# Long-term treatment of scleroderma-related digital ulcers with iloprost: a cohort study

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**ABSTRACT**

**Objective.** *Raynaud's phenomenon and chronic/recurrent digital ulcers (DU) are main features of systemic sclerosis (SSc). Their treatment includes both systemic (i.e., iloprost) and local therapies. We report the therapeutic effects of iloprost in a cohort of SSc patients during a long-lasting follow-up period.*

**Methods.** *Fifty consecutive SSc patients (M/F 7/43, age at SSc diagnosis 43.5±12.7SD years) received iloprost infusions for 10±4.2SD years. Iloprost schedule consisted in monthly infusion at 0.8-1 ng/kg body weight/min (average cumulative dose 25 μg), according to patients' tolerance. For recalcitrant cases, continuous infusion of iloprost (3 days, average 0.2 mg) was administered.*

**Results.** *31/50 (62%) patients showed DU at the beginning of iloprost therapy: among them, 22 (71%) resolved during the follow-up, while the other 9 presented recurrent or chronic DU, despite the treatment. With regards the 19/50 patients without DU at baseline, only one developed skin lesions at the end of 10-year follow-up, when severe pulmonary hypertension developed, which lead to exitus. Considering the 31 patients with DU at baseline, a diffuse skin subset was present in 3/22 patients with healed DU, and in 5/9 who did not (13.6% vs. 55.5%; p=0.027).*

**Conclusion.** *Iloprost is a long-term effective treatment to achieve healing and prevention in SSc-related DU. Besides the possible problems concerning patients' tolerability or clinical management, iloprost therapy may be considered of great help in the therapeutic strategy of SSc-related ischaemic manifestations.*

## Introduction

Systemic sclerosis (SSc) is characterised by endothelial dysfunction and widespread microangiopathy; consequently, in about 50% of cases, SSc patients develop ischaemic lesions of the skin, mainly at the fingertips (1, 2). In fact, digital ulcers (DU) are one of the most typical sign of SSc, often chronic and hard to heal, severely affecting patients' quality of life because of pain and obvious limitations of manual activities (3, 4). Therefore, the treatment of SSc DU represents a target priority for the physicians and a challenge in daily clinical practice.

Local wound management is always of primary importance in SSc DU therapy. Moreover, it is fundamental to establish a systemic therapeutic vasodilatory approach which may induce or facilitate the DU healing process (5, 6). Ideally, a disease-modifying therapy should restore the vasoregulative function of endothelial cells.

Iloprost, a synthetic stable prostacyclin-analogue, induces relaxation of smooth muscle cells, leading to a rapid vasodilatory effect against tissue hypoperfusion (7). Furthermore, the drug may theoretically be beneficial for several pathogenic mechanisms underlying the SSc vasculopathy, such as the inhibition of neutrophil adherence to endothelium (8) and the proliferation of smooth cells that causes the increase of the intima-media thickness (9). For these reasons, Iloprost is recognised as one of the pivotal character in the therapy of SSc patients, and it is indicated for the treatment of severe Raynaud's phenomenon and SSc DU (10).

In SSc, several studies have investigated the efficacy of iloprost on RP and DU healing (11-24). However, few data on the long-term effects of the drug on the natural history of SSc, including the frequency of DU onset in SSc patients, are present in the literature. Italian studies have retrospectively investigated the effect of iloprost considering main follow-ups longer than 50 months (21-24).

The aim of our study was to evaluate retrospectively the long-term efficacy of iloprost, in a homogeneous SSc case series, on DU healing and recurrence.

## Patients and methods

We retrospectively reviewed the clinical records of 50 consecutive non-selected SSc patients, referring to two Academic Rheumatology Units (the Policlinico of Modena and the Careggi Hospital in Florence) since 1st January 2003 to 31th December 2016. Patients were classified as SSc following the 2013 ACR/EULAR criteria (25). Patients receiving iloprost infusions for a period of at least 2 years, because of severe RP and/or presence of SSc-related DU were identified.

For this observational study, we used the data collected for the SSc Registry approved by the Ethics Committee of Modena (protocol n. 282/15). All patients gave their written consent.

All DU were defined as a loss of epidermal covering with a break in the basement membrane (26).

For all patients demographic, clinical, laboratory, and instrumental data were available for the study period. Patients' features at baseline were: males/females ratio 7/43; mean age at SSc diagnosis 43.5±12.7SD years; median disease duration at the beginning of therapy 2 years (range 0–18); mean follow-up with iloprost treatment 10±4.2 years; diffuse SSc cutaneous subset (dcSSc) in 13/50 (30%) patients; anti-Scl70 and anti-centromere autoantibodies in 25 (50%), and 14 (28%) subjects, respectively.

Iloprost schedule consisted in monthly *i.v.* infusion at 0.8–1 ng/kg body weight/min in sessions of 8 hours, according to patients' tolerance. The average cumulative dosage per each session was 25 μg. In the case of severe and/or multiple DU at high risk of gangrene, the patients were hospitalised and treated with iloprost (50 mcg of the drug in 500 ml of 0.9% saline solution) for 24 hours with an infusion pump (3 days, average 0.2 mg totally); this protocol was used yearly for 6/50 SSc patients.

The intravenous therapy was prepared introducing 50 mcg of the drug in 500 ml of 0.9% saline solution, and administered by means of infusion pumps. Before iloprost administration, all patients received premedication with ondansetron 8 mg in 0.9% 100 ml of saline solution. Moreover, during the 8 hours of iloprost infusion, analgesic therapy with acetaminophen 1000 mg was allowed. Almost all patients received also calcium-channel blockers and/or low-dose aspirin, as first-line vasoactive therapy for SSc-related ischaemic manifestations.

Data were presented as mean ± standard deviation (SD), or median (range) for non-normalised data series. Comparisons were made using the Wilcoxon signed-rank test for continuous variables and the chi-square or Fisher's exact test for proportional variables. *p*-values less than 0.05 were considered statistically significant.

**Table I.** SSc patients' features at baseline and at the end of follow-up.

| SSc features | Baseline | End of follow-up | *p*-value |
|---|---|---|---|
| Mean Rodnan skin score | 18.6 | 15 | NS |
| Digital ulcers | 31 | 10 | 0.0001 |
| Disphagia | 23 | 32 | NS |
| ESR (mm/h) | 19.8±12.3 | 22.4±15.8 | NS |
| FVC% | 94.8±16.5 | 92.2±21.4 | NS |
| DLCO% | 58.9±15.9 | 48.8±17.4 | <0.0001 |
| ILD | 26 | 36 | 0.005 |
| ECG alterations | 6 | 19 | 0.001 |
| PAPs ≥35 mmHg | 7 | 10 | NS |

ESR: erythrocyte sedimentation rate; FVC: forced vital capacity; DLCO: lung diffusing capacity for carbon monoxide; ILD: interstitial lung disease; ECG: electrocardiogram; PAPs: systolic pulmonary arterial pressure (estimated by means of ultrasounds).

## Results

The main outcome of the present study was to evaluate the efficacy of iloprost to healing and to prevention of SSc-DU, besides the known effect on RP. At baseline, 31/50 (62%) subjects showed at least one typical fingertip ischaemic lesion; pitting scars were excluded from this clinical evaluation. During the follow-up period, 22 (71%) patients were free from DU while the other 9, despite the treatment, experienced recurrent or chronic DU, showing a worse disease course (27, 28). In the other 19/50 patients without DU at baseline receiving iloprost, just one developed DU, only at the end of 8 years of follow-up, when his clinical conditions deteriorated with development of severe pulmonary hypertension and death.

During the follow-up of 10±4.2 years, we evaluated also the changes of other relevant clinical features (Table I). At the end of the study, a progressive deterioration of organ function due to SSc visceral involvement was observed, as expected for the natural history of the disease and the age progression. New patients with mild interstitial lung disease were identified at the end of follow-up; moreover, a 10% decline of the mean DLCO, without a significant impairment of the forced vital capacity, was reported. More frequently, minor heart electrical anomalies (*i.e.* extrasystoles, bundle branch blocks, non-specific repolarisation alterations) were found. Scleroderma renal crisis was never observed while only one patient developed pulmonary arterial hypertension. No progression of skin sclerosis was detected after 8 years of follow-up in particular in 13/50 dcSSc.

Considering only the 31 SSc patients with DU at baseline, patients with diffuse skin subset were significantly more frequent among those who did not heal by the end of follow-up (3/22 healing cases *versus* 5/9 not healing cases; Fisher's $p=0.027$). This finding may suggest that the subjects resistant to vasodilatory treatment belong to the dcSSc subset, in which DU healing is more difficult to reach. No other significant correlations were observed as regards visceral organ involvement, serological alterations, and concomi-

**Table II.** Main studies in literature evaluating the efficacy of intravenous Iloprost on SSc-related DU healing.

| First author/year (ref. 11-24) | n. of pts | Type of study | Dosage (ng/kg/min) | Iloprost schedule | follow-up (months) | Outcomes |
|---|---|---|---|---|---|---|
| McHugh /1988 | 26 | double blind placebo controlled crossover | 0.5-2.0 | I: 3days; F: every 3 weeks | 3 | significant RP improvement; trend to healing for 8/26 pts with DU |
| Rademaker /1989 | 23 | double blind placebo controlled | 0.5-2.0 | 3 days+1 at week 8 | 4 | significant increase of the microcirculatory flow and RP improvement; reduction of mean DU number from 3.5 to 0.6 at the end of follow-up in the iloprost group |
| Torley HI/1991 | 43 | double blind comparative | 0.5 vs. 2.0 | 3 days | 2 | up to 44% reduction of the number of DU (23 pts with DU at baseline ) |
| Wigley FM/1992 | 35 | double blind placebo controlled | 0.5-2.0 | 5 days | 2,5 | DU healing in 4/4 pts (0/4 in controls); significant RP improvement |
| Wigley FM/1994 | 114 | double blind placebo controlled | 0.5-2.0 | 5 days | 2,5 | significant reduction in DU number (35 pts with DU at baseline) and less new DU onset in the iloprost group; significant RP improvement |
| Zachariae H/1996 | 6 | prospective open-label | 0.5-2.0 | 8-13 days | <1 | complete ulcer healing in 4/6 pts, improvement in 2/6 |
| Biasi D/1998 | 20 | prospective open-label | 0.5-2.0 3 months | 5 days every | 12 | SSc skin lesion score reduced from 37.1±16.5 to 10.2±6.9 |
| Scorza /2001 | 46 | prospective single blinded | 2 | I: 5 days; F: every 6 weeks | 12 | DU healing in 12/14 (86%); 30% reduction of skin score; RP improvement; stable DLCO values |
| Bettoni L/2002 | 37 | prospective open-label | NA | I: 5days; F: every 3 weeks | median 36 | DU healing in 19/21 pts (90%); RP-VAS reduced of 50%; mean RSS* reduced of 37%; DLCO/va decreased from 71% to 62% |
| Marasini /2004 | 21 | head-to-head iloprost/ alprostadil | | I: 5 days; F: 2 days/month | 2 | 2/5 iloprost pts with DU healed; RP improvement |
| Scarsi M/2008 | 59 | retrospective | 1.25±0.45 | I: 5days; F: every 3 weeks | 52 (37-119) | DU healing in 35/50 pts (70%); RP-VAS reduced of 50%; mean RSS* reduced of 22% |
| Kawald A / 2008 | 50 | randomised, open-label | 0.5 vs. 2.0 | 21 days | 1 | 70% reduction of DU, RP improvement |
| Casigliani Rabl S/2012 | 73 | retrospective | 0.5-1.5 | n.a. | 50.1±38.8 | DU healing in 25/28 pts (89%); RP-VAS reduced of 18% |
| Caramaschi P/2012 | 115 | retrospective (complications survival) | 0.98±0.29 | monthly (93 pts); 5 days/3-4 months (22 pts) | 98.8 ± 37.5 | DU evolving in gangrene in 2 pts with concomitant peripheral arterial disease (incidence 0.31/100 pts-years) |
| Foti R/2017 | 68 | retrospective | 0.5-2.0 | 5-6 days monthly | 85.2±34.8 | Patients with DUs reduced from 42.6 to 11.8% at the end of follow-up; statistical reduction of RSS, PAPs (17 patients), BNP. |
| Colaci M/2017 | 50 | retrospective | 0.8-1.0 | I: 3 days; F: monthly | 120±50 | DU healing and no recurrence during follow-up in 22/31 (70%) pts; no RSS increase (-19.3%) |

RP: Raynaud's phenomenon; DU: digital ulcers; RSS: modified Rodnan skin score; PAPs: systolic pulmonary arterial pressure (estimated by means of ultrasounds); BNP: pro-brain natriuretic peptide.

tant administration of other vasoactive therapies (bosentan, sildenafil).

No severe adverse effects were noticed in our series. Only hypotension, flushing, headache were regularly controlled by diminishing the infusion rate or, at least, interrupting the drug administration for 10–20 minutes. Nausea and vomiting were avoided thanks to premedication.

## Discussion

Our data show that iloprost helps in healing and preventing DU in a long-lasting follow-up. Moreover, we confirm that the monthly administration of iloprost is effective, in agreement with previous reports (11-24); in particular, the Italian cohort studies (21, 22) evaluating iloprost efficacy during follow-ups of 50 months, DU healing

was observed in 70–89% of the cases. In other studies with a shorter follow-up, the efficacy of iloprost in healing of DU was invariably reported in the majority of cases; as example, Scorza *et al*. (18) found 89% of DU healing after one year of therapy (Table II) (11-17).

In the diffuse SSc subset, we found a non-progression of skin involvement (Table I). It is not clear if this may be due to the regular use of iloprost as suggested by other authors (18, 21, 24).

An interesting study by Tinazzi et al. (29) demonstrated that iloprost treatment progressively increased circulating endothelial cells and their progenitors (EPCs), and influenced the transcription of a number of genes (*i.e*. genes for chemokines, adhesion integrins, those related to apoptosis or to the stress response). Iloprost may be responsible for the recruitment of EPCs from the bone marrow and for their homing into the sites of ischaemic damage, such as DU. Furthermore, D'Amelio *et al*. (30) suggested also an immunomodulating role of iloprost in SSc, by means of the significant impairment of TNF-alpha production by T lymphocytes and of the number of T regulatory cells after 5 days of therapy.

In the rheumatologist's armamentarium, intravenous iloprost is one of the main therapies fighting SSc ischaemic manifestations (5-7, 31). Its regular administration seems to be very useful in the chronic tight-control of SSc patients that require DU monitoring and treatment. On the other hand, the monthly infusion may be considered as a burden both for the patient and for the health system. Therefore, to achieve a fair compromise between patients' needs and the treatment cost, an inter-infusions time-interval of 4 weeks and the administration of iloprost dosages of 0.8–1.0 ng/kg/min instead of the regular dose up to 2.0 ng/kg/min (50 μg for one session) is proposed by the data obtained in the present work. In fact, lower dosages/rates of infusions may guarantee a better patients' compliance and a lower incidence of adverse events. We found that the premedication with ondansetron is very effective to control nausea/vomiting, which are the main adverse effects. Overall, beside the general recommendations, we suggest that the iloprost regimen for SSc patients should be tailored on patients' clinical characteristics (27, 32) and specific tolerance.

A limit of the present study is the retrospective design; moreover, our data were achieved from a 'real-life' scenario, differently from clinical trials that investigate efficacy and safety of therapies in ideal conditions. Nonetheless, our data may have a useful impact of the use of iloprost in everyday clinical practice, carefully evaluating patients' tolerance, specific efficacy and cost for the Health System.

Another limit of the study is the absence of a control group, without iloprost administration. However, even though formally correct, this possibility was very hard to be applied in clinical practice, because of obvious ethical concerns.

## Conclusions

We provide the evidence that iloprost, in a real life setting, is effective in healing and prevention of SSc-DU. Still today, iloprost is a solid anchor-therapy for DU in SSc patients. In clinical practice, several difficulties concerning drug tolerance or healthcare management may discourage the use of iloprost. However, tailoring the treatment on patients' clinical features may overcome most of the obstacles and assure the best results in the management of DU.

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