Atherosclerosis 243 (2015) 389–394

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Impact of atorvastatin or rosuvastatin co-administration on platelet reactivity in patients treated with dual antiplatelet therapy

Monica Verdoia [a], Matteo Nardin [a], Chiara Sartori [a], Patrizia Pergolini [b], Roberta Rolla [b], Lucia Barbieri [a], Paolo Marino [a], Giorgio Bellomo [b], Harry Suryapranata [c], Giuseppe De Luca [a, *], on behalf of the Novara Atherosclerosis Study Group (NAS)[a]

[a] Division of Cardiology, Azienda Ospedaliera-Universitaria "Maggiore della Carità", Eastern Piedmont University, Novara, Italy
[b] Clinical Chemistry, Azienda Ospedaliera-Universitaria "Maggiore della Carità", Eastern Piedmont University, Novara, Italy
[c] Department of Cardiology, UMC St Radboud, Nijmegen, The Netherlands

ARTICLE INFO

Article history:
Received 16 March 2015
Received in revised form
15 May 2015
Accepted 2 October 2015
Available online 9 October 2015

Keywords:
Rosuvastatin
Ticagrelor
Clopidogrel
Cythocromes

ABSTRACT

Background: Residual high-on treatment platelet reactivity (HRPR) still represents a challenging matter in patients with coronary artery disease. Drug-to-drug interaction has been suggested between some statin and antiplatelet agents, despite their co-administration is mandatory in patients after an acute cardiovascular event or coronary stenting. Therefore, the aim of the current study was to investigate any impact of rosuvastatin or atorvastatin co-administration on platelet reactivity in patients receiving dual antiplatelet therapy (DAPT).

Methods: Our population is represented by patients on DAPT (ASA and either clopidogrel 75 mg or ticagrelor 90 mg b.i.d) after an ACS or percutaneous revascularization, and receiving rosuvastatin or atorvastatin. Platelet function was assessed by Multiplate Impedance Aggregometry (Roche Diagnostics AG).

Results: We included a total of 374 patients, 240 (64.2%) receiving atorvastatin, 134 (35.8%) rosuvastatin. Rosuvastatin treated patients were more often using beta-blockers ($p = 0.05$), diuretics ($p = 0.04$) and displayed higher HDL ($p < 0.001$) and lower LDL cholesterol ($p < 0.001$). The prevalence of HRPR for ASA was low, with no difference according to statin type (0.8% vs 1.5%, $p = 0.62$, adjusted OR[95%CI] = 2[0.23−16.6], $p = 0.52$). Concerning ADP-antagonists, in the 163 patients treated with clopidogrel, rosuvastatin co-administration was associated with a significantly increased rate of HRPR (55.6%vs 32%, $p = 0.01$, adjusted OR[95%CI] = 2.69[1.22−5.96], $p = 0.015$) with higher ADP-mediated platelet reactivity ($p = 0.01$) and TRAP-test results ($p = 0.04$). On the contrary, in the 211 ticagrelor treated patients, statin type did not affect mean platelet reactivity or the prevalence of HRPR with ticagrelor (10.5% vs 11.2%, $p = 0.99$, adjusted OR[95%CI] = 0.86[0.34−2.22], $p = 0.76$)

Conclusions: Among patients receiving DAPT, rosuvastatin but not atorvastatin is associated with an increased rate of HRPR for clopidogrel, without any influence on the antiplatelet effect of ASA or ticagrelor. Therefore, cautiousness should be exerted for clopidogrel and rosuvastatin therapeutic association.

1. Background

Improvements in percutaneous coronary revascularization techniques and pharmacological strategies have positively affected the outcome of patients with coronary artery disease (CAD), especially in acute coronary syndromes (ACS) [1,2], where largest benefits have been obtained from high-intensity statins and more potent dual antiplatelet therapy (DAPT) [3,4]. However, suboptimal platelet inhibition or high-residual on treatment platelet reactivity

Abbreviations: ASA = acetylsalicylic acid, DAPT = dual antiplatelet therapy; PCI = percutaneous coronary intervention, HRPR = high-residual on-treatment platelet reactivity; MEA = multiple electrode aggregometry, ADP = adenosine diphosphate; MI = myocardial infaction, CABG = coronary artery bypass grafting; ACE = angiotensin-converting enzyme, CAD = coronary artery disease; LDL = low-density lipoprotein, HDL = high density lipoprotein.

* Corresponding author. Ospedale "Maggiore della Carità", Eastern Piedmont University, C.so Mazzini, 18, 28100 Novara, Italy.
E-mail address: giuseppe.deluca@maggioreosp.novara.it (G. De Luca).

http://dx.doi.org/10.1016/j.atherosclerosis.2015.10.005
0021-9150/

(HRPR) still occurs in a large quote of patients on DAPT, enhancing the risk of recurrent ischemic events and stent thrombosis [5,6].

Thus, recently large attention has been paid to the identification of the causes of HRPR, with a special focus on potential drug-to-drug interactions, in particular for clopidogrel, whose complex metabolic activation via the hepatic cytochromes CYP2C19 and CYP3A4, has been identified as a major determinant of its interindividual variability of response [7,8].

However, contrasting results have been achieved with high intensity statins [9], such as rosuvastatin and atorvastatin. In fact, their co-administration with clopidogrel often occurs in patients with CAD and, being these statins inactivated by the CYP2C19 and CYP3A4 enzymes, they could interfere with clopidogrel activation. Moreover, even few data have been reported with the new antiplatelet agent ticagrelor that, not requiring hepatic activation, has partially overcome the phenomenon of HRPR observed with clopidogrel [10]. Nevertheless, a modest hepatic biotransformation into active metabolites has been documented also for ticagrelor via the CYP3A4 and 3A5, accounting for about 30% of the circulating drug [11] and potentially being exposed to the same risk of interaction with statins as for clopidogrel.

Therefore, the aim of present study was to evaluate the impact of different statin types on the antiplatelet effect of clopidogrel or ticagrelor among patients receiving dual antiplatelet therapy for CAD.

2. Methods

We included patients admitted to the Division of Cardiology, "Maggiore della Carità" Hospital, Eastern Piedmont University in Novara, Italy, from September 2011 to October 2014 and treated with DAPT and statins for either ACS or stable CAD. All patients receiving at discharge atorvastatin or rosuvastatin and DAPT with ASA (100–160 mg daily) and either ticagrelor (90 mg every 12 h) or clopidogrel (75 mg daily) were scheduled for chemistry and platelet function tests evaluation at 30–90 days from discharge. Invasive treatment with coronary angiography and eventual coronary stenting was not a required inclusion criteria. The study was approved by our local Ethical Commitee and informed consent was obtained by all patients.

Main demographic, clinical and angiographic data, together with the indication to dual antiplatelet therapy were recorded at discharge and included in a dedicated database, protected by password. Main cardiovascular risk factors were identified. Hypertension was defined as systolic pressure >140 mmHg and/or diastolic pressure was >90 mmHg or if the individual was taking antihypertensive medications. The diagnosis of diabetes was based on previous history of diabetes treated with or without drug therapies, fasting glucose >126 g/dL or HbA1c > 6.5% at the moment of admission [12]. Exclusion criteria were patients' refusal or non-adherence to prescribed medications.

High-intensity statin therapy was defined as atorvastatin ≥40 mg daily or rosuvastatin ≥20 mg daily according to 2013 AHA/ACC Guidelines [13]. Proton pump inhibitors were routinely administered in all patients on DAPT.

3. Biochemistry analysis

Blood samples were drawn in the early morning, following a fasting period of 12 h. Glucose, creatinine, glycosylated hemoglobin and lipid profile were determined as previously described [14]. Blood cells count was performed in a blood sample collected in tripotassium EDTA (7.2 mg) tubes. These blood samples were analyzed within 2 h of venipuncture by automatic blood cells counter (A Sysmex XE-2100).

4. Platelet aggregation

Platelet aggregation was assessed by Multiplate electrical impedance aggregometry (MEA), in the early morning (between 8 and 9 a.m.). The aggregation tests were performed from 30 min to 2 h from blood collection [15]. Platelets aggregation was assessed after stimulation with arachidonic acid (0.5 mm/L) (ASPI test), collagen (3.2 μg/mL) (COL test), ADP (6.4 μmol/L) with prostaglandin E1 and thrombin receptor activating peptide, (TRAP-6; 30 μmol/L). Results were expressed as arbitrary Aggregation Units (AU) and plotted against time, defining platelet function as the area under curve (AUC or AU*min). HRPR was considered for AU*min values above lower limit normal for ASA (HAPR), [range: 862–1344] or after ADP stimulation [range: 417–1030] [16]. In addition, the previously reported cut-off of 468AU*min was also applied [17].

5. Statistical analysis

Statistical analysis was performed by SPSS Statistics Software 17.0. (SPSS Inc., Chicago, Illinois). Continue variables were represented as mean ± SD, while categorical variables as percentage. Chi-Squared and ANOVA test were appropriately used to compare clinical and laboratory features according to the type of statin treatment. Multiple logistic regression analysis was performed to assess the potential association between the occurrence of HRPR and statin type, after correction for baseline differences that were entered in the model in block. A p value < 0.05 was considered statistically significant.

6. Results

Our population is represented by 374 patients, 240 of them (64.2%) were on atorvastatin, 134 (35.8%) on rosuvastatin.

Table 1 displays main demographic and clinical characteristics according to statin type. The percentage of patients receiving a high-dose statin did not differ between the two study groups. Rosuvastatin treated patients were more often using beta-blockers ($p = 0.05$), diuretics ($p = 0.04$) and displayed higher HDL ($p < 0.001$) and lower LDL cholesterol ($p < 0.001$) as compared to patients on atorvastatin.

No difference in the timing of platelet function tests from discharge was observed among our patients according to statin treatment (45 ± 14.2 vs 55.8 ± 15.3, $p = 0.62$).

No significant difference in mean platelet reactivity was observed between patients on rosuvastatin vs atorvastatin, but for higher values of TRAP-mediated aggregation in rosuvastatin treated patients ($p = 0.01$), as displayed in Table 2.

The prevalence of HRPR for ASA was low, with no difference according to statin type (0.8% vs 1.5%, $p = 0.62$, Fig. 1). Results were confirmed after correction for baseline differences, with no association between statin type and impaired ASA response (adjusted OR[95%CI] = 2[0.23–16.6], $p = 0.52$ for rosuvastatin vs atorvastatin).

In the 163 patients treated with clopidogrel, higher mean ADP-mediated platelet reactivity ($p = 0.01$) and TRAP-test results ($p = 0.04$) were observed for the concomitant use of rosuvastatin and clopidogrel (Table 2). Rosuvastatin co-administration was associated with a significant increase of HRPR (55.6%vs 32%, $p = 0.01$, Fig. 2), that was confirmed after adjustment for baseline confounders (adjusted OR[95%CI] = 2.69[1.22–5.96], $p = 0.015$).

On the contrary, in the 211 ticagrelor treated patients, statin type did not affect mean platelet reactivity (Table 2) or the prevalence of HRPR with ticagrelor (10.5% vs 11.2%, $p = 0.99$, Fig. 3), with results being confirmed at multivariate analysis (adjusted OR[95%