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CASE REPORT

Recurrent coronary disease in HIV-infected patients: role of drug–drug interactions

Correspondence Dr Iria Bravo, Internal Medicine Department, University Hospital of Ferrol, Av. da Residencia, s/n, 15405 Ferrol, A Coruña, Spain. Tel.: +34 981 334056; E-mail: iria.bravo.blazquez@sergas.es

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Iria Bravo[1], Hortensia Álvarez[2], Ana Mariño[2], Bonaventura Clotet[3,4,5,6,7] and José Moltó[3,4,5]

[1]Internal Medicine Department, University Hospital of Ferrol, A Coruña, Spain, [2]Infectious Diseases Unit, Internal Medicine Department, University Hospital of Ferrol, A Coruña, Spain, [3]Fundació Lluita contra la Sida, Hospital Universitari Germans Trias i Pujol, Badalona, Spain, [4]Infectious Diseases Department, Hospital Universitari Germans Trias i Pujol, Badalona, Spain, [5]Universitat Autònoma de Barcelona (UAB), Barcelona, Spain, [6]Fundació IrsiCaixa, Hospital Universitari Germans Trias i Pujol, Badalona, Spain, and [7]Universitat de Vic–Universitat Central de Catalunya (UVIC-UCC), Vic, Spain

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Cardiovascular disease represents a leading comorbidity in HIV populations. Different factors may contribute to the recurrence of cardiovascular events in HIV-infected patients. Here, we describe two patients with HIV infection and an acute coronary syndrome who developed in-stent thrombosis after a percutaneous revascularization procedure. Also, we discuss the potential role of drug interactions between antiretroviral and antiplatelet treatments as a contributing factor for recurrent coronary disease in HIV-infected patients.

Combined antiretroviral treatment (cART) has significantly decreased AIDS-related morbidity and mortality during the last few decades. However, HIV-infected patients are currently facing new health-related problems. In this regard, a higher relative risk of developing cardiovascular events among HIV-infected populations relative to HIV-negative populations has been reported by several authors [1]. Moreover, cardiovascular disease currently represents one of the main causes of morbidity and mortality in HIV-infected patients [1–5].

Although it remains a matter of debate, it has been suggested that cardiovascular disease in HIV-infected patients is characterized by earlier onset and more aggressive evolution compared with the general population [3]. Moreover, the rate of recurrence of coronary events after undergoing revascularization procedures has been reported to be higher in HIV-positive than in HIV-negative patients [2–4]. Several factors may contribute to the higher recurrence of coronary events in the HIV population. Among others, these include HIV RNA load, CD4+ T cell count, C-reactive protein levels or the prothrombotic status that has been described in this population [3, 5]. Additionally, drug interactions between antiretroviral and antiplatelet treatments may also have a potential role in the worse prognosis of coronary disease observed in HIV-infected patients.

We report two patients in whom the recurrence of coronary disease may have been mediated, at least in part, by drug interactions between cART and antiaggregant therapy. Both patients had signed written consent forms allowing us to report their clinical cases in an anonymized manner.

Patient 1 was a 39-year-old male, a current smoker, with HIV infection diagnosed since 2012. After HIV diagnosis, he started cART with tenofovir/emtricitabine/efavirenz, achieving optimal immune and virological control. In November 2014, the patient was admitted to hospital due to chest pain. The ECG showed signs compatible with an acute inferior myocardial infarction, and coronary angiography revealed occlusion of the right coronary artery. A conventional stent was inserted, and the patient started therapy with **aspirin**, **ticagrelor**, **enalapril**, **bisoprolol**, **atorvastatin** and

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pantoprazole. One week later, the patient returned to the hospital with a new episode of chest pain, and an ECG showed findings suggestive of recurrent acute inferior coronary syndrome. A new coronary angiography revealed the presence of thrombosis in the recently inserted stent. Thromboaspiration and implantation of a drug-eluting stent were performed. At discharge, ticagrelor was replaced by **prasugrel**, and efavirenz was replaced by raltegravir. After 2 years, no recurrence of coronary events had been detected in this patient.

Patient 2 was a 45-year-old male with HIV infection diagnosed since 2004. Following diagnosis, he started cART with **lopinavir**/**ritonavir** plus tenofovir/emtricitabine, which was later simplified to darunavir/ritonavir monotherapy. The patient maintained complete virologic suppression throughout the follow-up. In November 2014, he complained of progressive dyspnoea, being diagnosed with acute pulmonary oedema secondary to severe systolic dysfunction. A significant stenosis at the anterior descending coronary artery was shown by coronary angiography, and a conventional stent was implanted. The patient started treatment with aspirin, **clopidogrel**, enalapril, bisoprolol, atorvastatin and **omeprazole**, with no change in his antiretroviral regimen. Six months later, the patient had an episode of chest pain, accompanied by electrocardiographic signs of acute anterior myocardial infarction, and evidence of thrombosis of the implanted stent. He then underwent thromboaspiration and implantation of a drug-eluting stent, and clopidogrel was replaced by prasugrel. No changes were made in his antiretroviral regimen. After 2 years of follow-up, the patient had no evidence of further ischaemic events.

Platelet reactivity, which is an independent risk factor for major cardiovascular events after percutaneous coronary intervention, has been shown to be higher in HIV-infected compared with HIV-uninfected patients, regardless of dual antiplatelet therapy [6, 7]. Several factors have been suggested to contribute to such a prothrombotic status. In our opinion, potential drug interactions between antiretroviral and antiplatelet drugs could have resulted in decreased antiaggregant effect and therefore in higher risk of recurrent ischaemic events in the two clinical cases reported here. This was supported by the Drug Interaction Probability Scale (DIPS) score, which was 5 points for patient 1, and 6 points for patient 2 [8].

Ticagrelor is metabolized mainly by the isoenzyme **CYP3A4** of the cytochrome P450, present in the liver and the gut lumen. Thus, co-administration of ticagrelor with CYP3A4 inducers can lead to decreased ticagrelor concentrations in plasma and thus loss of its antiplatelet effect. In this regard, Teng *et al*. reported a decrease of 86% in ticagrelor exposure when it was given with **rifampin** [9]. Similarly, CYP3A4 induction by efavirenz might have contributed to the recurrence of the acute coronary syndrome seen in patient 1.

Regarding patient 2, clopidogrel and prasugrel are both administered as prodrugs that are metabolized to their active forms through the CYP3A4 pathway. Therefore, inhibition of CYP3A4 by ritonavir in this case may have led to subtherapeutic plasma concentrations of active clopidogrel, putting the patient at risk of a recurrence of his coronary disease. In this regard, it has been reported that co-administration of **ketoconazole** with clopidogrel decreased the concentrations of the active metabolite of clopidogrel in a range between 22% and 29%, which resulted in a decrease of the antiaggregant effect of clopidogrel from 28% to 33%. On the other hand, although co-administration of ketoconazole with prasugrel also decreased the plasma concentration of the active metabolite of prasugrel by 34% to 46%, such a decrease in active prasugrel plasma concentrations did not result in a decrease in its antiaggregant effect. This difference between clopidogrel and prasugrel is possibly a reflection of the higher potency of prasugrel as a **P2Y12** inhibitor, compared with clopidogrel [10]. In addition to the clinical case reported here, Metzger and Momary showed the lack of antiaggregant effect of clopidogrel in a patient whose antiretroviral regimen included ritonavir [11]. Similarly, Carvalho *et al*. recently described an early stent thrombosis in a patient treated with both clopidogrel and ritonavir [12]. In our opinion, this drug–drug interaction could also have played a role in these cases and it may also explain the association between exposure to protease inhibitors and increased platelet reactivity which was described by Hauguel-Moreau *et al*. in a cohort of HIV-infected patients with an acute coronary syndrome on dual antiplatelet therapy (mainly aspirin plus clopidogrel) [7]. If so, the use of antiretroviral regimens including unboosted integrase inhibitors or rilpivirine could be prioritized in HIV patients on antiaggregant therapy. However, in order to optimize efficacy and safety, this should be discussed by an interdisciplinary team in a case-by-case basis.

In conclusion, the clinical cases reported here are examples of how drug interactions between cART and antiplatelet therapy may contribute to the worse prognosis of coronary disease described in HIV-infected patients. Thus, interdisciplinary collaboration between cardiologists and HIV specialists is crucial for the optimal treatment of both the coronary disease and the HIV infection, while minimizing the risk of adverse outcomes for the patient.

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [13], and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 [14, 15].

Competing Interests

I.B. has no competing interests to declare. H.A. has received support for attending meetings from Janssen-Cilag, Gilead Sciences, ViiV Healthcare, AbbVie and Merck Sharp & Dohme. A.M. declares no relevant competing interests to the content of the manuscript. B.C. and J.M. have received research funding, consultancy fees and lecture sponsorships from and have served on advisory boards for various laboratories (MSD, AbbVie, Boehringer Ingelheim, Gilead Sciences, ViiV Healthcare, Janssen-Cilag and Bristol-Myers-Squibb).

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