

Treatment of HIV-Associated Pulmonary Hypertension With Treprostinil

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Background and objective. The treatment of pulmonary hypertension associated with infection by human immunodeficiency virus has not been well defined. Treprostinil is a prostacyclin analogue that has recently been shown to be useful for the treatment of pulmonary hypertension, whether primary, secondary to congenital heart disease, or associated with collagen disease, in a 12-week, double-blind study. We report the results of a one-year follow-up of three patients with pulmonary hypertension associated with human immunodeficiency virus infection who are being treated with treprostinil at our center.

Patients and method. After secondary causes of pulmonary hypertension were excluded by a routine work-up, patients started treatment with subcutaneous prostacyclin (treprostinil) with progressive up-titration of the dose. Functional status and effort capacity were assessed every three months and an echocardiographic study was performed every six months.

Results. All patients showed improvement in clinical status, as shown by the NYHA functional class and the results of the six-minute walking test (increase of at least 75 meters). All the patients remain alive after one year of follow-up. Echocardiographic systolic pulmonary pressure decreased in two patients. No serious adverse events were observed.

Conclusions. Subcutaneous prostacyclin (treprostinil) seems to be an effective and safe therapeutic option for the treatment of pulmonary hypertension associated with human immunodeficiency virus infection.

Key words: *Hypertension pulmonar. Treprostinil. Prostaglandins. Human immunodeficiency virus.*

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Tratamiento de la hipertensión pulmonar asociada a la infección por VIH con treprostinil

Introducción y objetivo. El tratamiento de la hipertensión pulmonar asociada a infección por virus de la inmunodeficiencia humana no está bien definido. El treprostinil es un análogo de la prostaciclina que recientemente ha demostrado eficacia en el tratamiento de la hipertensión pulmonar primaria, secundaria a cardiopatías congénitas y asociada a colagenosis, en un estudio doble ciego de 12 semanas de duración. Describimos el seguimiento al año de los 3 pacientes con hipertensión pulmonar asociada a infección por virus de la inmunodeficiencia humana tratados con treprostinil en nuestro centro.

Pacientes y método. Tras descartar hipertensión pulmonar secundaria a otra causa mediante el estudio rutinario, los 3 pacientes comenzaron tratamiento con prostaciclina subcutánea (treprostinil) a dosis progresivamente crecientes. Se realizó una evaluación trimestral de la clase funcional y de la capacidad de esfuerzo, así como una ecocardiografía semestral.

Resultados. Los 3 pacientes mejoraron clínicamente según la clase funcional NYHA y la distancia caminada en el test de 6 min (aumento de al menos 75 metros), y permanecen vivos tras un año de seguimiento. En dos pacientes disminuyó la presión pulmonar sistólica estimada por ecocardiografía. No se observaron complicaciones graves asociadas.

Conclusiones. La prostaciclina subcutánea (treprostinil) parece ser una opción de tratamiento segura y eficaz en pacientes con hipertensión pulmonar asociada a infección por virus de la inmunodeficiencia humana.

Palabras clave: *Hipertensión pulmonar. Treprostinil. Prostaglandinas. Virus de la inmunodeficiencia humana.*

INTRODUCTION

The prevalence of symptomatic pulmonary hypertension (PHT) among the population infected with the human immunodeficiency virus (HIV) is estimated to be 0.5%, much higher than in the general population,^{1,2} and it does not appear to be related to the stage of the

ABBREVIATIONS

PHT: pulmonary hypertension.
 HIV: human immunodeficiency virus.
 sAPP: systolic arterial pulmonary pressure.
 NYHA: New York Heart Association.
 PVR: pulmonary vascular resistance.

disease or the degree of immunodepression.³ The prognosis for untreated acute PHT is ominous, and in the HIV-infected population mean survival from the time of diagnosis is 6 to 8 months.³ Continuous infusion of intravenous prostacycline is an efficacious treatment for primary PHT^{4,5} or PHT associated with collagenosis.^{6,7} It improves symptoms and the survival rate, but requires continuous intravenous administration via a central catheter, and complications occur frequently, such as catheter displacement, local catheter infection (estimated at the rate of 0.22-0.68 episodes per patient per year), and even septicemia (0 to 0.39 episodes per patient per year), and often with fatal results.⁸ In HIV-infected patients there is little experience with this treatment, but it also appears to be beneficial.⁹

Treprostinil is a stable analog of prostacycline that can be administered subcutaneously with a continuous infusion pump. In a recent multicenter study the short-term (12 weeks) clinical efficacy, and a good safety profile of treprostinil was shown for the treatment of pre-capillary PHT.¹⁰ Nevertheless, this study did not include HIV-infected patients, so there is no reported data on its usefulness in this subgroup of patients. We describe the one-year course of 3 patients with HIV-associated PHT treated with subcutaneous prostacycline.

PATIENTS AND METHODS

Between January, 2000 and January, 2001, 3 patients with HIV-associated PHT were referred to our hospital for evaluation. Patient 1 is a 39-year-old man, ex-parenteral drug user, diagnosed with HIV infection 3 years previously, in CDC group A1, without associated opportunistic disease and being treated with zidovudine, lamivudine, and indinavir. At the time of diagnosis with PHT he presented with an undetectable viral load and an immunology test with a CD4 lymphocyte count of 1234/ μ L. Patient 2 is a 40-year-old woman, ex-intravenous drug user, diagnosed with HIV infection at the time of a pregnancy (CDC group A1), with an undetectable viral load and 856 CD4 lymphocytes/ μ L. At the time of diagnosis she was not undergoing antiviral treatment and had no history of HIV-infection related disease. Patient 3 is a 43-year-old man, homosexual, diagnosed with HIV infection 6 years previously, CDC group B3 (history of oral candidiasis and oral leukopla-



Fig. 1. Device for the continuous infusion of subcutaneous prostacycline (treprostinil) with the insertion point in the abdominal wall (MiniMed Pump 507).

sia), being treated with stavudine, lamivudine, and nelfinavir. At the time of evaluation, his viral load was undetectable and CD4 lymphocytes were 321/ μ L. HLA DR52 (typical of PHT associated with HIV infection) was found in patients 1 and 3.

All patients underwent complete evaluation per the protocol for assessment of pulmonary hypertension, including gated Doppler abdominal echography, thyroid hormone testing, complete respiratory function tests, pulmonary gammagraphy, and autoimmune testing to rule out secondary PHT and other diseases associated with PHT. The diagnosis of PHT and its hemodynamic degree of severity were evaluated by echocardiography, right catheterization, and acute vasodilation test with intravenous prostacycline (epoprostenol), according to the protocol described in the guidelines of the Spanish Cardiology Society.¹¹ The patients were considered to be positive for PHT if they produced a mean pulmonary pressure reduction of more than 10 mm Hg, or more than 20% with maintenance of arterial pressure and cardiac output.¹² Prior to beginning treatment, we evaluated the patients' functional class with the New York Heart Association (NYHA) questionnaire, and their functional capacity by the 6-minute walk test.

Treatment with treprostinil infusion was begun with a subcutaneous continuous release device (Minimed pump 507; Figure 1), as part of an open international clinical trial of patients with PHT in NYHA functional class II-IV, in which 27 patients from our center were included. The initial dose was 2 ng/kg/minute for all patients, and this was progressively increased according to the patients response and tolerance. Clinical followup and functional class evaluation according to the NYHA questionnaire and the 6-minute walk test were performed every 3 months. Followup of hemodynamic parameters (systolic arterial pulmonary pressure

TABLE 1. Baseline data from the 3 patients

	RA	sAPP	dAPP	map	mAPP (vd)	PCP	Sat	CO	CI	Est sAPP
Patient 1	2	75	30	48	48	4	62	3.5	2	77
Patient 2	8	107	44	70	77	7	56.6	4.4	2.5	103
Patient 3	14	99	40	67	66	10	56.5	4.2	2.4	110

RA indicates mean right atrium pressure (mm Hg); sAPP, systolic arterial pulmonary pressure (mm Hg); dAPP, diastolic arterial pulmonary pressure (mm Hg); map, mean arterial pulmonary pressure (mm Hg); mAPP (vd), mean arterial pulmonary pressure after vasodilator testing with prostacycline (mm Hg); PCP, pulmonary capillary pressure (mm Hg); Sat, pulmonary artery saturation (%); CO, cardiac output (l/min); CI, cardiac index (l/min/m² of body surface); Est sAPP, estimated systolic arterial pulmonary pressure per echography (mm Hg).

TABLE 2. Patient clinical and hemodynamic course

	NYHA functional class	6 min test (m)	Est sAPP (mm Hg)	Cardiac output (b/min)	Treprostinil dose (ng/kg/min)
Patient 1					
Baseline	III	335	77	4.2	0
3 months	II	390			9
6 months	II	436	71	4.8	13
12 months II	430	64	5.7	24	
Patient 2					
Baseline	II	500	103	2.5	0
3 months	II	525			11
6 months	I	532	95	4.0	20
12 months	I	576	65	3.6	24
Patient 3					
Baseline	III	313	110	4.7	0
3 months	III	376			10
6 months	II-III	375	114	4.7	13
12 months	II-III	388	103	5.2	26

6 min test indicates 6-minute walk test; Est sAPP est, estimated systolic arterial pulmonary pressure per echography. Cardiac output estimated by echography.

[sAPP] and estimated cardiac output) was performed every 6 months with echocardiography, as there is concordance between these values and baseline values measured by right catheterization.

RESULTS

We ruled out, through routine studies, the PHT being secondary to another illness. The 3 patients had hemodynamically severe PHT (Table 1) and, according to the Evian criteria (reduction of mean pulmonary pressure greater than 10 mm Hg or greater than 20%),¹² none of the patients had a positive response to the acute vasodilator test with intravenous prostacycline, resulting in a worse prognosis and excluding the possibility of treatment with calcium antagonists. As a result of these findings, treatment was begun with subcutaneous prostacycline. We briefly describe the clinical and hemodynamic course of our patients (Table 2).

The use of subcutaneous prostacycline was efficacious in all 3 patients, as they showed subjective clinical improvement according to the NYHA questionnaire and functional improvement on the 6-minute walk test. At 1 year, all the patients were alive and had evident clinical improvement. Their NYHA functional

class had improved, and the distance walked during the 6-minute test had increased by at least 75 meters (105, 776, and 75 meters, respectively). The 3 patients already showed improvement at the 12-week evaluation (an increase in the distance walked of 55, 25, and 63 meters, respectively). This improvement had not only been maintained but had been progressive during the first year of treatment.

The estimated sAPP per echography decreased in 2 patients (13 and 38 mm Hg), and did not change in the third. Estimated cardiac output increased in the first 2 patients and hardly changed in the third patient. None of the patients had serious side-effects. Two patients needed topical analgesia for pain in the puncture area, and 1 patients needed gabapentin at a dose of 600 mg per day for pain control. In no case did the pain prevent a progressive increase in the prostacycline dose.

DISCUSSION

The use of intravenous prostacycline in the treatment of patients with severe PHT associated with HIV infection has rarely been evaluated. Aguilar and Farber⁹ reported their experience with the treatment of 6 patients with continuous infusion intravenous

epoprostenol, 3 of them with a 2-year followup. All the patients showed clinical improvement with regard to their NYHA functional class, and, in re-catheterized patients, a decrease of mAPP and PVR, and an increase in cardiac output. Clinical and hemodynamic efficacy were similar to that described in previous studies on primary PHT,^{4,5} probably due to the similarity between the histological lesions of both entities. Nevertheless, there is reticence regarding the use of intravenous prostacycline in HIV-infected patients, especially among those who present with a higher level of immunodepression, due to the high risk of associated complications, particularly that of infection, and different administration methods are needed that do not require a central catheter.

The efficacy of subcutaneous prostacycline (treprostinil) for the short-term treatment of pre-capillary PHT has recently been reported by Simonneau et al¹⁰ in a multicenter double-blind study, which showed improvement in NYHA functional class, the 6-minute walk test, and the hemodynamic profile after 12 weeks of treatment. This study included patients with primary PHT associated with collagen disease and a congenital shunt, but patients with HIV infection were excluded, so there is no data on its efficacy in this group of patients. Nevertheless, subcutaneous prostacycline may be a safe and efficacious alternative for treatment of HIV-associated PHT, as its local release mechanism in subcutaneous tissue does not carry the risks associated with epoprostenol perfusion via central catheter. In addition, prostacycline does not interfere with the metabolism of anti-retroviral agents, so that it can also be used safely in this respect.

In our patients, treatment with subcutaneous prostacycline was effective in terms of improvement in NYHA functional class and the number of meters walked during the 6-minute test. Although this was an open study (the poor prognosis for arterial PHT prevents, for ethical reasons, the performance of long-term studies versus a control group), it is unlikely that the improvement was due to the placebo effect, as the patients' course is consistent with that reported by other clinical trials with prostacycline.^{4,6,10}

We also noted a decrease in systolic pulmonary pressure and an increase in cardiac output, estimated by echography in 2 of the patients. Although in 1 patient the hemodynamic parameters scarcely changed, their performance also improved with regard to the distance walked in 6 minutes. This effect was also described in patients treated with prostacycline, due to distinct action mechanisms (vasodilator, anti-proliferative, and anti-aggregate), not all of which are quantifiable from a hemodynamic point of view.⁸

After 12 weeks of treatment, the distance walked on the 6-minute walk test had increased for all patients. The increase was greater than that found in the study by Simonneau et al (overall difference between the

treatment group and the control group was 16 meters). This is probably due to the doses of treprostinil reached in our patients at 12 weeks (9, 11, and 10 ng/kg/min, respectively). In the Simonneau trial, the patients who experienced the most improvement were those taking a higher dose of treprostinil. Our patients' improvement was maintained 1 year following initiation of treatment, and there was actually a tendency to a progressive increase as the treprostinil dose was increased (24 to 26 ng/kg/min per year of treatment). As described with epoprostenol, there was an improvement in patients despite the absence of a response to the acute vasodilator test.

Serious side-effects have not been described with treprostinil. The side-effect that has been most often described with the use of this drug is pain in the puncture area. In the study mentioned above,¹⁰ 85% of patients presented with pain in the puncture area. In the majority of cases the pain is moderate, can be controlled with local analgesia, and does not prevent increasing the treprostinil dose. Two of our patients had pain and required analgesia (1 of them, conventional topical analgesia and the other, oral gabapentin). The latter drug (at a dose of between 300 and 900 mg/day) is more efficacious for the control of pain associated with the subcutaneous infusion of prostacycline, and in HIV-infected patients can also be used in conjunction with other anti-retroviral agents.

At the present time, as far as we know, the efficacy of treatment of PHT associated with HIV infection with treprostinil has not been described in even the short-term. Our group has already reported good results in the treatment of pre-capillary PHT with treprostinil at 1-year followup.¹³ The 3 cases described in our study show for the first time the efficacy and safety of treprostinil for the medium-term treatment of PHT associated with HIV infection.

Nevertheless, it is not known what the long-term effect will be on the survival of these patients, although in our case the 3 patients were not only alive following 1 year of treatment, but their functional situation is much better than it was at baseline.

CONCLUSIONS

In our initial experience, subcutaneous prostacycline seems to be a safe treatment option for patients with PHT associated with HIV infection, although greater experience is needed, both with regard to the number of patients studied and the length of patient followup in order to define its role.

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