Aerosolized Iloprost in CREST Syndrome Related Pulmonary Hypertension

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ABSTRACT. ***Objective.*** To assess the outcome of patients with CREST syndrome associated severe pulmonary hypertension treated by aerosolized iloprost in a noncomparative study.

Methods. Five patients with CREST syndrome associated severe pulmonary hypertension were treated with 100 μg/day of aerosolized iloprost. New York Heart Association functional class and exercise tolerance (6 min walk test) were assessed at baseline, after one month, and then every 6 months. A right heart catheterization was performed at baseline in all but one patient. Systolic pulmonary artery pressure (PAP) was measured with Doppler echocardiography after one month and every 6 months.

Results. The mean followup was 13.2 ± 8.8 months (median 6, range 6–24). Subjective quality of life improved in all patients. NYHA functional class decreased from Class III to II in 3 patients, from Class III to I in one patient, and from Class IV to III in one patient. At 6 months, the distance walked in 6 min had increased from 352 ± 48 to 437 ± 56 m (p = 0.06). At one month the mean systolic PAP was 58 ± 13 vs 81 ± 9 mm Hg at baseline (p = 0.04). At 6 months the mean systolic PAP was 57 ± 13 mm Hg (p = 0.06). The improvement of both clinical and hemodynamic status was maintained in the 2 patients treated for 2 years. Neither adverse effects nor need to increase the daily dose of iloprost were observed. One patient died of right heart failure and one patient did not experience any improvement of exercise tolerance and hemodynamics.

Conclusion. Aerosolized iloprost might be potentially useful as treatment for CREST syndrome associated pulmonary hypertension. However, patients who could benefit from this treatment will probably have to undergo careful criteria selection. (J Rheumatol 2001;28:2252–6)

Key Indexing Terms:
SCLERODERMA CREST PULMONARY HYPERTENSION ILOPROST AEROSOL

Pulmonary hypertension (PH) has been reported to be the major cause of morbidity and mortality in systemic sclerosis (SSc)[1]. PH is more frequent in limited SSc, especially in the CREST variant (calcinosis, Raynaud's phenomenon, esophageal involvement, sclerodactyly, telangiectasia associated with anticentromere antibodies)[2]. Management of SSc related PH includes anticoagulation, oxygen therapy, vasodilators, and/or heart-lung or lung transplant[3]. Among vasodilators, continuous intravenous prostanoids (epoprostenol or its stable analog iloprost) have been shown to be effective, improving clinical status and hemodynamics[4,5]. However, continuous intravenous administration can produce potentially life-threatening complications, i.e., catheter linked sepsis or PH rebound during pump malfunction[5]. Many authors have therefore searched for an alternative way of administration. Olschewski, *et al* first showed that iloprost by inhalation decreased the pulmonary vascular resistance (PVR) and pulmonary artery pressure (PAP), increased cardiac output in the short term, and was selective for pulmonary circulation[6]. One patient with CREST syndrome was treated for one year with sustained hemodynamic improvement[6]. Since then, to our knowledge, no other patients with SSc have been treated for more than one year with aerosolized iloprost.

We report the clinical and hemodynamic outcome of 5 patients with CREST syndrome associated severe PH treated by aerosolized iloprost.

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Submitted September 20, 2000; revision accepted April 16, 2001.

MATERIALS AND METHODS

Patients. This study was performed in 5 patients who were referred to our institution between April 1998 and October 1999. Patients had SSc according to the American College of Rheumatology criteria[7] and all had CREST syndrome (diagnosed if anticentromere antibodies were associated with at least 3 of the 5 following items: calcinosis, Raynaud's phenomenon,

esophageal involvement, sclerodactyly, telangiectasia). All 5 patients received oral warfarin but none had received calcium-channel blockers. Patient 2 was treated for 6 months with angiotensin converting enzyme (ACE) inhibitor, introduced in November 1997, and for 4 months with oxygen therapy, introduced in January 1998. ACE inhibitor, oxygen therapy, and anticoagulation were continued. Patient 4 also received oxygen at the beginning of the treatment with aerosolized iloprost. During the study, no changes to patient medication were made such as addition of diuretics or vasodilators. Informed consent was obtained from all patients.

Baseline evaluation. Dyspnea was graded according to the New York Heart Association (NYHA). Exercise tolerance was assessed by 6 min walk test[8]. Diagnosis of pulmonary hypertension was made by Doppler echocardiography and confirmed by right heart catheterization in all patients except Patient 3, who refused this procedure. During right heart catheterization, patients received nitric oxide (NO) nebulization in order to assess the reversibility of PH. Responding patients were defined by a decrease of PVR ≥ 25% or mean PAP ≥ 25% and with no decrease in the cardiac index. Other causes of PH such as chronic pulmonary thromboembolism related PH were excluded systematically by 2D color echocardiography, lung ventilation-perfusion scan, and pulmonary artery computed tomography (CT) scan. Pulmonary fibrosis was assessed by chest CT scan and spirometry.

Aerosolized iloprost. Iloprost (Ilomedine®, Schering AG, Berlin, Germany) 100 μg (1 ml) was diluted with 12.5 ml of NaCl 0.9% producing a concentration of 7.4 μg/ml of iloprost. The 2.25 ml (16.5 μg iloprost) of solution was totally jet-nebulized during 15 min, 6 times per day. The total nebulized dose of iloprost was 100 μg/day. The inhalator used was a Pari TurboBOY® (Pari, Ascletech Sarl, France). Iloprost was jet-nebulized with room air at a pressure of 1.10 bar (fluid flux 4.20 l/min, mass median aerodynamic diameter of particles 3.8 μm, percentage of particles < 5 μm: 78%).

Outcome. NYHA functional class, exercise tolerance (6 min walk test), and systolic PAP measured by Doppler echocardiography, always performed in the same laboratory, were assessed at one month and then every 6 months after the beginning of the treatment. Each measurement was performed before the patients began the first inhalation of the day. Patients were also asked about their subjective quality of life. Possible side effects, including systemic manifestations of prostanoids[5], were systematically evaluated in each patient.

Statistical analysis. Results are presented as the mean ± SD. Comparisons were done using the nonparametric Wilcoxon test. Statistical analyses concerning systolic PAP were made with the Doppler echocardiography derived values.

RESULTS

Baseline evaluation. Baseline data are shown in Table 1. Patient 3 was bedridden because of toe necrosis and could not perform the 6 min walk test. The mean echocardiograph derived systolic PAP was 81 ± 9 mm Hg, whereas the mean right heart catheterization derived systolic PAP was 81 ± 11 mm Hg (p = 0.85). No patients had pulmonary fibrosis except for Patient 4, who had mild fibrosis of the lung base, but this was insufficient to explain PH [forced vital capacity 3.32 l (86% of that predicted) and D/VA : 2.47 ml/min/mm Hg/l (45% of that predicted)]. The 5 patients were thus determined to have CREST syndrome pulmonary arteriopathy associated PH.

Followup, side effects, and deaths. Table 2 shows the outcome of each patient. The mean duration of followup was 13.2 ± 8.8 months (range 6–24). All patients except Patient 3 are still receiving aerosolized iloprost. To date no adverse effects have been observed, in particular, flushing, headache, gastrointestinal upset, and jaw pain, which are common systemic side effects observed with intravenous prostanoids. Toe lesions of Patient 3 healed and she resumed her day-to-day activities after one month. Unfortunately, she had to return to her country of origin (Lebanon), where she continued to be treated with aerosolized iloprost. She died 6 months after beginning treatment because of severe right cardiac failure.

Subjective quality of life. After one month, all patients reported a dramatic improvement of their subjective quality of life. Particularly, Patient 1, who could not previously do housework because of the dyspnea, could then work in her home. Patient 2, who was not able to previously work in his home, could do minor chores. These 2 patients, treated for 24 months, have now resumed a satisfying quality of life.

Dyspnea and 6 min walk test. After one month, the NYHA functional class improved in all patients and the mean distance walked was 421 ± 74 m vs 352 ± 48 m at baseline (p = 0.06). At 6 months, mean distance walked was 437 ± 56 m (p = 0.06). Except for Patient 1, the 6 min walk test was performed before and after the aerosol treatment. The distance walked was 528 m before the aerosol and 704 m 15 min after the aerosol vs 300 m at baseline.

Cardiopulmonary hemodynamics (Figure 1). At one month, systolic PAP decreased in all patients except Patient 4. The mean systolic PAP was 58 ± 13 vs 81 ± 9 mm Hg at baseline (p = 0.04). At 6 months, the mean systolic PAP was 57 ± 13 mm Hg (p = 0.06). Concerning Patient 2, the systolic PAP continues to improve after 24 months of treatment (45 vs 79 mm Hg at baseline). For Patient 1, after a period of stability at 70 mm Hg, after 24 months a new and controlled improvement of systolic PAP at 40 vs 90 mm Hg at baseline was experienced, with no modification in the treatment. This patient has been removed from the lung graft list.

DISCUSSION

Potentially life-threatening complications and lack of pulmonary selectivity of continuous epoprostenol infusion[5] have encouraged investigators to search for an alternative method of administration of prostanoids to treat PH[6]. Inhaled agents with a short biological half-life decrease pulmonary vascular tone but are inactivated before reaching the systemic circulation and therefore have a better pulmonary selectivity[6]. Subsequently, aerosolized prostanoids have been attempted in primary and secondary PH, including a few cases of SSc related PH[6,9-12]. The short duration treatment has produced significant reduction in mean PAP and PVR and selective pulmonary vasodilatation, and has increased cardiac output. The difference between epoprostenol and iloprost was essentially a longer lasting effect for iloprost than for epoprostenol (60–120 vs 10–30

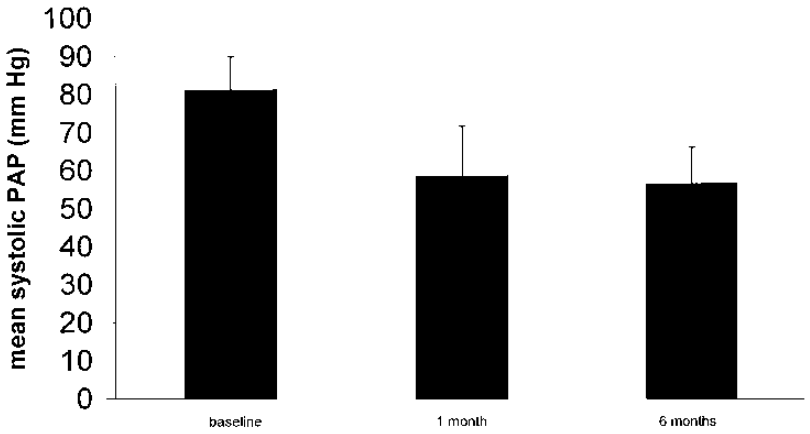

Figure 1. Evolution of mean systolic pulmonary artery pressure (PAP) at baseline and one and 6 months after beginning aerosolized iloprost

Table 1. Baseline characteristics.

Patient	Age/ Sex	Diagnosis	Yrs Since RP	NYHA Class	6 min walk (m)	Lung Fibrosis	DLCO*	PaO_2/SaO_2 (mm Hg/%)	Right Heart Catheterization					
									Systolic PAP	Diastolic PAP	Mean PAP	PVR	CO	Reversibility of PH
1	32 F	CREST	10	III	300	No	55	92/95	94	41	57	1876	3.1	Yes
2	65 M	CREST	7	IV	400	No	37	63/92	81	32	51	1229	4.2	Yes
3	56 F	CREST	32	III	Toe necrosis	No	30	68/93	86	ND	ND	ND	ND	ND
4	37 F	CREST	14	III	400	Yes	46	60/91	61	48	52	2299	3.2	No
5	67 F	CREST	2	III	308	No	63	70/93	84	30	59	1446	4.6	Yes
Mean			13		352		46	71 (11)/	81	37.8	54.8	1712	3.8	
(SD)			(10.3)				(12)	93/(1)	(11)	(7.2)	(3.3)	(411)	(0.7)	

* Percentage of predicted. RP: Raynaud's phenomenon; NYHA: New York Heart Association; 6 min walk: distance (variation of pulse rate bpm); PAP: pulmonary artery pressure (mm Hg); PVR: pulmonary vascular resistance (dyne/$cm^{-5}m^{-2}$); CO: cardiac output (l/min); PH: pulmonary hypertension; ND: not done.

Table 2. Outcome with aerosolized iloprost.

	Baseline	1 mo	6 mo	12 mo	18 mo	24 mo
Patient 1						
NYHA class	III	II	II	II	II	I
6 min walk (m)	300	500	500	488	488	528
Systolic PAP (mm Hg)*	90	45	70	70	ND	40
Patient 2						
NYHA class	IV	III	III	III	III	III
6 min walk (m)	400	473	468	470	470	470
Systolic PAP (mm Hg)*	79	70	50	50	45	45
Patient 3						
NYHA class	III	II	II	Death	—	—
6 min walk (m)	Toe necrosis	Toe necrosis	100	—	—	—
Systolic PAP (mm Hg)*	86	75	ND	—	—	—
Patient 4						
NYHA class	III	II	II	—	—	—
6 min walk (m)	400	401	402	—	—	—
Systolic PAP (mm Hg)*	65	60	60	—	—	—
Patient 5						
NYHA class	III	II	II	—	—	—
6 min walk (m)	308	310	380	—	—	—
Systolic PAP (mm Hg)*	85	42	50	—	—	—

* Doppler echocardiograph derived values of systolic pulmonary artery pressure (PAP).

min, respectively). To our knowledge, only 4 patients with CREST syndrome have been treated with longterm aerosolized iloprost[6,11]. The first patient described by Olschewski, *et al* was treated for one year with a sustained improvement of NYHA functional class, PAP, and PVR and with no complication[6]. Three other patients described by Olschewski, *et al*[11] were treated during 51, 42, and 179 days, respectively, and all died because of chronic heart failure, sepsis, or myocardial infarction.

We describe the first study of aerosolized iloprost with a mean followup of 13.2 ± 8.8 months in 5 patients with CREST syndrome associated PH. Our study concerns a small number of patients. However, the individual descriptions of each of the patients may give interesting data to assess this new treatment in SSc related PH and to support further studies. First, in this study, aerosolized iloprost was well tolerated. Particularly, the usually systemic side effects observed with intravenous prostanoids[5] were not noticed. Coughing, a common secondary effect described by Hoeper, *et al*[12], was not noted either. There was no need to increase the daily dose to maintain efficacy (i.e., tachyphylaxia), a frequently observed phenomenon in intravenous administration of prostanoids[5]. Further, a dramatic and sustained improvement in subjective quality of life was reported by all patients. However, we have not used any standardized quality of life questionnaires to quantify this improvement. NYHA functional class, evaluation of which can be subjective, improved in all patients. This improvement paralleled the objective increase of exercise tolerance, which began as early as the first month of treatment and was then sustained. However, Guyatt, *et al* reported that there is a learning curve for the 6 min walk test: patients walk farther after the first 2 tests even without hemodynamic improvement. This may have influenced our results[8]. Interestingly, improvement of exercise tolerance was maintained in the 2 patients treated for 2 years. For Patient 1, at 24 months, the acute administration of aerosolized iloprost increased the distance walked. Thus, even after 2 years, the treatment could show not only a persistent but also an acute effect. Hoeper, *et al* also showed that exercise tolerance was usually highest immediately after inhalation and slowly deteriorated over the following 2 or 3 hours until the next inhalation[12]. Altogether, these findings are additional arguments to divide the total dose of iloprost in 6 inhalations. Systolic PAP decreased significantly after the first month, with a sustained and continuous improvement for the 2 patients treated for 2 years. To assess outcome, PAP was measured using Doppler echocardiography. Although some authors suggest that systolic PAP could be underestimated by the Doppler technique in case of technically inadequate signals[13], several studies reported very close correlations between direct measurements of systolic PAP and noninvasive estimates based on continuous-wave Doppler measurements[14].

Patient 4 was the sole patient who did not show any improvement of either objective exercise tolerance or systolic PAP. However, this patient had a functional NYHA class decreasing from III to II and subjective improvement of her quality of life. Discordance between improvement of dyspnea and stability of hemodynamics has already been reported[15]. It is interesting that Patient 4 was the only individual with no reversible PH during baseline right heart catheterization. However, acute response in this test does not systematically predict longterm response. Patient 4 was put on the graft list but has continued aerosol treatments in order to maintain hemodynamic stability.

In conclusion, we describe the outcome of 5 patients with severe CREST syndrome associated PH treated with aerosolized iloprost. This procedure was well tolerated and offered patients the possibility of a greatly improved quality of life, although we have not used a standardized questionnaire to quantify it. Three patients experienced an improvement of both clinical and hemodynamic variables. Two patients were treated for 2 years and their improvement was maintained. One patient had a stable condition and one patient died of right cardiac failure. These results suggest that aerosolized iloprost might be a potential therapeutic option for patients with CREST associated PH, as well as having lasting beneficial effects, even after 2 years. However, patients certainly have to be carefully selected, with criteria that remain to be established, to identify those who will have a favorable response to iloprost nebulization. A multicenter, prospective, double blind, randomized, placebo controlled study is in progress to achieve this aim and to confirm these initial encouraging results, not only in CREST associated PH but also in other secondary PH and in primary PH.

ACKNOWLEDGMENT

The authors are grateful to Richard Medeiros for his advice in editing the manuscript.

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