, and 3% had neutropenia [20].

Recently, Cheema et al. [21] evaluated 62 patients on a group of 84 patients with suspected clopidogrel hypersensitivity. They identified about 3 distinct clinical patterns of cutaneous allergy to clopidogrel:

- 1) a first group of 49 patients (79%) had developed a generalized pruritic exanthema or maculopapular rash predominantly affecting the trunk, with or without involvement of the upper and lower extremities. The rash was limited to the chest, abdomen, and back in 40 patients (65%) and extended to extremities in 9 patients (15%);
- 2) a second group was represented by 10 patients (16%), in whom the rash limited to localized area in a focal and symmetrical manner. These reactions involved neck, face, back, axilla, palm of the hands, or soles of the feet;
- 3) lastly, the third group consisted 3 patients (5%) with urticaria and/or facial angioedema [21]. Moreover, two patients reported symptoms of fever and arthralgia even [21]. Urticaria/angioedema rarely show an immediate onset [20,21].

Other unusual cutaneous hypersensitivity reactions are represented by fixed drug eruption to ticlopidine [22,23] and to clopidogrel [24]. Acute generalized exanthematous pustulosis (AGEP) induced by ticlopidine [25] and, above all, by clopidogrel [26–29] is usually the most serious adverse cutaneous reaction associated to thienopyridines assumption, because cases of Steven Johnson syndrome/toxic epidermal necrolysis have been exceptionally reported in literature [30,31] or have been doubtfully attributed to THPs [32].

Moreover, there is no report that ticlopidine may cause a photosensitive reaction but a photosensitive lichenoid eruption due to clopidogrel has been described [33] as a single case report of erythroderma, always caused by clopidogrel [34].

In the same way, no case report of THPs-induced anaphylaxis has been described in literature, although an IgE-mediated mechanism has been suggested by skin tests [35]. Most of the patients with urticaria/angioedema display those symptoms hours after clopidogrel exposure [21]. Such a delayed onset may be dependent from two different reasons. Firstly, although the clinical aspect seems to be the typical picture of an immediate-type reaction, the mechanism is cell-mediated as sometimes demonstrated for systemic corticosteroids, which may induce urticarial-like contact dermatitis [36]. Alternatively, the delayed onset of symptoms could be due to the metabolic transformation of the THP pro-drug with a specific IgE-mediated response only toward the THP active metabolite, as it has been described for cyclophosphamide, too [37]. Furthermore, actually no specific IgE to THPs has been isolated *in vitro*, probably because *in vitro* tests should be performed with the metabolites of THPs and not with the commercial native formulation. Additionally, it has been shown that approximately 85% of a THP as clopidogrel's initial dose is metabolized to an inactive thiolactone derivative [38] and that may explain why no IgE-mediated anaphylaxis to THPs has been reported since such a drug metabolism avoids a fast and high serum concentration of the active metabolite, necessary to elicit an anaphylactic response.

2.3. Hypersensitivity Type R (rheumatologic)

Arthritis associated to THPs has been firstly reported back to 2000 following the assumption of ticlopidine [39] and clopidogrel [40]. Then other case reports of clopidogrel-induced polyarthralgia have been evidenced in literature [21,41–46]. Autoantibodies were absent except for 1 case with low positive levels of antinuclear antibodies [42], while an elevated level of serum immunoglobulin E was reported in 1 case [45].

Polyarthritis induced by thienopyridines can be explained as a manifestation of a serum-sickness-like disease [47], although polyarthritis is not present in case of clopidogrel-induced leucocytoclastic vasculitis [48,49].

Alternatively, because ADP receptor P2RY12 plays a role in bone homeostasis [50], the use of thienopyridines seems to be a worsening factor of arthritis in rats with a chronic, erosive, and recurrent experimental polyarthritis induced by peptidoglycan–polysaccharide injected intraperitoneally [51]. In such an experiment, rats treated with clopidogrel had increased joint diameter, showed elevated plasma levels of pro-inflammatory cytokines, both to an elevated neutrophil count, and an increased platelet count compared to untreated rats [51].

So the administration of THPs may induce the onset of mono- or pauci arthritis in animal models and it seems to be a class-related side effect because prasugrel has demonstrated to aggravate erosive arthritis in experimental rats even [52].

However, in human beings, polyarthritis may be a true manifestation of a Coombs and Gell-III-type hypersensitivity reaction which disappears when changing the culprit thienopyridine molecule with another one [46,53–56]. Lastly, a lupus-like syndrome with antinuclear antibody (ANA) title positive and sometimes renal involvement has been described following ticlopidine consumption only [57–62].

2.4. Overlap Hypersensitivity Type SHORES (systemic and/or hematologic and/or organ related and/or epidermal symptoms)

There is a further pattern of thienopyridines hypersensitivity syndrome, in which cutaneous allergic manifestations, different from a purpuric eruption, are associated with hematologic abnormalities as pancytopenia, while systemic symptoms, as fever, for instance, may be

present [63–65]. Abdominal pains and pulmonary involvement may occur too [66–69]. Although drug-induced hepatitis with cholestasis due to thienopyridines has been reported in literature [70–73], such adverse effect was attributed to toxic mechanisms because these drugs undergo to hepatic metabolism by cytochrome P450 [1] and experimental studies in rat liver seems to confirm such toxic effects of THPs [74]. However, it has been estimated that 40% of thienopyridines-induced hepatitis are genuinely immune-mediated in their pathogenesis because the interaction of reactive clopidogrel metabolites with other proteins than glutathione also leads to the formation of neoantigens that could possibly trigger an immune response in the liver [75]. Such a hypothesis is confirmed by various evidences: 1) a hypersensitivity T-cell-mediated mechanism has been evidenced by a lymphocyte transformation test in drug induced hepatitis [76], 2) hepatitis may regress following a corticosteroid therapy [77], 3) associated systemic symptoms of hypersensitivity are often present [78–82], 4) hepatic granulomas have been found in human liver biopsies [69,83] and in experimental rats [52], so suggesting an immune-allergic response to THPs 5) HLA-A*33:03 was significantly associated with ticlopidine-induced cholestatic liver injury in Japanese patients [84]; 6) hepatitis may be accompanied by ANA positivity [85] or by eosinophils and lymphocytes infiltrates in the hepatic tissue [74,83]; 7) hepatic symptoms may disappear switching from a thienopyridine to another one, suggesting a specific immune response and not always a class-related side effect: clopidogrel has been successfully used in three patients with ticlopidine-induced hepatotoxicity [86, 87], and prasugrel has been substituted to clopidogrel in case of clopidogrel-induced acute hepatitis [88]. Furthermore, there are recent reports according to which clopidogrel has caused a Kounis syndrome, that is a cutaneous hypersensitivity associated to myocardial ischemia as given to prevent coronary stent thrombosis [89]. Paradoxically, clopidogrel has induced allergic reaction and subsequently a recurrent acute stent thrombosis with Kounis syndrome, despite it has been administered to avoid stent occlusion in coronary vessels [90]. A particular pattern of type SHORES reaction is the systemic inflammatory response syndrome (SIRS). It is a clinical response to a nonspecific insult of either infectious or noninfectious origin so it can be caused by ischemia, inflammation, trauma, infection, or several insults combined and exceptionally by drugs as THPs [82,91–93]. A drug-induced SIRS to THPs is possible because it has been suggested that P2Y may be expressed in other cells of the immune system such as lymphocytes, monocytes, and dendritic cells rather than platelets [94,95] and that could induce an increased pro-inflammatory effect from THPs resulting rarely in such a general systemic inflammatory response.

3. Pathogenetic mechanisms of thienopyridines hypersensitivity

Park et al. have demonstrated that for some drugs the process of haptation is strictly linked to their bioactivation: the drug is a pro-hapten needing to be metabolized and turned in a reactive metabolite by the enzymatic pathways of specific cells. In that form, it is more likely to bind irreversibly with certain proteins residues, thus becoming a complete antigen. Furthermore, the accumulation of such reactive metabolites, which frequently are toxic compounds, provides the “danger signal,” necessary to generate a specific immune response. The same researchers have suggested that tissues where the metabolic bioactivation occurs are at a greater risk to become the target organ by an immune response and not only by a toxic reaction [96]. Liu and Uetrecht have evidenced and confirmed *in vitro* that ticlopidine can be oxidized by neutrophil granulocytes myeloperoxidase (MPO) to a reactive tiophene-S-chloride derivative, probably responsible for bone marrow toxicity, but surely associated with neutropenia [97]. Because thienopyridines's toxic effects on human neutrophil granulocytes and lymphocytes [98] and on liver, through the generation of metabolites carrying highly reactive mercapto-groups [75], have been confirmed by *in vitro* studies, it was not a surprising result that hypersensitivity reactions from THPs may involve more frequently blood cells and hepatocytes. The skin is

often involved in most of the hypersensitivity reactions because it possesses its own enzymatic activity which may activate a pro-hapten-type contact allergen and an iatrogenic pro-hapten even [99]. Cheema investigated THPs hypersensitivity through patch tests with clopidogrel (20% in petrolatum alba and 30% in water), ticlopidine (75% in water), and prasugrel (5% in water) with delayed reading 48 and 72 h after their applications in 62 patients [21]. In his study, patch testing was positive in 81% of tested patients with clopidogrel hypersensitivity [21]. The long-standing of the drugs on the skin of sensitized patients allowed their bioactivation by skin enzymatic pathways [99], so leading to a specific cell-mediated immune response by drug selected T-cells [96]. Another aspect involving THPs hypersensitivity is the possibility of allergic cross-reaction among the different THP molecules. It has been evidenced firstly between ticlopidine and clopidogrel in some case reports [34,100], even in severe cutaneous adverse reactions [34] and in an investigation on a little cohort of patients [20] and between clopidogrel and prasugrel even [101]. However, the study of Cheema et al. [21] was the first to include prasugrel extensively and patch tests demonstrated allergenic cross-reactivity between ticlopidine and clopidogrel in 10 (24%), clopidogrel and prasugrel in 7 (17%), and among clopidogrel, ticlopidine, and prasugrel in 3 (7%) of the tested patients, because contemporary cross-reactivity among ticlopidine, clopidogrel, and prasugrel had not been investigated previously. Because Pichler had already suggested that in cell-mediated drug reactions, drug-specific T lymphocytes are more likely to recognize the drug core structure, which is commonly shared with its derivatives [102], allergic cross-reactivity towards all the three THPs seems to have an incidence lower than expected on the basis of the narrow similarity of their basic stereo-chemical structure.

4. Management of thienopyridines hypersensitivity

Useful management strategies have been elaborated to overcome THPs hypersensitivity in sensitive patients without stopping the drug assumption and they consist mainly in three approaches: 1) pharmacological premedication with a course of oral tapering steroids and anti-allergic drugs; 2) drug desensitization; 3) substitution of a thienopyridine molecule with another one, although unpredictable immunologic cross-reactivity may occur in some cases or with another anti-coagulant drug [103,104]. However, only the first approach allows to continue THP assumption, because either drug desensitization or administration of an alternative antiplatelet THP or drug requires a wash out period because THP therapy needs to be interrupted until symptoms resolution. Then, in the light of our proposed classification of THPs hypersensitivity, the management strategies should be adapted to the type of hypersensitivity. Pharmacological premedication for instance has got some limitations: firstly, it may be used to treat only mild or moderate cutaneous reactions, and probably in type R reactions, but surely it cannot be used on a severe cutaneous adverse reactions like AGEP or Steven Johnson syndrome, as evidenced by the same authors [21,105] or in type H hypersensitivity. As far as drug desensitization is concerned, although various protocols for clopidogrel [104,106] and prasugrel [107] have been elaborated, however, the desensitization strategy seems to show the same limitations of pharmacological premedication: it cannot be used in case of a severe hypersensitivity reaction or in hematologic reactions, indeed the European Academy Allergy Clinical Immunology (EAACI) position paper on slow drug desensitization recommends to avoid that procedure in serious hypersensitivity reactions because of the risk of a fatal evolution [108]. Thus, the substitution of the culprit THP molecule with another one remain the more efficacious solution and in literature are reported the step-down from the second-generation THP back to ticlopidine [27,109] or the switch therapy towards the third-generation prasugrel [110–113], especially in type E and in type R hypersensitivity [46, 53–56], more rarely in type SHORES reactions [88–90] and anecdotally in case of type H adverse events, too [114,115]. Although prasugrel has been introduced recently on the market, it has caused cutaneous eruption,

such as generalized skin rash, too, and the clinical presentations are very similar to the clopidogrel rashes [116–118]. In that case, clopidogrel has been successfully administered as an alternative to prasugrel without any signs of further hypersensitivity in some reports [117]. Skin tests may be helpful to predict potential cross-reactivity among the various THP molecules, but they can be carried out in type E hypersensitivity mainly. Recently, a new antiplatelet agent, ticagrelor, has been introduced on pharmaceutical market. Ticagrelor does not require metabolic activation for antiplatelet activity and binds reversibly to the P2Y₁₂ receptor [119]. Ticagrelor is a direct-acting oral antagonist of the adenosine diphosphate receptor P2Y₁₂, providing faster, greater, and more consistent P2Y₁₂ inhibition than clopidogrel [119]. Moreover, being ticagrelor a cyclopentyl–triazolo–pyrimidine, that is a new chemical class of antiplatelet agents, its chemical structure should be apparently different from thienopyridines [119], enough to avoid allergic cross-reactivity phenomenon. Thus, ticagrelor may represent a valuable alternative molecule in case of THPs hypersensitivity, and, above all, in case of extensive allergic cross-reactivity to THPs, as suggested by some preliminary reports [120–122], but much more studies are required to confirm its security profile in THPs-sensitive patients.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

References

- [1] M.J. Quinn, D.J. Fitzgerald, Ticlopidine and clopidogrel, *Circulation* 100 (1999) 1667–1672.
- [2] ACC/AHA, Guidelines for percutaneous coronary intervention, *J. Am. Coll. Cardiol.* 37 (2001) 2239i–2249i.
- [3] D. Girja, B.D. Singh, S. Komal, Thienopyridines: platelets ADP receptor antagonist, *J. Drug Deliv. Ther.* 1 (2011) 8–16.
- [4] D.J. Angiolillo, A. Fernandez-Ortiz, E. Bernardo, et al., Variability in individual responsiveness to clopidogrel: clinical implications, management, and future perspectives, *J. Am. Coll. Cardiol.* 49 (2007) 1505–1516.
- [5] L. Wallentin, P2Y₁₂ inhibitors: differences in properties and mechanisms of action and potential consequences for clinical use, *Eur. Heart J.* 30 (2009) 1964–1977.
- [6] A. Akcay, M. Kanbay, E. Agca, S. Sezer, F.N. Ozdemir, Neutropenia due to clopidogrel in a patient with end-stage renal disease, *Ann. Pharmacother.* 38 (2004) 1538–1539.
- [7] M.W. McCarthy, D.R. Kocker, Clopidogrel-associated leucopenia, *Ann. Pharmacother.* 37 (2003) 216–219.
- [8] S. Balamuthusamy, R. Arora, Hematologic adverse effects of clopidogrel, *Am. J. Ther.* 14 (2007) 106–112.
- [9] B. Meyer, T. Staudinger, K. Lechner, Clopidogrel and aplastic anaemia, *Lancet* 357 (2001) 1446–1447.
- [10] J.M. Trivier, J. Caron, M. Mathieu, N. Cambier, C. Rose, Fatal aplastic anemia associated with clopidogrel, *Lancet* 357 (2001) 446.
- [11] J. Chemnitz, D. Sohngen, A. Schulz, V. Diehl, C. Scheid, Fatal toxic bone marrow failure associated with clopidogrel, *Eur. J. Haematol.* 71 (2003) 473–474.
- [12] K.E. Matthews, B. Hameed, S. Jawed, Acute severe pancytopenia associated with clopidogrel, *Br. J. Hosp. Med.* 70 (2009) 52.
- [13] D.R. Terrell, L.A. Williams, S.K. Vesely, B. Lämmle, J.A. Hovinga, J.N. George, The incidence of thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: all patients, idiopathic patients, and patients with severe ADAMTS-13 deficiency, *J. Thromb. Haemost.* 3 (2005) 1432–1436.
- [14] Ticlopidine- and clopidogrel-associated thrombotic thrombocytopenic purpura (TTP): review of clinical, laboratory, epidemiological, and pharmacovigilance findings (1989–2008), *Kidney Int. Suppl.* 112 (2009 February) S20–S24.
- [15] C.L. Bennett, B. Kim, A. Zakarija, et al., Two mechanistic pathways for thienopyridine-associated thrombotic thrombocytopenic purpura. A report from the SERF-TTP Research Group and the RADAR Project, *J. Am. Coll. Cardiol.* 50 (2007) 1138–1143.
- [16] M. Furlan, R. Robles, M. Galbusera, et al., Von Willebrand factor-cleaving protease in thrombotic thrombocytopenia purpura and the hemolytic-uremic syndrome, *NEJM* 339 (1998) (15778–1584).
- [17] Y. Yamaguchi, T. Moriki, A. Igari, T. Nakagawa, H. Wada, M. Matsumoto, Y. Fujimura, M. Murata, Epitope analysis of autoantibodies to ADAMTS13 in patients with acquired thrombotic thrombocytopenic purpura, *Thromb. Res.* 128 (2001) 169–173.
- [18] G. Yosipovitch, E. Rechavia, M. Feinmesser, M. David, Adverse cutaneous reactions to ticlopidine in patients with coronary stents, *J. Am. Acad. Dermatol.* 41 (1999) 473–476.
- [19] K.F. Von Thiel, M.J. Price, R. Valencia, et al., Clopidogrel desensitization after drug-eluting stent placement, *J. Am. Coll. Cardiol.* 50 (2007) 2039–2043.

- [20] J.O. Lokhandwala, P.J.M. Best, J.H. Butterfield, et al., Frequency of allergic or hematologic adverse reactions to ticlopidine among patients with allergic or hematologic adverse reactions to clopidogrel, *Circ. Cardiovasc. Intervent.* 2 (2009) 348–351.
- [21] A. Cheema, A. Mohammad, T. Hong, H.R. Jakubovic, G.S. Parmar, et al., Characterization of clopidogrel hypersensitivity reactions and management with oral steroid without clopidogrel discontinuation, *J. Am. Coll. Cardiol.* 58 (2011) 1445–1454.
- [22] C. Martín-García, R. Carmona, R. García, P. Berges, E. Camacho, M.P. Cotter, B. De La Hoz, Fixed drug eruption from ticlopidine with positive lesional patch test, *Contact Dermatitis* 44 (2001) 40–41.
- [23] J. Borrás-Blasco, A. Navarro-Ruiz, A. Gutiérrez-Casbas, J. Matarredona-Catalá, M. González-Delgado, Multiple fixed-drug eruption and diarrhea with ticlopidine, *Ann. Pharmacother.* 36 (2002) 344–345.
- [24] S.K. Ghosh, D. Bandyopadhyay, Clopidogrel induced fixed drug eruption, *J. Eur. Acad. Dermatol. Venereol.* 23 (2009) 1202–1203.
- [25] S.P. Cannavò, F. Borgia, F. Guarneri, M. Vaccaro, Acute generalized exanthematous pustulosis following use of ticlopidine, *Br. J. Dermatol.* 142 (2000) 577–578.
- [26] S. Nakamizo, S. Kobayashi, T. Usui, Y. Miyachi, K. Kabashima, Clopidogrel-induced acute generalized exanthematous pustulosis with elevated Th17 cytokine levels as determined by a drug lymphocyte stimulation test, *Br. J. Dermatol.* 162 (2010) 1402–1403.
- [27] J.C. Ellebroeck, M.C. Cleveland, Clopidogrel associated acute generalized exanthematous pustulosis, *Cutis* 87 (2011) 181–185.
- [28] M. Meissner, C. Beier, M. Wolter, R. Kaufmann, J. Gille, Sub-erythrodermic pustular psoriasis induced by clopidogrel, *Brit. J. Dermatol.* 155 (2006) 630–631.
- [29] C.A. Ulman, D.G. Palmer, J.J. Trevino, T.G. Olsen, S. Krishnamurthy, R.K. Gandhi, Acute generalized exanthematous pustulosis induced by clopidogrel, *Int. J. Dermatol.* 53 (2014) e461–e462.
- [30] D.I. Strippoli, G. Russo, V. Simonetti, A. Motolese, Lyell syndrome due to ticlopidine, *G. Ital. Dermatol. Venereol.* 146 (2011) 497–500.
- [31] D.H. Hsi, D.J. Mock, T.A. Rocco Jr., Toxic erythroderma due to ticlopidine, *N. Engl. J. Med.* 340 (1999) 1212.
- [32] X.M. Hou, W.Y. Wu, Toxic epidermal necrolysis after percutaneous coronary intervention: which drug is the culprit? *Chin. Med. J.* 124 (2011) 467–468.
- [33] S. Dogra, A.J. Kanwar, Clopidogrel bisulfate-induced photosensitive lichenoid eruption: first report, *Br. J. Dermatol.* 143 (2003) 609–610.
- [34] A.I. Ziakas, E.K. Theofilogiannakos, M. Daniilidis, D. Sotiriadis, A. Parisiadou, P. Kotsaftis, K. Gemitzis, G. Parharidis, Clopidogrel and ticlopidine cross-reactivity-induced erythroderma following drug-eluting stenting, *Cutis* 92 (2013) e16–e17.
- [35] P.G. Vigo, A.L. MacDowell, H.J. Wedner, Successful desensitization with clopidogrel after a positive skin test, *Ann. Allergy Asthma Immunol.* 94 (2005) 132.
- [36] A. Padial, S. Posadas, J. Alvarez, M.J. Torres, J.A. Alvarez, C. Mayorga, M. Blanca, Non-immediate reactions to systemic corticosteroids suggest an immunological mechanism, *Allergy* 60 (2005) 665–670.
- [37] N.A. Popescu, M.G. Sheehan, P.A. Kouides, J.E. Loughner, J.J. Condemni, R.J. Looney, J.P. Leddy, Allergic reactions to cyclophosphamide: delayed clinical expression associated with positive immediate skin tests to drug metabolites in five patients, *J. Allergy Clin. Immunol.* 97 (1996) 26–33.
- [38] D.S. Small, N.A. Farid, C.D. Payne, et al., Effects of the proton pump inhibitor lansoprazole on the pharmacokinetics and pharmacodynamics of prasugrel and clopidogrel, *J. Clin. Pharmacol.* 48 (2008) 475–484.
- [39] H. Dakik, I. Salti, R. Haidar, I. Ulthman, Ticlopidine associated with acute arthritis, *BMJ* 324 (2002) 27.
- [40] A. Garg, J. Radvan, N. Hopkinson, Clopidogrel associated with acute arthritis, *BMJ* 320 (2000) 48.
- [41] K.K. Chen, I. Ginges, N. Manolios, Clopidogrel-associated acute arthritis, *Intern. Med. J.* 33 (2003) 618–619.
- [42] L. Blauwet, E. Matteson, Acute inflammatory arthritis: an adverse effect of clopidogrel? *J. Clin. Rheumatol.* 9 (2003) 128–129.
- [43] N. Boulman, M. Rozenbaum, G. Slobodin, I. Rosner, Acute polyarthritis associated with clopidogrel treatment, *Isr. Med. Assoc. J.* 7 (2005) 670–671.
- [44] Y. Tayyareci, Acute arthritis associated with loading dose of clopidogrel, *J. Clin. Rheumatol.* 14 (2008) 254–255.
- [45] S.Y. Kawashiri, M. Taguchi, A. Kawakami, K. Eguchi, Clopidogrel associated acute arthritis, *Rheumatol. Int.* 32 (2012) 449–450.
- [46] S. Agrawal, J. Harburger, G. Stallings, N. Agrawal, J. Garg, Clopidogrel-induced recurrent polyarthritis, *J. Invest. Med. High Impact Case Rep.* 1 (2013), <http://dx.doi.org/10.1177/2324709613500239>.
- [47] E.J. Phillips, S.R. Knowles, N.H. Shear, Seum sickness like reaction associated to clopidogrel, *Brit. J. Clin. Pharmacol.* 56 (2003) 583.
- [48] S. Erpolat, Y. Nazli, N. Colak, S. Yenidunya, Leucocytoclastic vasculitis associated to clopidogrel, *Cutan. Ocul. Toxicol.* 31 (2012) 171–173.
- [49] R.K. Shetty, M. Madken, K. Naha, G. Vivek, Leucocytoclastic vasculitis as late complication of clopidogrel therapy, *BMJ Case Rep.* (2013), <http://dx.doi.org/10.1136/bcr-2012-007861>.
- [50] X. Su, D.H. Floyd, A. Hughes, J. Xiang, J.C. Schneider, O. Uluckan, E. Heller, et al., The ADP receptor P2RY12 regulates osteoclast function and pathologic bone remodeling, *J. Clin. Invest.* 122 (2012) 3580–3592.
- [51] A.E. García, S.R. Mada, M.C. Rico, R.A. DeLa Cadena, S.P. Kunapuli, Clopidogrel, a P2Y12 receptor antagonist, potentiates the inflammatory response in a rat model of peptidoglycan polysaccharide-induced arthritis, *PLoS* 6 (2011), e26035.
- [52] A.E. García, M.C. Rico, E. Liverani, R.A. DeLa Cardena, P.F. Bray, S.P. Kunapuli, Erosive arthritis and hepatic granuloma formation induced by peptidoglycan polysaccharide in rats is aggravated by prasugrel treatment, *PLoS* 8 (e69093) (2013) 1–9.
- [53] M.K. Kanadiya, S. Singhal, V.B. Koshal, Prasugrel as a safe alternative for clopidogrel-associated arthritis, *J. Invasive Cardiol.* 23 (2011) e137–e138.
- [54] E.A. Khan, J.W. Blake, L.K. Stamp, Ticlopidine as a safe alternative for clopidogrel-associated arthritis, *J. Rheumatol.* 36 (2009) 855–856.
- [55] C.J. Coulter, S.V. Montandon, Prasugrel as a safe alternative for clopidogrel-induced polyarthralgias, *Pharmacotherapy* 32 (2012) e24–e26.
- [56] M.F. Williams, J.A. Maloof 3rd, Resolution of clopidogrel-associated polyarthritides after conversion to prasugrel, *Am. J. Health Syst. Pharm.* 71 (2014) 1097–1100.
- [57] R.F. Spiera, R.S. Berman, A.J. Werner, H. Spiera, Ticlopidine-induced lupus: a report of 4 cases, *Arch. Intern. Med.* 162 (2002) 2240–2243.
- [58] T.I. Yokoyama, T. Usui, K. Kiyama, R. Nakashima, N. Yukawa, D. Kawabata, T. Nojima, K. Ohmura, T. Fujii, T. Mimori, Two cases of late-onset drug-induced lupus erythematosus caused by ticlopidine in elderly men, *Mod. Rheumatol.* 20 (2010) 405–409.
- [59] H. Okada, T. Kikuta, Y. Watanabe, Y. Kanno, S. Sugahara, H. Suzuki, Ticlopidine induces lupus in a haemodialysis patient, *Nephrol. Dial. Transplant.* 19 (2004) 2685–2686.
- [60] T. Ohtake, S. Kobayashi, K. Okamoto, M. Oka, K. Maesato, T. Yasu, H. Moriya, Ticlopidine-induced lupus with renal involvement, *Nephrol. Dial. Transplant.* 21 (2006) 1992–1993.
- [61] A. Reich, R. Bialynicki-Birula, J.C. Szepietowski, Drug-induced subacute cutaneous lupus erythematosus resulting from ticlopidine, *Int. J. Dermatol.* 45 (2006) 1112–1114.
- [62] Y.C. Chen, Y.H. Wu, Ticlopidine-induced subacute cutaneous lupus erythematosus : a case report and literature review, *Dermatol. Sin.* 32 (2014) 183–186.
- [63] A. Comert, S. Akgun, S. Civelek, M. Kavala, S. Sarigul, T. Yildirim, S. Arsan, Clopidogrel induced hypersensitivity syndrome associated with febrile pancytopenia, *Int. J. Dermatol.* 44 (2005) 882–884.
- [64] M.P. Doogue, E.J. Begg, P. Bridgman, Clopidogrel hypersensitivity syndrome with rash, fever and neutropenia, *Mayo Clin. Proc.* 80 (2005) 1368–1370.
- [65] E. Andres, A.E. Perrin, M. Alt, B. Goichot, J.L. Schlienger, Febrile pancytopenia associated with clopidogrel, *Arch. Intern. Med.* 161 (2001) 125.
- [66] F. Sarrot-Reynaud, L. Bouillet, J.L. Bourrain, Severe hypersensitivity associated with clopidogrel, *Ann. Intern. Med.* 135 (2001) 305–306.
- [67] P.C. Oon, J.S. Jerng, H.L. Kao, Y.L. Chang, C.Y. Yu, P.C. Yang, Diffuse alveolar damage associated with ticlopidine use: a case report, *J. Formos. Med. Assoc.* 102 (2003) 262–265.
- [68] R. Nakamura, T. Imamura, H. Omitsuka, K. Mishima, T. Ishikawa, T. Nagoshi, et al., Interstitial pneumonia induced by ticlopidine, *Circ.* 106 (2002) 773–776.
- [69] C.F. Persoz, F. Cornella, P. Kaeser, T. Rochat, Ticlopidine-induced interstitial pulmonary disease: a case report, *Chest* 119 (2001) 1963–1965.
- [70] M. Iqbal, P. Goenka, M.F. Young, E. Thomas, T.R. Bortwick, Ticlopidine-induced cholestatic hepatitis: report of three cases and review of literature, *Dig. Dis. Sci.* 43 (1998) 2223–2226.
- [71] R.K. Goyal, D. Srivastava, K.D. Lessnau, Clopidogrel-induced hepatocellular injury and cholestatic jaundice in an elderly patient: case report and review of the literature, *Pharmacotherapy* 29 (2009) 608–612.
- [72] L. Adams, G.P. Jeffrey, B. Deboer, G. Garas, Ticlopidine associated cholestatic hepatitis, *Intern. Med. J.* 32 (2002) 350–360.
- [73] K.F. Chau Tn Yim, N.S. Mak, W.K. Chan, V.K.S. Leung, M.F. Leung, S.T. Lai, Clopidogrel induced hepatotoxicity after percutaneous coronary stenting, *Hong Kong Med. J.* 11 (2005) 414–416.
- [74] D. Alvaro, A. Gigliozzi, E. Gaudio, E. Pescarmona, M. Ripani, C. Peric, et al., Ticlopidine induced cholestasis: reports of two cases and experimental evidence of the drug adverse effect in the isolated perfused rat liver, *Eur. J. Gastroenterol. Hepatol.* 6 (1994) 943–950.
- [75] A. Zahno, J. Bouitbir, S. Maseneni, P.W. Lindinger, K. Brecht, S. Krähenbühl, Hepatocellular toxicity of clopidogrel: mechanisms and risk factors, *Free Radic. Biol. Med.* 65 (2013) 208–216.
- [76] Y.D. Skurnik, A. Tcherniak, K. Edlan, Z. Stoecker, Ticlopidine-induced cholestatic hepatitis, *Ann. Pharmacother.* 37 (2003) 371–375.
- [77] L. Alberti, J.J. Alberti-Flor, Ticlopidine-induced cholestatic hepatitis successfully treated with corticosteroids, *Am. J. Gastroenterol.* 97 (2002) 1072.
- [78] S. Pascual, J.V. Sarrion, I. Jarque, L. Arguello, J. Berenguer, Cholestatic hepatitis and anemia induced by ticlopidine, *Gastroenterol. Hepatol.* 19 (1996) 208–209.
- [79] C. Ceylan, O. Kirmli, M. Akarsu, B. Undar, S. Guneri, Early ticlopidine induced hepatic dysfunction, dermatitis and irreversible aplastic anemia after coronary artery stenting, *Am. J. Haematol.* 59 (1998) 260.
- [80] N. Yamamoto, K. Shiraki, Y. Saitou, T. Kawakita, H. Okano, K. Sugimoto, K. Murata, T. Nakano, Ticlopidine induced acute cholestatic hepatitis complicated with pure red cell aplasia, *J. Clin. Gastroenterol.* 38 (2004) 84.
- [81] J.A. Ng, N. Goldberg, M.J. Tafreshi, Clopidogrel induced hepatotoxicity and fever, *Pharmacotherapy* 26 (2006) 1023–1026.
- [82] J. Lo'pez-Vicente, C. Garfia, F. Lo'pez-Medrano, C. Yela, Hepatic toxicity and clopidogrel-induced systemic inflammatory response syndrome, *Rev. Esp. Cardiol.* 60 (2007) 323–324.
- [83] P. Ruiz-Valverde, C. Zafon, A. Segarra, R. Ribeira, L. Piera, Ticlopidine-induced granulomatous hepatitis, *Ann. Pharmacother.* 29 (1995) 633–634.
- [84] K. Hirata, H. Takagi, M. Yamamoto, T. Matsumoto, T. Nishiya, K. Mori, et al., Ticlopidine-induced hepatotoxicity is associated with specific human leukocyte antigen genomic subtypes in Japanese patients: a preliminary case-control study, *Pharmacogenomics* 9 (2008) 29–33.
- [85] M.H. Tsai, S.L. Tsai, T.C. Chen, Y.F. Liaw, Ticlopidine-induced cholestatic hepatitis with anti-nuclear antibody in serum, *J. Formos. Med. Assoc.* 99 (2000) 866–869.
- [86] P.T. Tsui, S.T. Lai, W.S. Leung, et al., Prolonged jaundice following percutaneous coronary intervention and ticlopidine therapy, *Hong Kong Med. J.* 8 (2002) 57–59.
- [87] M.M. Zeolla, J.J. Carson, Successful use of clopidogrel for cerebrovascular accident in a patient with suspected ticlopidine-induced hepatotoxicity, *Ann. Pharmacother.* 33 (1999) 939–941.

- [88] M. Fernandez-Ruiz, A. Carbonell-Porras, A. Garcia-Reyne, M.F. Lopez, Management of a hypersensitivity reaction to thienopyridines: prasugrel induced fever and hepatitis resolved after switching to clopidogrel, *Rev. Esp. Cardiol.* 65 (2012) 773–774.
- [89] Z. Liping, H. Bin, F. Qiming, An extraordinary case associated with an allergic reaction to clopidogrel: coronary artery spasm or Kounis syndrome? *Heart Lung Circ.* 24 (2015) e180–e183.
- [90] C.Y. Karabay, M.M. Can, I.H. Tanboğa, G. Ahmet, A. Bitigen, V. Serebruany, Recurrent acute stent thrombosis due to allergic reaction secondary to clopidogrel therapy, *Am. J. Ther.* 18 (2011) e119–e122.
- [91] I. Wolf, M. Mouallen, S. Rath, Z. Farfei, Clopidogrel induced systemic inflammatory response syndrome, *Mayo Clin. Proc.* 78 (2003) 618–620.
- [92] J. Lopez-Vincente, V. Garfia, F. Lopez-Medrano, C. Yela, Hepatic toxicity and clopidogrel induced systemic inflammatory response syndrome, *Rev. Esp. Cardiol.* 60 (2007) 323–329.
- [93] V.L. Serebruany, N. Kipshidze, I.V. Pershukov, W. Kuliczkowski, J. Carnes, D. Atar, Fatal sepsis and systemic inflammatory response syndrome after off-label prasugrel: a case report, *Am. J. Ther.* 21 (2014) e229–e233.
- [94] P. Diehl, C. Olivier, C. Halscheid, T. Helbing, C. Bode, M. Moser, Clopidogrel affects leukocyte dependent platelet aggregation by P2Y12 expressing leukocytes, *Basic Res. Cardiol.* 105 (2010) 379–387.
- [95] L.I. Wang, S.E. Jacobsen, A. Bengtsson, D. Erlinge, P2 receptor mRNA expression profiles in human lymphocytes, monocytes and CD34+ stem and progenitor cells, *BMC Immunol.* 5 (2004) 16.
- [96] B.K. Park, M. Pirmohamed, N.R. Kitteringham, Role of drug disposition in drug hypersensitivity: a chemical, molecular and clinical perspective, *Chem. Res. Toxicol.* 11 (1998) 969–987.
- [97] Z.C. Liu, J.P. Uetrecht, Metabolism of ticlopidine by activated neutrophils: implications for ticlopidine-induced agranulocytosis, *Drug Metab. Dispos.* 28 (2000) 726–730.
- [98] S. Maseneni, M. Donzelli, K. Brecht, S. Krahenbuhl, Toxicity of thienopyridines on human neutrophil granulocytes and lymphocytes, *Toxicology* 308 (2013) 11–19.
- [99] C.K. Smith Pease, D.A. Basketter, G.Y. Patlewicz, Contact allergy: the role of skin chemistry and metabolism, *Clin. Exp. Dermatol.* 28 (2003) 177–183.
- [100] K. Makkar, R.L. Wilensky, M.B. Julien, H.C. Herrmann, S.A. Spinler, Rash with both clopidogrel and ticlopidine in two patients following percutaneous coronary intervention with drug-eluting stents, *Ann. Pharmacother.* 40 (2006) 1204–1207.
- [101] B.H. Raccach, M. Shalit, H.D. Danenberg, Allergic reaction to prasugrel and cross-reactivity with clopidogrel, *Int. J. Cardiol.* 157 (2012) e48–e49.
- [102] J.P. Depta, W.J. Pichler, Cross-reactivity with drugs at the T cell level, *Curr. Opin. Allergy Clin. Immunol.* 3 (2003) 261–267.
- [103] K.L. Campbell, J.R. Cohn, M.P. Savage, Clopidogrel hypersensitivity: clinical challenges and options for management, *Expert. Rev. Clin. Pharmacol.* 3 (2010) 553–561.
- [104] C.J. Beavers, N.W. Carris, K.M. Ruf, Management strategies for clopidogrel hypersensitivity, *Drugs* 75 (2015) 999–1007.
- [105] K.L. Campbell, J.R. Cohn, D.L. Fischman, P. Walinski, R. Mallya, W. Jaffrani, M.P. Savage, Management of clopidogrel hypersensitivity without drug interruption, *Am. J. Cardiol.* 107 (2011) 812–816.
- [106] P. Owen, J. Garner, L. Hergott, R.L. Page, Clopidogrel desensitization: case report and review of published protocol, *Pharmacotherapy* 28 (2008) 259–270.
- [107] J.L.M. Mutnick, Desensitization to prasugrel: cardiology's increased need for allergy consultation, *Ann. Allergy Asthma Immunol.* 108 (2012) 123–124.
- [108] K. Scherer, K. Brockow, W. Aberer, J.H. Gooi, P. Demoly, A. Romano, B. Schnyder, P. Whitaker, J.S. Cernadas, A.J. Bircher, et al., Desensitization in delayed drug hypersensitivity reactions – an EAACI position paper of the Drug Allergy Interest Group, *Allergy* 68 (2013) 844–852.
- [109] S.K. Khambekar, J. Kovac, A.H. Gershlick, Clopidogrel induced urticarial rash in a patient with left main stem percutaneous coronary intervention: management issues, *Heart* 90 (2004), e14.
- [110] J.W. van Werkum, T.L. Braber, P.W. Verheggen, S.M. Van Der Have-Roefel, Prasugrel as alternative treatment strategy in a case with a hypersensitivity reaction to clopidogrel, *Platelets* 22 (2011) 77–78.
- [111] P. Chopra, P. Verma, W.B. Klaustermeyer, Successful use of prasugrel, an alternative antiplatelet agent, in a patient with clopidogrel allergy, *Ann. Allergy Asthma Immunol.* 107 (2011) 541–542.
- [112] S.R. Peppard, B.M. Held-Godgluck, R. Beddingfield, Use of prasugrel in a patient with clopidogrel hypersensitivity, *Ann. Pharmacother.* 45 (2011), e54.
- [113] E. Felix-Getzik, L.M. Sylvia, Prasugrel use in a patient allergic to clopidogrel: effect of a drug shortage on selection of dual antiplatelet therapy, *Am. J. Health Syst. Pharm.* 70 (2013) 511–513.
- [114] T.N. Patel, M. Kreindel, A.M. Lincoff, Use of ticlopidine and cilostazol after intracoronary drug-eluting stent placement in a patient with previous clopidogrel-induced thrombotic thrombocytopenic purpura: a case report, *J. Invasive Cardiol.* 18 (2006) e211–e213.
- [115] S. Khangura, W.L. Gordon, Prasugrel as an alternative for clopidogrel-associated neutropenia, *Can. J. Cardiol.* 27 (869) (2011) e9–e11.
- [116] A.J. Deshmukh, S. Pant, J. Cook, R. Sachdeva, D. Rutlen, B.F. Uretsky, Prasugrel-induced rash, *Ann. Pharmacother.* 46 (2012) 1123–1125.
- [117] S.H. Kim, S.D. Park, Y.S. Baek, S.Y. Lee, S.H. Shin, S.I. Woo, D.H. Kim, J. Kwan, Prasugrel-induced hypersensitivity skin reaction, *Korean Circ. J.* 44 (2014) 355–357.
- [118] D.C. Yang, D.N. Feldman, L.K. Kim, R.M. Minutello, G. Bergman, S.C. Wong, R.V. Swaminathan, A strategy of 'treating through' a prasugrel-induced rash, *Int. J. Cardiol.* 168 (2013) 4381–4382.
- [119] P.P. Dobesh, J.H. Oestreich, Ticagrelor: pharmacokinetics, pharmacodynamics, clinical efficacy, and safety, *Pharmacotherapy* 34 (2014) 1077–1090.
- [120] A.M. Manchette, A.G. Drucker, J.L. Januzzi, Acute coronary syndrome antiplatelet alternatives in clopidogrel allergy, *Pharmacotherapy* 34 (2014) e152–e156.
- [121] J.R. Harris, J.C. Coons, Ticagrelor use in a patient with a documented clopidogrel hypersensitivity, *Ann. Pharmacother.* 48 (2014) 1230–1233.
- [122] R. Shah, L.A. Keough, A. Belalcazar-Portacio, K.B. Ramanathan, Ticagrelor as an alternative in clopidogrel-associated neutropenia, *Platelets* 26 (2015) 80–82.