Disease-modifying effects of long-term cyclic iloprost therapy in systemic sclerosis. A retrospective analysis and comparison with a control group

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Abstract

Objective

To evaluate the role of iloprost, a derivative of prostacyclin, as a possible disease-modifying agent for systemic sclerosis (SSc).

Methods

Fifty-six consecutive SSc patients treated for a median period of 4 years with cyclic infusions of iloprost for severe Raynaud's phenomenon and ischemic ulcers were compared with 56 control patients matched for age, sex, disease subset and duration. Control patients were also similar to the iloprost group with regard to autoantibody status, the presence of major disease-related organ manifestations at baseline, and the use of other treatments. The evolution of lung function test results, the frequency of major disease-specific complications and the survival of the cohorts were the objects of this analysis.

Results

No significant difference was observed between the two groups with regard to changes in lung function tests over time, or the number of patients who presented with the onset of active interstitial lung disease, pulmonary arterial hypertension or scleroderma renal crisis. Survival did not differ between the two groups.

Conclusion

The evolution of lung function test results, the frequency of major disease-specific complications, and survival did not differ significantly between SSc patients treated with cyclic iloprost and a group of patients matched for sex, age, and disease subset and duration. However, no cases of severe pulmonary arterial hypertension were observed in the patients treated with iloprost, suggesting that studies focusing on the possible preventive action of iloprost on the progression of SSc-associated mild pulmonary arterial hypertension would be warranted.

Key words

Systemic sclerosis, iloprost, survival, lung function test, pulmonary arterial hypertension.

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Introduction

Iloprost is a chemically stable derivative of prostacyclin that has been demonstrated to be useful in the short-term treatment of severe Raynaud's phenomenon and ischemic ulcers in patients with systemic sclerosis (SSc) (1, 2). Its long-term use, administered by cyclic intravenous infusion, has been shown to reduce the symptoms of Raynaud's phenomenon and the recurrence of ischemic ulcers, and to improve the quality of life in patients (3-8). Based on its biologic properties (9), it has been proposed that the drug might influence the fundamental mechanisms underlying the pathogenesis of SSc, and act as a disease modifying agent (6). However, information from controlled studies specifically designed for this purpose is very scanty. In order to assess the long-term disease-modifying effects of iloprost, we have re-evaluated data prospectively collected in terms of disease-specific complications and survival, in a cohort of 56 consecutive patients treated with iloprost for a median period of 4 years. This cohort was compared with 56 control patients specifically matched for age, sex, disease subset and disease duration with each of the iloprost-treated patients.

Materials and methods

Patient cohorts

Written informed consent from the patients and ethical committee approval were not sought because this was a retrospective survey of usual clinical practice.

The charts of all 56 SSc patients who received cyclic infusions of iloprost at our institution since 1995 were reviewed. Data concerning 30 patients followed up between 1995 and 1999 have already been reported (7). A group of control patients was selected by filtering a database consisting of 398 SSc patients regularly followed at our institution (either as in- or out-patients), matching each case with an individual paired for sex, age (by decade), disease subset [limited (lSSc) or diffuse (dSSc) systemic sclerosis], according the criteria of LeRoy *et al*. (10), and disease duration. In accordance with Medsger and Steen (11), early disease was defined as < 3 years from the onset of the first symptom other than Raynaud's phenomenon for dSSc, and < 5 years for lSSc; all other patients were defined as having late disease. For 3 young female patients with early dSSc treated with iloprost, perfect matching was not possible, and patients who were one decade older were used as the controls. The main demographic and clinical data of the patients included in the study are shown in Table I.

For the iloprost group, the last assessment before starting the treatment was used as the baseline, and the last assessment during the period of treatment as the last observation. The median duration of iloprost treatment and follow-up considered in this study was 48 months (Table I). For the controls, all the assessments available were used. Data were collected up to June 30, 2006. No patient or control was lost to follow-up.

Treatment

Patients treated with iloprost received the drug by 6-hour continuous intravenous infusion at the maximal tolerated dose (mean ± DS: 1.25 ± 0.45 ng/kg/min) via a syringe pump controller for 5 consecutive days initially, and then for one day every 3 weeks as maintenance therapy. In some patients the infusions were temporarily interrupted during summer, or for other reasons.

Most patients also received low-dose corticosteroids, calcium-channel blockers or other vasodilators, and low-dose aspirin. All patients with active interstitial lung disease (ILD) except for one (in the control group) were treated with iv cyclophosphamide as described (12, 13). A small number of patients received methotrexate or, during the 1990s, D-penicillamine or cyclosporine A, to control their cutaneous and articular symptoms. Severe pulmonary arterial hypertension (PAH) arising during the observation period in 2 control patients, and the development of severe ischemic ulcers refractory to iloprost in 2 patients, were treated with bosentan.

Outcome measures

At our institution, SSc patients are routinely evaluated according to standard

procedures analogous to those recommended by a consensus conference for the identification of a core set of variables for SSc studies (14). Skin thickness was measured using the modified Rodnan skin score (15). A self-administered 10-point visual analogue scale (VAS) was used to determine the severity score for Raynaud's, in which 0 represented no attack and 10 represented very severe attacks. Patients were asked to take into consideration in the scoring the number and duration of attacks (2). Disability was measured using the Health Assessment Questionnaire (HAQ) (16). A lung function test with evaluation of the forced vital capacity (FVC) and diffusion lung capacity for carbon monoxide (DLCO) was performed at the time of diagnosis, and at least yearly in the first 5 years of follow-up. Results were expressed as percentages of the predicted values based on age, sex, and height. Normal values were calculated based on the reference standard provided by the European Coal & Steel Community (17, 18). A total of 232 lung function tests were recorded in the clinical charts of the iloprost group, and 299 tests in the control group. Patients with worsening dyspnoea, or a decrease in FVC and/or DLCO, or chest x-ray abnormalities were further evaluated by high resolution computed tomography (HRCT), and, in most cases, broncho-alveolar lavage (BAL).

Active ILD was identified on the basis of ground glass opacities documented by HRCT and/or BAL findings. Pulmonary arterial hypertension (PAH) was evaluated using Doppler echocardiography (performed at least yearly) as a screening test, and right heart catheterization as the gold standard (14). Scleroderma renal crisis was diagnosed according standard procedures (14). PAH secondary to severe ILD was not considered as a separate outcome.

Survival

No patient or control was lost to follow-up. The assignment of the cause of death was based on all available information (hospital records, autopsy reports). Deaths were classified as SSc-related when caused directly or indirectly by the disease manifestations. Deaths caused by diseases that occur with increased frequency in SSc (such as lung cancer) were not classified as SSc-related.

Statistical analysis

Data are expressed as the median (10^{th}-90^{th} percentile) unless otherwise indicated. The between-group comparisons were made using the Mann-Whitney test for continuous variables and the chi-square test with Yates' correction for dichotomous variables. The variations in the lung function test results over time were evaluated by repeated-measures analysis of variance. Survival rates were computed by Kaplan-Meyer analysis and the difference between survival curves evaluated using the Mantel-Cox (log-rank) test. Statistical analysis was performed using StatView 5.0.1 (SAS Institute, Cary, NC).

Results

Long-term cyclic iloprost therapy

Indications for treatment with iloprost were: ischemic ulcerations (n = 47) of the hands (n = 41), feet (n = 4), or both (n = 2); severe Raynaud's phenomenon with minor digital cutaneous lesions such as fissures and paronychia (n = 8); and PAH with New York Heart Association class II dyspnoea (n = 1).

On 30 June 2006, 34 patients were still receiving iloprost, while in 22 (39%) the therapy had been discontinued because of disease improvement (n = 6), death (n = 8), lack of compliance (n = 2), renal crisis (n = 2), ischemic cardiopathy (n = 2), pregnancy (n = 1), or neoplasm (n = 1). Analysis of the efficacy of iloprost was made at the moment of the last observation in 54 patients who received more than 2 months of therapy. Among the 47 patients with ischemic ulcers at the start of therapy, 29 (62%) did not show lesions at the last observation, whereas ulcers were present on the hands in 10 patients, on the feet in 6, and both in 2. Despite iloprost therapy, in one patient with dSSc the second finger of the left hand had to be amputated at its distal extremity (7), and in 2 patients with significant comorbidity (1 with diabetes mellitus, 1 with HCV-associated cryoglobulinemia) the forefoot was amputated.

Compared to the pre-treatment point, at the end of the study we observed a decrease in the Raynaud's phenomenon VAS from 10/10 (5-10) to 5/10 (2-9) ($p < 0.001$) and, in patients with diffuse cutaneous involvement, of the modified Rodnan skin thickness score from 23 (9-40) to 18 (10-30) ($p = 0.002$). The HAQ score, on the contrary, worsened from 0.9 (0.3 – 2.2) to 1.1 (0.2 – 2.7), although the difference was not significant.

No severe reactions to the therapy were recorded. Iloprost infusion was generally well tolerated, but occasionally patients reported minor side effects such as headache, nausea, vomiting, or mild hypotension crisis with flushing. Iloprost was discontinued due to acute ischemic cardiac events in 2 patients with lSSc and arterial hypertension – a 77-year-old female who received iloprost for 19 months and a 65-year-old woman who received iloprost for 7 months.

Comparison with the control group

The control subjects were well matched for sex, age, disease subset and duration with the iloprost group. At baseline there were no significant differences in the main clinical and demographic features between the two groups; moreover, no differences were found in terms of the presence of severe complications (Table I), except for the absence of ischemic ulcers in the controls. The period of observation was significantly longer in the control group than in the iloprost group (Table I). There was no difference between the two groups with regard to the number of patients receiving cyclophosphamide (10 in the iloprost group *vs.* 16 in controls) or bosentan (2 *vs.* 2) at any time point during the period of observation.

To evaluate the effect of iloprost on disease progression, a detailed analysis of changes in the lung function test results was carried out: data from 232 tests recorded in the iloprost group were compared with 299 tests in the control group. No significant difference was observed when the analysis of variance test was applied (FVC: $F = 1.24$; $p = 0.26$; DLCO: $F = 0.12$; $p = 0.73$). These results were not influenced by other treatments, since in the two groups a similar number of patients received immunosuppressive

Table I. Main demographic and clinical data on the patients included in the study.

	Iloprost	Controls	*p*
Sex (F/M)	49 / 7	49 / 7	NS
Age (years)	55 (32-72)	54 (36-67)	NS
Disease duration (years)	6 (1-20)	4 (0.4-13)	NS
Early diffuse SSc (%)	14 (25%)	14 (25%)	NS
Late diffuse SSc (%)	17 (30%)	17 (30%)	NS
Early limited SSc (%)	5 (9%)	5 (9%)	NS
Late limited SSc (%)	20 (36%)	20 (36%)	NS
Anti Scl-70 antibodies (%)	25 (45%)	22 (39%)	NS
Anti-centromere antibodies (%)	15 (27%)	17 (31%)	NS
Baseline FVC (% predicted)	104 (76-126)	105 (62-126)	NS
Baseline DLCO (% predicted)	68 (47-89)	72 (47-104)	NS
Active ILD at baseline (%)	6 (11%)	11 (20%)	NS
Isolated PAH at baseline (%)	1 (2%)	0	NS
Renal crisis at baseline (%)	0	0	NS
Follow-up (months)	48 (17-108)*	71 (18-176)	0.002

If not otherwise indicated, data are presented as the median (10th-90th percentile).
*For the iloprost group, the follow-up time considered in this study was the duration of iloprost therapy (see Methods).
ILD: interstitial lung disease; PAH: pulmonary arterial hypertension.

Table II. Onset of major disease-specific complications during the period of observation.

	Iloprost	Controls	*P*
Active ILD	4	6	NS
Isolated PAH	0	2	NS
Renal crisis	2	1	NS
Deaths (total)	8	7	NS
Deaths (disease-related)	4	6	NS
Deaths (for other causes)	4*	1**	NS

*Lung cancer: 2; intracranial haemorrhage: 1; suicide: 1.
**Uterine cancer: 1.
ILD: interstitial lung disease; PAH: pulmonary arterial hypertension.

therapy for active ILD. The mean rate (S.E.) of FVC loss was -2.4%/year (1.0) in the iloprost group and -3.2%/year (1.7) in the control group and the mean loss of DLCO was -2.1%/year (0.3) in the iloprost group *vs*. -2.6%/year (1.2) in the controls.

With regard to major disease-specific complications, the numbers of patients who presented the onset of active ILD, PAH, or scleroderma renal crisis during the period of observation were not significantly different between the two groups (Table II).

As shown in Figure 1, Kaplan-Meyer analysis demonstrated a slightly lower survival rate in the iloprost group than in the controls (difference not significant) (log-rank test; $p = 0.13$). Survival at 4 years of follow-up was estimated to be 91.1% (S.E. 4.8%) in the iloprost group and 96.0% (S.E. 2.8%) in the controls.

Discussion

The aim of this study was to evaluate the possible disease-modifying effect of long-term cyclic iloprost therapy in patients with SSc. It has been shown that this treatment can control the symptoms relating to Raynaud's phenomenon (4-7) and improve the patients' quality of life (8). The drug has several properties, including vasodilatation, the inhibition of platelet aggregation (9) and leukocyte chemotaxis and adhesion to the endothelium, enhanced fibrinolytic activity, and the suppression of profibrotic cytokine connective tissue growth factor production (19-23), by which it could influence the fundamental mechanisms underlying the pathogenesis of SSc. However, information on the effect of this therapy on the principal disease-related outcome measures is limited to a single, small controlled study (6) and to few uncontrolled observational studies (4, 5, 7, 24, 25).

We therefore evaluated a cohort of patients treated with cyclic iv iloprost at our centre (one of the largest series and with the longest follow-up to appear in the literature), and compared them with a group of SSc patients carefully matched for age, sex, disease subset and disease duration, who were being followed by our clinic. Matching for these parameters allowed us to gather a control group of patients that was similar to the iloprost group in terms of their autoantibody profile, the presence of major disease-related organ manifestations at baseline, and use of other treatments. The only significant differences between the two groups were the presence of ischemic ulcers in the iloprost group (the indication for treatment in almost all the patients), and a slightly longer follow-up in the control group. The evolution of the lung function test results, the onset of severe disease complications such as active ILD, PAH or renal crisis, and survival were evaluated. Given the careful matching of subjects, if a difference was observed in these outcome measures it could be attributed to the treatment effect, or to the indication for treatment (the presence of ischemic ulcers).

Our results showed no differences between the iloprost group and the controls as far as the major disease outcomes were concerned.

To the best of our knowledge, this is the first study to address the effect of iloprost therapy on the survival of patients with SSc. We found that survival in the cohort of patients treated with iloprost was not different from that in control patients. Since the presence of ischemic ulcers is not considered to be a negative prognostic factor for survival, this observation suggests that a significant positive effect of iloprost on survival should not be expected, at least in the first years of follow-up.

The possibility of a disease-modifying action of iloprost was suggested not

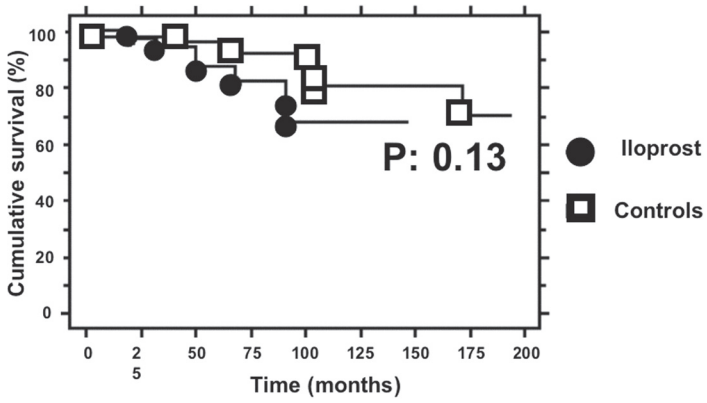

Fig. 1. Survival rates for SSc patients treated with iloprost and for matched controls.

only by the pharmacodynamic properties of the drug, but also by some of its favourable effects on disease markers, including measures that were evaluated in the present study such as lung function tests. In particular, in a controlled trial DLCO was reported to remain stable in patients with recent onset SSc who were being treated with iloprost (53.2 ± 4.8% before treatment *vs.* 56 ± 4.6% after 1 year of treatment), but to decrease significantly in control patients treated with nifedipine (from 69.6 ± 7.4 to 61.5 ± 6.5 afterwards) (6). However, the validity of this observation was limited by the non-homogeneous basal DLCO between the two groups, and by the very small number of patients analysed (5 patients in the iloprost group and 3 in the nifedipine group). Studies involving long-term observations in larger numbers of patients conducted by others (24) and by us (7) have demonstrated instead a progressive worsening of DLCO despite treatment with iloprost. Data presented here show that the decline in FVC and DLCO in these patients was comparable to that observed in the control group. Therefore, the number of patients who developed active ILD was not different in the two groups of patients (Table II), and our study failed to demonstrate any protective effect on lung function of the cyclic infusion protocol adopted. It is of interest that in a controlled study designed to evaluate the acute effect of iloprost given for 3 consecutive days, the drug failed to improve DLCO by the end of the therapy cycle (26).

A possible disease modifying effect of iloprost was suggested by reports of mild, but statistically significant improvement in the skin thickness score in patients treated with iloprost (4, 6, 7), and this finding was confirmed in the present series as far as patients with diffuse cutaneous involvement were concerned. We have already underlined, however, that it is difficult to attribute these results to the effect of the drug, as longitudinal studies show that skin scores in patients with dSSc increase rapidly in the first few years and thereafter stabilize or decrease (7). Moreover, it should be considered that the skin score evaluation may also be affected by sometime notable inter-operator differences (15). A comparison with controls to evaluate the rate of changes, similar to the lung function evaluation over time, was not possible in the present study due to the large amount of missing data.

As far as the clinical manifestations of SSc resulting directly from microvascular damage are concerned, in the present series two patients with dSSc (1 with early and 1 with late disease) experienced a renal crisis while receiving infusions with iloprost (and this complication was more frequent, though not significantly so, than in the controls), and similar cases have been reported elsewhere (6). Therefore, it can be concluded that in some patients cyclic iloprost is insufficient to prevent renal crises.

Finally, 2 of our control patients, but none of those receiving iloprost, developed PAH during follow-up. This observation is in agreement with Caramaschi *et al*. (25), who did not observe the development of severe PAH in a series of 81 patients with SSc who were treated with cyclic iloprost for at least 15 months (mean: 61 months). These authors reported that some patients showed a mild increase in systolic pulmonary arterial pressure estimated by Doppler echocardiography, which remained stable during follow-up. In interpreting these results, one must keep in mind reports that ischemic ulcers are more severe in patients with SSc who develop severe PAH than in other patients (27). Therefore, patients treated with iloprost might be particularly at risk for the onset of severe PAH. Whether iloprost may prevent this complication could not be established by our study because, due to the rarity of the manifestation, the statistical power of our results was insufficient to detect any differences between the groups. This particular question deserves further study. It is interest, however, that in experimental models of PAH an anti-remodelling effect of iloprost combined with a phosphodiesterase 3/4 inhibitor was demonstrated (28), and this effect was suggested to be a mechanism by which the development of severe PAH in patients with mild abnormalities could be prevented (25). In this context the history of a patient of ours (described in ref. 7) is of interest – a 55-year-old woman with lSSc, in whom, in July 1998, recent-onset isolated PAH (estimated systolic pulmonary arterial pressure on Doppler echocardiography 68 mmHg) with mild dyspnoea (New York Heart Association class II) furnished the indication for treatment with iloprost. This patient is still receiving cyclic iloprost with no significant worsening of her subjective, objective (6-min walking test) or echocardiogram findings.

In conclusion, in our experience, the evolution of lung function, the frequency of major disease-specific complications, and the survival rate of patients with SSc treated for a median period of 4 years with cyclic infusions of iloprost for severe Raynaud's phenomenon and ischemic ulcers was not significantly different from effects observed in a group of patients matched for sex, age, disease subset and disease duration. However, further studies are warranted, particularly as far as the possible preventive action of iloprost on the worsening of SSc-associated mild PAH is concerned.

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