SCIENTIFIC LETTER

Highly active antiretroviral therapy compared with HAART and bosentan in combination in patients with HIV-associated pulmonary hypertension

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Pulmonary arterial hypertension (PAH) is an increasingly recognised complication of HIV disease. The effects of highly active antiretroviral therapy (HAART) on the clinical course of HIV-associated PAH are still debated.¹ Bosentan, a dual endothelin 1 receptor antagonist, may be an effective approach to treatment of PAH in both HIV-uninfected and HIV-infected patients.^{2–4} We report the results of an open-label, six-month prospective, observational, preliminary study of previously untreated HIV-infected patients with PAH. They were followed up to assess the effect of HAART compared with HAART and bosentan in combination on their exercise capacity and cardiopulmonary haemodynamic parameters.

METHODS

Previously untreated HIV-infected patients with PAH were eligible for the study. The patients were screened by clinical examination and transthoracic echocardiography. Patients with an echocardiographic right ventricular systolic pressure > 35 mm Hg underwent right heart catheterisation. PAH was defined on the basis of mean pulmonary artery pressure (mPAP) at rest > 25 mm Hg, pulmonary capillary wedge pressure < 15 mm Hg and pulmonary vascular resistance > 240 dyn·s·cm⁻⁵ by right heart catheterisation.⁴ Exclusion criteria were age < 18 years; history of drug addiction and use of drugs known to have a definite cardiotoxic action (for example, cocaine and amphetamines); recent HIV-associated opportunistic infections; previous treatment with antiretroviral or immunomodulating drugs, or both; history of chronic obstructive pulmonary disease (assessed by analysis of clinical records and by pulmonary function tests); previous congenital or acquired heart disease (assessed by analysis of clinical records and by transthoracic echocardiography); treatment with prostacyclin analogues; moderate to severe liver impairment or liver enzyme above three times the upper limit of normal; portal hypertension; chronic diseases not specifically related to HIV infection (for example, autoimmune diseases); and inability to provide informed consent. HAART was given either as two nucleoside reverse transcriptase inhibitors and protease inhibitors in combination, or as non-nucleoside reverse transcriptase inhibitors on a backbone of dual nucleoside reverse transcriptase inhibitors. Bosentan was given at a dose of 62.5 mg twice daily for four weeks (weeks 0–4) and then at a maintenance dose of 125 mg twice daily up to the end of the study period (weeks 5–24). Downtitration to the lower dose for tolerability or safety reasons was possible.

The end point of the study was to evaluate the efficacy of HAART alone or HAART and bosentan in combination on exercise capacity, assessed by a 6 min walk test at weeks 12 and 24, and on the cardiopulmonary haemodynamic parameters at week 24 compared with baseline. The safety profile was assessed on the basis of recorded adverse events and

clinical and laboratory variables. The study was performed in agreement with the Declaration of Helsinki. Written informed consent was obtained from all patients selected for the study. The Mann-Whitney test and the Wilcoxon signed ranks test were used for analysis of continuous variables. Logistic regression analysis was performed to assess the covariates predictive of response to treatment with related odds ratios and 95% confidence interval (CI).

Table 1 Baseline demographic and clinical characteristics of the patients

Characteristic	Treatment group	
	HAART (n = 18)	HAART + bosentan (n = 18)
Men	15 (83%)	16 (88%)
Age (years)	45 (37–55)	47 (36–58)
Homosexuals	13 (72%)	11 (61%)
Heterosexuals	4 (22%)	5 (28%)
Unknown factors	1 (6%)	2 (11%)
Duration of documented seropositivity (months)	25 (11–32)	28 (14–43)
CD4 count (cells/mm ³)	330 (175–653)	350 (160–730)
Plasma HIV RNA (log ₁₀)copies/ml	4.3 (3.3–5.5)	4.5 (3.5–6.1)
Positivity for HBV/HCV	3 (17%)	2 (11%)
CDC class		
A1	3 (17%)	2 (11%)
A2	12 (66%)	13 (72%)
A3	3 (17%)	3 (17%)
Antiretroviral drug given at enrolment		
Combination (ritonavir + indinavir)	6 (33%)	7 (39%)
Nelfinavir	3 (17%)	2 (11%)
Zidovudine	18 (100%)	18 (100%)
Didanosine	18 (100%)	18 (100%)
Nevirapine	3 (17%)	2 (11%)
Efavirenz	6 (33%)	7 (39%)
Cardiopulmonary haemodynamic parameters		
Right atrial pressure (mm Hg)	11 (6–18)	12 (7–17)
mPAP (mm Hg)	52 (42–63)	53 (44–65)
PCWP (mm Hg)	7.5 (5–8)	7.7 (6–9)
PVR (dyn·s·cm ⁻⁵)	770 (610–930)	780 (625–950)
Cardiac index (l/min/m ²)	2.7 (2.2–3.3)	2.6 (2–3.2)
NYHA class		
III	17 (94%)	16 (89%)
IV	1 (6%)	2 (11%)
Six-minute walk distance (m)	270 (197–343)	265 (205–325)
Duration of symptoms (months)	12 (6–18)	11 (5–16)
Concomitant PAH treatment		
Anticoagulants	1 (6%)	2 (11%)
Oxygen	1 (6%)	2 (11%)

Data are mean number (%) or median (range).

CDC, Centers for Disease Control and Prevention; HAART, highly active antiretroviral therapy; HBV, hepatitis B virus; HBC, hepatitis C virus; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance.

Figure 1 (A) Six-minute walk distance documented in the patients of the two study groups at baseline and at weeks 12 and 24 and (B–F) cardiopulmonary haemodynamic parameters documented in the patients of the two study groups at baseline and at week 24. The values are reported as mean (SD). HAART, highly active antiretroviral therapy; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure.

RESULTS

Table 1 lists the baseline demographic and clinical characteristics of HIV-infected patients selected for the study. The median duration of follow up was 26 weeks (range 24 to 32 weeks).

Figure 1A shows mean baseline and week 12 and 24 distances for the 6 min walk test. Compared with patients treated with HAART alone, the patients treated with HAART and bosentan in combination had a mean improvement of exercise capacity by 15% (range 5–32%) both at week 12 ($p < 0.01$) and at week 24 ($p < 0.01$). NYHA classification improved by at least one class in six patients (33%) treated with HAART alone and in 14 patients (78%) treated with HAART and bosentan in combination ($p < 0.01$). Figure 1(B–F) shows the mean values of the principal cardiopulmonary haemodynamic parameters observed at week 24 compared with baseline in the two study groups. Compared with patients treated with HAART alone, the patients treated with HAART and bosentan in combination had a reduced mPAP by 21% (range 4–38%, $p < 0.001$) and reduced pulmonary capillary wedge pressure by 12% (range 10–52%, $p < 0.001$). Logistic regression analysis showed that a baseline mPAP ≤ 50 mm Hg (odds ratio 9.4, 95% CI 2.9 to 16.2; $p < 0.001$) and a 6 min walk distance ≥ 200 m (odds ratio 4.3, 95% CI 1.7 to 7.5; $p < 0.01$) were independent predictors of response to HAART alone but not to HAART and bosentan in combination. Bosentan treatment (odds ratio 7.0, 95% CI 1.3 to 12.5; $p < 0.001$) was a covariate predictor of response independently of HIV-1 viral load, CD4 count and type of HAART regimen. Bosentan treatment was well tolerated and had no negative impact on control of HIV infection. Asymptomatic increases in liver transaminase concentration (more than three times the upper limit of normal compared

with baseline) were observed in two patients. Both these patients were co-infected with hepatitis C virus. Transaminase concentrations returned to baseline values in these two patients after reduction of bosentan to 62.5 mg twice daily. No patient in either study group died during the study period.

DISCUSSION

Effective treatment options for HIV-associated PAH remain limited. Epoprostenol is an effective treatment but data on HIV-associated PAH are limited.⁵ Data on the therapeutic role of HAART in HIV-associated PAH are mostly limited to retrospective analysis of uncontrolled subsets of patients.¹ The pathogenetic role of pulmonary interstitial cells, which are not sensitive to HAART, and their chronic release of cytokines, such as endothelin 1, may justify the debated role of HAART in the treatment of HIV-associated PAH. Prospective analysis of the end point of our study showed that HAART alone did not significantly influence the cardiopulmonary haemodynamic parameters and exercise capacity compared with HAART and bosentan in combination, especially in patients with mPAP > 50 mm Hg and exercise capacity < 200 m at baseline. These findings support the pathogenetic role of endothelin 1 in the development of HIV-associated PAH and suggest that HIV-infected patients should be examined for PAH as early as possible, as HAART alone has no significant therapeutic role in more advanced stages of the disease. The combination of bosentan with antiretroviral treatment appears to be safe and effective, independently of baseline mPAP and exercise capacity, and to have no adverse impact on the control of HIV infection. Owing to the limitations of this study (small sample size, open-label design), more data are needed to support the use of bosentan in HIV-infected patients with PAH. Nevertheless,

treatment with bosentan in combination with HAART appears to be a suitable option in the management of patients with symptomatic HIV-associated PAH, especially those with a baseline mPAP > 50 mm Hg and a 6 min walk test < 200 m, because in this subset of patients the combination treatment appears to be more effective than HAART alone.

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IMAGES IN CARDIOLOGY

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Triple-barrelled aortic dissection in Ehlers-Danlos syndrome

An 18-year-old female student with a history of asthma and Ehlers-Danlos syndrome presented with chest pain and shortness of breath. She was hospitalised, treated with antibiotics for presumed pneumonia, and discharged home. She continued to be very dyspnoeic, with minimal exercise tolerance. On repeat examination, a diastolic murmur was noted. Transoesophageal echocardiography revealed a dilated aortic root with proximal dissection and severe aortic regurgitation. Multidetector-row computed tomography (MDCT) confirmed the proximal dissection and also revealed a distinct dissection of the descending aorta. A Bentall procedure was performed to replace the aortic root and ascending aorta. On repeat postoperative MDCT, a three-channelled dissection of the descending aorta was observed (panels A and B; to view video clip visit the *Heart* website—<http://www.heartjnl.com/supplemental>). An intimal flap arises from the medial posterior wall of the distal aorta arch. The resulting false lumen communicates with the true lumen via a re-entry tear. At the level of the aortic hiatus, a second focal dissection arises from the lateral anterior wall of the descending aorta, forming what has been referred to as the

Mercedes-Benz mark sign (panel C). Nearly two years postoperatively, the patient has been asymptomatic and the complex dissection remains radiographically stable.

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To view video clip visit the *Heart* website—<http://www.heartjnl.com/supplemental>

Volume rendered image of the thoracic aorta. (A) Anterior view. (B) Posterior view. (C) Maximal intensity projection image of the thoracic aorta, demonstrating three luminal compartments (Mercedes-Benz mark sign).