

Long-term cyclic intravenous iloprost in systemic sclerosis: clinical experience from a single center

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SUMMARY

The aim of the present study was to retrospectively evaluate response to therapy in 73 patients affected by systemic sclerosis (SSc) who underwent long-term cyclic treatment with intravenous iloprost for peripheral vascular involvement (average duration of treatment 54.12±41.04 months).

Seventy-three SSc patients were enrolled. Data were collected by reviewing clinical records and by phone or direct interview. Patients underwent a thorough physical examination at the end of follow up. The incidence of severe vascular manifestations was also assessed. Statistical analysis was performed by Wilcoxon's signed rank test and descriptive statistics using Statview software.

In this study cohort, 55 of 73 (75.2%) patients had a history of ischemic digital ulcers (DUs); 28 patients (38.4%) had active DUs at the beginning of treatment. Skin ulcers healed completely in 25 of 28 patients (89.3%) at the end of the first treatment. However, 40 of 55 patients (72.6%) relapsed after an average of 24 months. There was a significant correlation between relapse rate and/or number of ulcers and clinical factors (diffuse subset, changes in results of Allen's test, NT-pro BNP levels). The annual incidence of pulmonary arterial hypertension (PAH) was 2.34 (95%CI: 0.94-4.83) per 100 person years, the rate of gangrene was 2.7%, and no cases of scleroderma renal crisis were recorded. The incidence of PAH and of digital gangrene was higher than that observed in unselected SSc case series.

These data suggest that our patients treated with iloprost have a higher vascular involvement than large case series of unselected SSc patients. A number of clinical factors are correlated to the severity of vascular involvement and could have an impact on the response to therapy. The clinical significance of these findings requires clarification and further investigation is needed.

Key words: Systemic sclerosis, ischemic digital ulcers, iloprost.

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INTRODUCTION

Scleroderma is a systemic autoimmune disease characterized by fibrosis of the skin and numerous internal organs, such as lung, heart, gastrointestinal tract and kidney (1). The pathogenetic events of the disease are activation of the immune system, activation of fibroblasts, and endothelial damage (2). Raynaud's phenomenon is the earliest expression of the disease and is typically associated with major capillaroscopic abnormalities, such as megacapillaries and reduced numbers that represent what is defined as the scleroderma pattern (3). The most important clinical expression of the microangiopathy associated

with the scleroderma is the very frequent appearance of ischemic digital ulcers with resultant disability (4). Evolution of the microangiopathy often also reflects the extent of visceral involvement, since there is a significant association between the severity of capillaroscopic alterations and the systemic involvement of the disease (5-8). The disappearance of modulation of the endothelial barrier and the progressive loss of capillaries are distinctive characteristics of scleroderma. The obliterative microangiopathy is, in fact, a common histological element in many manifestations of the disease (9). For this reason, today there is an increasing interest in the use of vasoactive therapy both in the treatment of peripheral vascular

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manifestations and in order to change the natural course of the disease (10).

Iloprost is a stable analog of prostacycline, a molecule produced in physiological conditions which regulates vasomotor tone. This molecule, besides having a vasodilatory action on numerous body areas, also determines important modulation of the immune system and of fibrosis through mechanisms which are still only partly understood (11). Among these is the increase in nitric oxide bioavailability, the reduction of which increases endothelin levels, antiplatelet action, reduced expression of adhesion molecules (VCAM-1, ICAM-1, VEGF, E-selectin), inhibition of some fibrogenetic cytokines (TGF-beta, CTGF) (12-14).

The aim of the present study was to analyze the medical records of patients with scleroderma undergoing long-term cyclic treatment with iloprost to identify clinical and therapeutic factors correlated with therapy.

■ MATERIALS AND METHODS

Patients

Data were collected retrospectively through evaluation of patient medical records and, where necessary, by telephonic or direct interview of patients. Information was collected concerning the disease, organ involvement, presence and number of ulcers, presence of macrovascular co-morbidities and classical risk factors for atherosclerosis, and therapy. We also evaluated the incidence of severe peripheral vascular manifestations, such as scleroderma renal crisis, pulmonary arterial hypertension, digital gangrene or the need for amputation. On completion of follow up, patients were examined. Clinical and serological parameters, and treatment received were recorded. Questionnaires evaluating quality of life (HAQ) and hand function were also distributed (15). A total of 73 patients were evaluated. The diagnosis of scleroderma was established on the basis of clinical and serological data, and supported by capillaroscopic and instrumental tests. On first presentation of the disease, each patient

underwent a standardized clinical evaluation based on a single core set of tests defined on the basis of an analysis of the literature (16). Further tests were carried out according to the principle organ involved.

Capillaroscopy

The investigation was carried out after acclimitization to room temperature for 20 min. An optical probe videocapillaroscope at 200 magnification was used (Scopeman, Pico charm view, Moritex) and information on general architecture, mean capillary density, background and visibility was collected. When a sclerodermic pattern was found, this was further classified according to the criteria of Cutolo et al. (10).

Iloprost therapy

All patients received iloprost at 100 mcg in 500 mL isotonic saline or glucose solution 5% starting at a concentration of 0.5 ng/kg/min in continuous administration until the maximum tolerated dose, up to a concentration of 1.5 ng/kg/min. The intervals between administration varied according to the peripheral vascular manifestations. On the basis of clinical manifestations, patients received combined therapy with a variety of other drugs either together with or subsequent to iloprost therapy. Drug medication was decided on the basis of clinical signs and individual tolerability.

Vascular outcome

Recorded outcome and clinical variables related in particular to peripheral vascular involvement were: survival free of ulcers, latency between presentation of Raynaud's phenomenon and the 1st appearance of ulcer:

- number of ulcers before and after therapy,
- time to heal,
- relapse rate of ulcers (n. of relapses/months of follow up),
- latency of relapse of ulcers,
- Allen's test to evaluate hand perfusion,
- Visual analog scale (VAS) for Raynaud's phenomenon,
- VAS for pain,
- global health assessment (GH).

Statistical analysis

Data collected were uploaded onto a computerized database and analyzed using Statview software. Analyses included: 2x2 contingency tables for the correlation of categorical variables and Fisher's exact test when appropriate, non-parametric tests for quantitative data (Mann-Whitney to compare dichotomous variables and continuous data, Wilcoxon's signed rank test to compare continuous data, Spearman's rank correlation coefficient for the correlation of continuous variables).

■ RESULTS

Demographic and clinical characteristics

Main patient demographic characteristics are summarized in Table I. A total of 73 patients were recruited: 7 men and 66 women; male:female ratio 1:9.3. Median age at follow up was 59.6±15.2 years. There were 42 patients with limited form and 31 with diffuse form of the disease while 2 patients presented overlap with rheumatoid arthritis. Mean age at first presentation of Raynaud's phenomenon (RP) was 43.8±16.7 years and mean age at presentation of first non-RP symptom was 49.4±15.4 years. There were a mean six years between RP and first non-RP symptom. Mean disease duration from first presentation of RP was

15.6±13.8 years. Mean disease duration from first non-RP symptom was 10±8.4 years. Given that first presentation of disease could include more than one non-RP symptom, in this present cohort we recorded: 35.5% ulcers, 20.4% arthralgias, 12.4% sclerodactyly, 8.1% dysphagia, 8% dyspnea, 1.4% asthenia, 1.4% polyarthrititis and, finally, 1.4% painful and swollen ankles. Mean years of follow up were 4.4 (range 0.25-17.35). Blood tests showed 69 ANA+ antibodies (94%), 25 had ACA+ antibodies (33.2%), 25 had Scl-70 antibodies (33.2%). Four patients did not test positive for any antibodies (5.4%).

Data concerning patients' clinical characteristics are shown in Table II. Skin involvement, defined as thickening of the skin, independently of the extent, was found in 98.6% of patients. Involvement of the esophagus, which was the second most frequent manifestation, was found in 93.2%, while involvement of the stomach, small or large intestine was 45.1%. Pulmonary interstitiopathy was found in 78.1%. Pulmonary arterial hypertension was found in 17.7%, with 7 new cases confirmed during therapy but no death. Incidence of pulmonary hypertension during follow up was 2.34 (95% CI:0.94-4.83) per 100 person years. Cardiac involvement was found in 25% of patients. Sjögren's syndrome, confirmed by glandular biopsy, was found

Table I - Demographic and epidemiological characteristics.

Total n. patients	73	
Male/female	1/9.4	
Mean age at follow up	59.6±15.2 years	(range 27-91)
Limited form	42	57.5 %
Diffuse form	31	42.5%
Overlap	2	2.7 %
Mean age presentation RP	43.8±16.7	(range 11-80)
Mean age presentation 1st non-RP symptom	49.2±15.6	(range 20-89)
Years from RP to 1st non-RP symptom	6	(range -2-48)
Mean disease duration (RP)	15.6±13.8	(range 1-54)
Mean disease duration (1st non-RP symptom)	10±8.4 anni	(range 2-47)
Follow up	4.6±3.4	(range 0.25-17.35)
ANA+	69	94%
ACA+	25	33.2%
Scl-70	25	33.2%
Seronegative	4	5.4%

Table II - Clinical data.

Organ involvement	N. patients	%
Skin	72	98.6%
Esophagus	68	93.1%
Other gastrointestinal	33	45.2%
Pulmonary interstitiopathy (ILD)	57	78%
Pulmonary arterial hypertension (PAH)	13	17.8%
Cardiac	18	25%
Sjögren's syndrome	7	9.6%
Kidney	4	5.5%
History of ulcers	55	75.2%
Macrovascular	12	17.38%
Skin score modified according to Rodnan	10.7±10.9	(range 0-51)
Allen's test	+	57.5%

in 9.6%, kidney involvement was found in 5.5%, in all cases characterized by chronic nephropathy and with no case of scleroderma renal crisis and rheumatoid arthritis in 2.6%. There were 75.2% of patients with a history of ulcer or who at any time during the disease course developed at least one ulcer. Macrovascular involvement was found in 12 patients (16.3%). One or more risk factors for atherosclerosis were presented by 65.8% of patients. Of these, 32% had arterial hypertension, 26.7% were exposed to tobacco smoke, 9.2% were overweight or obese, 6.7% had dyslipidemia, 3% had hyperhomocysteinemia. Correlation of the presence of risk factors with macrovascular involvement showed that the 12 patients with overt pathology had one or more risk factors for atherosclerosis (100%). This decreased to 64% of subjects without macrovascular involvement. In fact, of the 61 patients without overt pathology, 39 were positive for risk factors ($P<0.05$). Rodnan skin score on completion of follow up was 10.7 ± 10.9 . Allen's test was performed on 40 patients to verify patency of the medium caliber hand arteries; 23 cases (57.5%) were found to have alterations and the remaining 17 (42.5%) were normal.

We evaluated the correlation of alterations according to Allen's test, prevalence of ulcers, relapse rate, and rate of cure. No difference in the prevalence of ulcers in subjects with or without this parameter was found. However, there was a statistically significant difference ($P=0.05$) in relapse

rate between patients with positive Allen test (0.137) and patients with negative Allen test (0.034).

Furthermore, there was a difference in time to heal between patients with positive Allen test (3.8 months) and patients with negative Allen test (2.4 months) ($P=0.03$). No correlation was found between traditional risk factors for atherosclerosis and testing positive for Allen's test, and number and relapse of ulcers.

Subjects with increased NT-pro BNP values on completion of follow up had a significantly higher number of ulcers (1.7) than subjects with values in the normal range (0.7) ($P=0.05$).

There was a significant ($P=0.0073$, $\rho=0.54$) correlation between the difference in values of NT-proBNP molecules in patients' blood samples at the start and on completion of follow up, and the number of ulcers at the end of follow. The high NT-pro BNP values also correlated with pulmonary hypertension.

No association was found between the presence and number of ulcers and organ involvement, in particular, cardiac involvement and pulmonary hypertension. There was also no difference seen in the prevalence of ulcer, relapse rate and rate of healing in subjects with different capillaroscopic patterns.

A correlation was seen between the number of ulcers on completion of follow up and compromised hand function ($r=0.525$, $P=0.0009$). Alterations in hand function

Table III - Therapy received.

Therapy	N. patients	%
Iloprost	44	60%
Iloprost + revatio	16	22%
Iloprost + bosentan	10	13.6%
Iloprost + revatio + bosentan	3	4%
Antiplatelets	33	45.2%
Calcium antagonists	50	68.4%
ACE inhibitors	9	12.3%
Sartans	6	8.2%
Statins	12	16.4%

were also more frequent in the subset of diffuse form of disease ($P=0.05$) in which a higher rate of relapse than that seen in the limited form of disease was observed ($P=0.03$).

Therapeutic data

All patients in the cohort received iloprost 100 mcg in continuous infusion. Infusion velocity was adjusted according to weight and individual tolerability. Forty-six patients used only iloprost and 27 patients received this drug in combination with other peripheral vascular system medication (Table III). Of these 27, 16 also used sildenafil, 10 received bosentan, and 3 received a combined therapy with sildenafil and bosentan. Furthermore, 33 patients used antiplatelets, 50 calcium antagonists, 9 ACE inhibitors, 6 sartans and 12 statins (Tab. IV). In subjects receiving combined therapy with sildenafil, the ulcer relapse rate was significantly higher (0.13) than that seen in subjects treated with iloprost as monotherapy (0.052) ($P=0.04$). No difference was seen, however, in patients receiving the association bosentan and iloprost or in patients receiving bosentan, iloprost and sildenafil.

Mean time of iloprost therapy was 50.1 ± 38.8 months. Number of treatment

cycles over the months of the study were calculated as the ratio between these two values for a mean of 0.46 ± 0.2 months (range 0.07-0.88 months). Eight patients did not interrupt therapy over the summer (July and August) while the remaining 65 did. Fifty-four patients received continuous treatment while 19 discontinued treatment, i.e. six months or more between two treatments.

Of the information recorded: 28 (38.4%) patients had one or more ulcers before starting iloprost therapy; mean number of lesions 4.3 range 1-23). Of these 28 (89.3%) 25 were healed and 2 (2.7% of total) were not and required amputation of the fingers/toes involved. There were a mean of 0.55 ± 1.2 ulcers presented on completion of follow up (range 0-10). There was a statistically significant difference between the mean number of ulcers presented at the start of therapy (1.6) and on completion of follow up (0.5) ($P=0.03$). Forty patients had relapse of ulcers during the therapy course (72.6%); mean rate of relapse (ratio ulcers/months of follow up) was 0.08 ± 0.13 (range 0-1). Mean time to relapse was 25 ± 26.4 months (approx. 2 years) after start of iloprost therapy (range 1-94 months). Mean survival time free of ulcers, i.e. years from first presentation of Raynaud's phenome-

Table IV - Questionnaires distributed to study subjects.

Questionnaire	Mean before iloprost	Mean after iloprost	P
HAQ	1.5	1.3	Ns
VAS RP	7.3	6	0.025
VAS DOLORE	5.5	4.3	0.0023
GH	50	62	0.0038

non to appearance of lesions, was 3.55 ± 7.9 years (range 0-38 years). Mean time to heal was 3.2 ± 3.8 months (range 1-24 months). Regarding site, 96.4% of patients had ulcers in the hands, 12.3% in the feet, 9% to elbows, and 1.8% in the pavilion of the ear. Evaluation of ulcers of the lower limbs did not include those cases reporting occluded arteriopathy.

No statistically significant difference was found in data relating to quality of life before or after therapy. However, a significant difference was found between values relating to VAS RP, VAS PAIN and GH ($P=0.015$, $P=0.0024$, $P=0.0026$, respectively) (Tab. IV).

An evaluation of the possible correlation between continuous/discontinued therapy and cure of the ulcer showed that time to cure for those patients who discontinued therapy was 4.6 months compared to 3.6 months in those patients who underwent continuous therapy ($P=ns$).

Information on side effects was collected from 66 patients. These were, in order of frequency: cephalaea (34.7%), numbness (13.5%), vomiting (12%), nausea (7.6%), hypotension (5.9%), asthenia (5.9%), diarrhea (2.9%), stomachache (2.9%), vertigo (1.4%) and widespread pain (1.4%); 33 patients experienced no side effects (48.5%). No side effects were so severe as to result in an interruption of therapy.

■ DISCUSSION

Iloprost has been used for many years in the treatment of peripheral vascular involvement of scleroderma. Wigley et al. Showed that even short-term treatment with iloprost is efficacious in curing ulcers. This was reconfirmed by the same group in a second study published two years later. (17, 18) Over the years, other studies have followed confirming the efficacy of this treatment: Bettoni et al. (2002), Bali et al. (2003), Caramaschi et al. (2009), Alivernini et al. (2009) (19-23). The short-term effect of the drug on the cure of ulcers and of Raynaud's phenomenon has been universally recognized. This effect is likely due

to a reduction in oxidative stress (24). The long-term action on ulcers and the impact on the natural course of the disease are less well understood. In 2002, Bettoni et al. reported that long-term therapy with iloprost, besides being safe and well-tolerated, is efficacious in healing ulcers. However, they underlined that such treatment was unable to modify outcome. In contrast, Caramaschi et al. reported a reduction in the incidence of severe vascular complications, in particular pulmonary hypertension, and suggested that the drug could modify the natural course of the disease (21). The efficacy of short-term therapy with iloprost was confirmed in our study cohort. In fact, 89.3% of patients with active ulcers at the time of therapy saw their ulcers healed. The drug was generally well-tolerated with only slight side effects. However, over two-thirds of patients experienced a relapse of the ulcer during the treatment cycle, confirming the scarce long-term efficacy, with a significant reduction in the number of ulcers during follow up. There was significant heterogeneity in administration of the drug in our study cohort, with variable administration frequency and a significant number of patients ($n=19$) who interrupted therapy for over six months between cycles. Only 8 patients did not interrupt therapy over the summer. In addition, a significant number of patients received combined therapy which could have influenced the impact on peripheral vascular manifestations. In our study cohort, incidence of pulmonary hypertension was 2.34 (95% CI:0.94-4.83) per 100 person years; around 4 times higher than that found in non-selected series (25), while frequency of gangrene was 2.7% and no case of scleroderma renal crisis was reported. Frequency of gangrene in large cohorts in literature was 1.6% and 11% in cohorts of patients selected for studies on healing ulcers. (26-27) However, interpretation of data also varies in these studies. Scleroderma renal crisis is, in fact, reported to have a lower frequency in Italian cohorts than in Anglo-Saxon study populations (28) and the increase in incidence of pulmonary hypertension could be explained by selection bias of patients with

more severe vascular involvement. We find data related to gangrene in an intermediate position between non-selected cohorts and those with more severe vascular involvement (26, 27). Subjects with active ulcers had significant impairment of hand function. The improvement in quality of life, and of the subjective perception of Raynaud's syndrome and pain, indirectly demonstrate an effect on peripheral vascular manifestations.

The study of a selected cohort allowed the correlation between clinical manifestations and response to therapy to be analyzed. For example, even though no significant difference was seen between the two subsets of skin involvement in relation to the prevalence of ulcers, diffuse scleroderma was aggravated by a slightly higher frequency and, consequently, had a greater impact on hand function.

In the present study, abnormal Allen test results were found in 57.5% of patients. These results showed a reduction in circulatory reserves of the hand in scleroderma patients and frequent involvement of the ulnar artery (29). Allanore et al., in a study on angio-magnetic resonance, frequently reported impairment of flow in digital arteries in scleroderma subjects. Impairment of a greater number of digital arteries was associated to the presence and number of ulcers, and also tissue ischemia was consistent with pulmonary systolic pressure. (30) Our observations indirectly confirm this. In fact, subjects with abnormal Allen test results showed an almost significant increase in relapse of ulcers and a significant extension of time to heal.

No correlation was seen between the presence and number of ulcers and pulmonary pressure. However, subjects with alterations in Nt-pro BNP values showed a significantly greater number of ulcers, and a significant correlation between the variation in Nt-pro BNP values during follow up and the number of ulcers at the end of the observation period. This could indicate sub-clinical cardiac involvement in these subjects. Here it is interesting to underline how some studies have reported a correlation between indexes of acute phase and

Nt-pro BNP values in subjects with collagenopathy, and the recent observation of a strict concordance between disease severity and increased values of this molecule in scleroderma (31, 32).

In comparison with data from non-selected studies reported in literature, our results suggest that our patient cohort had a generally more severe vascular involvement than the scleroderma population at large. Response to treatment, in spite of the limitations inherent in a retrospective study of patients undergoing combined therapies, confirmed short-term efficacy of iloprost but did not show a significant long-term effect in terms of efficacy or the natural course of the disease. This could partly be due to the administration methods adopted, and above all to the variable intervals between administration and the high number of patients who did not follow a continuous treatment course. Some clinical factors, such as resulting positive for Allen's test, the diffuse subset, NT-pro BNP values, are correlated to severity of vascular involvement and could influence response to treatment. Further studies are needed to clarify the significance of these correlations.

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