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Case Report

Association of Macitentan and Tadalafil in the Treatment of Pulmonary Arterial Hypertension Associated with HIV

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Abstract

Pulmonary arterial hypertension is a serious disease with a poor short-term prognosis if adequate treatment is not instituted early. The association of this disease with human immunodeficiency virus is well known.

We present the case of a patient diagnosed with pulmonary arterial hypertension associated with human immunodeficiency virus whose evolution has been very favourable due to a possible interaction between tadalafil and antiretroviral drugs.

Keywords: *Pulmonary Arterial Hypertension; Human Immunodeficiency Virus; Tadalafil; Right Cardiac Catheterization; Right Atrium*

Abbreviations

FC: Functional Class; PAH: Pulmonary Arterial Hypertension; 6MWT: Six Minutes Walking Test; DLCO: Single Breath Carbon Monoxide Diffusing Capacity; VE/VCO_2: Ventilatory Equivalent for Carbon Dioxide; VO_2: Peak Oxygen Consumption

Introduction

The use of highly active antiretroviral therapies and the aggressive management of opportunistic infections have contributed to improving the life expectancy of HIV-infected patients. Consequently, the spectrum of complications has changed, with a higher prevalence of other chronic pathologies namely Pulmonary Arterial Hypertension (PAH) [1]. In this article we will present the clinical case of a patient, with PAH associated with HIV, treated using the combination of macitentan and tadalafil.

Clinical Case

A 45-year-old male with no known drug allergies, former parenteral drug addict. Ex-smoker, diagnosed with HIV infection 22 years ago. HCV positive without liver disease data. In treatment with trimethoprim-sulfamethoxazole on alternating days, tenofovir, darunavir, ritonavir and raltegravir. The patient was referred from the Infectious Diseases Unit with suspected pulmonary hypertension, presenting symptoms compatible with FC III. On physical examination, patient showed good general conditions, with 97% basal SpO_2.

The following complementary tests were performed:

- **Analytical:** Renal, hepatic, thyroid and NT-proBNP (43.26 pg/mL) normal function values. Lymphocyte populations: CD4: 111.35 x 106/µL (1.7%). Negative lupus anticoagulant. antinuclear antibodies and negative neutrophil anti-citoplasma. HIV viral load 59 copies/mL. Hepatitis C viral load negative.

- **Electrocardiogram:** Sinus rhythm at 75 beats per minute, axis at 90, incomplete blocking of the right branch of the Hiss Beam and indirect signs of growth of the right ventricle.
- **Respiratory function tests:** FEV1/FVC 75.95%, FEV1 4L (102.5%), FVC 5.27L (109.7%), with negative bronchodilator test. DLCOc 8.29 mmol/min/kPa (76%); DLCOc/VA 78.4%.
- **6MWT:** 425m travelled, with initial SpO_2 97%, final 94%.
- **Pulmonary ventilation/perfusion scan:** No segmental lung perfusion defects.
- **Abdominal ultrasound:** No portal hypertension data.
- **Echocardiogram:** RV very dilated with an anterior-posterior diameter of 33 mm and hypertrophy of the free wall (9 mm thick); area RA 28.4 cm^2. Severe deterioration of the RVEF. Mild TR with PsP > 80 mmHg. Normal LVEF, left displacement of septum at inspiration start. No pericardial effusion.
- **Right cardiac catheterization:** Confirms pre-capillary pulmonary hypertension with increased pulmonary vascular resistance (Table 1a).

The diagnosis of pulmonary arterial hypertension associated with HIV is established.

Given the absence of clinically relevant interactions between macitentan and its active metabolite on the enzymes of cytochrome P450, it was decided to initiate monotherapy treatment with macitentan 10 mg daily oral doses.

After 6 months of treatment, the patient is in FC II, without angina, syncope or congestive signs. Presents NT-proBNP: 31.2 pg/mL. In 6MWT it travels 500m, without desaturation. Good tolerance to macitentan without adverse events throughout the first months of treatment.

At 9 months, a new echocardiogram is performed, without major changes with the previous one, with an RA area of 24 cm^2. A further evaluation whereby a cardiac magnetic resonance was performed for a better morphological and functional evaluation of RV with the following findings: Focal late intramyocardial enhancement in RV insertions (score 2); interventricular septum type 2 (protodiastolic flattening); TDIV RV 89 ml/m^2 (N < 108 ml/m^2), RVEF 44%, CI 2.4 $L/min.m^2$; RA area 21cm^2; Pulsatility of PA 36%, Flow in PA type 3, Vmedia 10.5 cm/s. Given the above-mentioned data and the lack of achievement of therapeutic objectives in the imaging studies, it was decided to associate treatment with tadalafil up to 40 mg a day with good tolerance and without interference with antiretroviral treatment.

At 14 months, five on combined oral treatment, echocardiogram (RA area 13.8 mm2, no TR or pericardial effusion) and hemodynamic control study were performed (Table 1a).

Hemodynamic parameters	Basal	14 months macitentan + tadalafil
PAP systolic/diastolic/media (mmHg)	73/32/48	44/17/27
PEP (mmHg)	15	7
PAD (mmHg)	10	5
CO (l/min)	3.45	6.22
CI ($l/min/m^2$)	1.65	2.9
PVR (UW)	13	9
O_2 saturation in aorta (%)	97	97
O_2 saturation in pulmonary artery (%)	63.9	69.2

Table 1a: *Basal haemodynamic parameters and After 14 months of treatment.*

At 19 months, 10 months after combination therapy was started, the patient is in FC I, with no syncope or signs of right heart failure (Table 1b).

	Syncope	FC	6MWT (m)	NT-BNP (pg/mL)	RA area (cm^2)	PE	mRAP (mmHg)	CI (mL/min/Kg)	SvO_2 (%)	VO_2 peak ml/kg/min (%)	VE/VCO_2 (%)
Basal	NO	**III**	**425**	43.26	**28.4**	NO	**10**	**1.7**	**63.9**	15,9 (56%)	37,3
14 - 19 months	NO	I	500	31.2	13.8	NO	5	2.9	69.2	21,8 (78)	32

Table 1b: *Risk assessment according to ESC/ERS 2015 criteria, baseline and between 14 and 19 months of treatment*

Bold: Evolutionary parameters at intermediate or high risk level.

Abbreviations: *6MWT: 6-minute Walking Test; CF: Functional Class; CI: Cardiac Index; CO: Cardiac Output; FEV1: Forced Exhaled Volume on First Second; FVC: Forced Vital Capacity; HAP: Pulmonary Arterial Hypertension; HIV: Human Immunodeficiency Syndrome; HCV: Hepatitis C Virus; mRAP: Mean Right Atrial Pressure; LV: Left Ventricle; LVEF: Left Ventricle Ejection Fraction; NT-proBNP: Atrial Natriuretic Peptide Precursor; PA: Pulmonary Artery; PD: Pericardial Effusion; mRAP: Right Atrial Mean Pressure; PE: Pericardial Effusion; PAP: Pulmonary Arterial Pressure; PEP: Pulmonary Interlocking Pressure; PVR: Pulmonary Vascular Resistances; RA: Right Atrium; RV: Right Ventricle; RVEF: Right Ventricle Ejection Fraction; TDIV RV: Teledyastolic Indexed Volume of Right Ventricle; TI: Tricuspid Insufficiency; SvO_2: O_2 Saturation in Mixed Venous Blood.*

The patient has presented undetectable viral load figures since the initiation of antiretroviral therapy, which has not been modified at any time.

Discussion

Pulmonary arterial hypertension is a fatal disease with an increased prevalence in HIV-infected patients.

Ritonavir is a potent CYP3A4 cytochrome inhibitor that has been shown to increase the area under the plasma tadalafil concentration curve by 124%, without modifying the maximum concentration. One case has been reported in which a patient on ritonavir treatment had increased clinical effects of tadalafil, when taken simultaneously. According to the probability of drug interaction scale (DIPS), the event/drug ratio in this case was likely [3]. Interactions between tadalafil and other CYP3A4 cytochrome inhibitors have been previously described, including ketoconazole and itraconazole, producing an increase in the area under the curve and priapism [4]. A randomized clinical trial with tadalafil has demonstrated its efficacy as an initial monotherapy at a dose of 40 mg per day in the treatment of PAH, improving exercise capacity, FC, hemodynamic parameters and the time to clinical worsening [5].

In the clinical case that we present, the patient presents a great improvement both clinically and in exercise parameters, echocardiographs and hemodynamics, practically all of which are located in low risk stage defined in current guidelines (Table 1b).

Thus, treatment of PAH has to be ambitious keeping patients in a low risk profile according to evaluated parameters in guidelines, not using FC and 6MWT isolated.

Conclusions

In this case, we have to underline the combination between tadalafil and macitentan and their improvement in haemodynamic parameters.

There is a known pharmacological interaction between both with increased levels of tadalafil that can explain the results and opens up gates about tadalafil dose.

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