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Treatment with intravenous iloprost in patients with systemic sclerosis: A short review

Elisa Visalli[1], Giorgio Amato[1], Marcella Di Gangi[1], Alessia Benenati[1], Nicolò Cino[1], Caterina Gagliano[2], Raffaele Falsaperla[3], Alberto Farina[4], Rosario Foti[1*]

[1]Rheumatology Unit, A.O.U. Policlinico Vittorio Emanuele, Catania, Italy
[2]General Pediatrics and Pediatric Acute and Emergeny Unit, A.O.U. Policlinico Vittorio Emanuele, Catania, Italy
[3]Ophthalmology, NEST (Neurovisual Science Technology) and Rare Disease Center (Ra.Di.Ce.), Santa Marta Hospital, Catania, Italy
[4]Medical Affairs Department, Italfarmaco S.p.A., Milano, Italy

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***Correspondence:**
Rosario Foti, Rheumatology Unit, A.O.U. Policlinico Vittorio Emanuele, Catania, Italy; Email: rosfoti@tiscali.it

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ABSTRACT

Systemic sclerosis (SSc) is a severe, chronic disease characterised by small vessel vasculopathy, autoantibodies production, and fibroblast dysfunction leading to an excessive deposition of collagen in the skin and internal organs. The beneficial effects of iloprost in improving symptoms of ischemia such as Raynaud's phenomenon (RP) and digital ulcers (DUs) in patients with SSc are largely due to modulating the disordered microcirculation. Literature data show that the long-term IV iloprost administration maintains efficacy in the treatment of vasculopathy, representing a rational therapeutic approach, since Raynaud's phenomenon and digital ulcers are two of the major causes of pain and disability in scleroderma patients. Intravenous iloprost may also play a role in promoting a favourable disease course, as a stabilization of cardio-pulmonary were observed in long-term studies. Current evidences are encouraging, but further randomized and controlled trials are needed to confirm these results.

Introduction

Scleroderma (systemic sclerosis or SSc) is a severe, chronic disease characterised by small vessel vasculopathy, autoantibodies production, and fibroblast dysfunction leading to an excessive deposition of collagen in the skin and internal organs[1,2,3]. Severe Raynaud's phenomenon (RP) is the early onset symptom in most SSc patients and may precede other clinical manifestations of the disease by many years[4]. The clinical course of the disease often involves the cardiovascular and respiratory systems; the heart can be directly or indirectly involved with the involvement of other organs, especially kidneys and lungs[5] while for the respiratory system, SSc can affect lung parenchyma and pulmonary blood vessels, leading to interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH). The presence of a cardio-pulmonary involvement generally leads to a poor prognosis for the patient[2]. Patients with significant internal organ involvement remain often asymptomatic until the late stages of SSc; therefore, routine monitoring for the underlying disease and an intensive medical treatment are essential after the first diagnosis. Despite recent advances in the disease management, SSc remains a treatable but not curable disease[2].

Current European League Against Rheumatism (EULAR) guidelines recommend Iloprost in the treatment of Raynaud's phenomenon and in the healing of ischemic digital ulcers. In

particular, intravenous iloprost reduces the frequency and severity of SSc-RP attacks and should be considered for severe SSc-RP and should also be used for the treatment of milder SSc-RP attacks when oral therapy have failed[6]. It should also be considered that treatment with iloprost may offer greater efficacy than calcium antagonists[7,8]. Despite EULAR's recommendations, the correct therapeutic approach is still debated and large differences occur between centres administering such treatment, with implications on clinical practice and health of patients.

Iloprost

Iloprost is a stable prostacyclin presenting vasodilating, anti-platelet, cytoprotective and immuno-modulating properties, with long-lasting effects at the level of cutaneous microcirculation[8,9,10]. The synthetic prostacyclin analogue iloprost closely mimics the whole range of endogenous prostacyclin's physiological effects (figure 1), and is therefore ideally suited for the treatment of micro and macrocirculatory diseases, including disorders in the pulmonary vascular bed, basically determined by an imbalance between prostacyclin with its vasodilatory and anti-platelet effects and thromboxane which acts as a vasoconstrictor and platelet activator. Endogenous prostacyclin assumes a key role in the finely tuned interaction between platelets, leucocytes and endothelium, especially at the level of the microcirculation acting as a vascular repair and protection factor[11,12,13].

Tissue ischemia beyond the often long standing arterial stenosis or resulting from vasospastic attacks, may be barely adequate to support nutrition in normal circumstances but when intercurrent infection or minor injury is superimposed, the microcirculation breaks down leading to pain, ulceration or gangrene. The low perfusion pressure and decreased microcirculatory blood flow precipitate cellular and biochemical changes, which however can be reversible. The typical changes in severely ischemic areas are an uneven distribution of the nutritive capillary blood flow associated with capillary plugging. The key players are the platelets, white cells and the endothelium. It has been suggested that the low perfusion pressure in the severely ischemic microcirculation causes unbalanced activation of these components. The endothelial damage/disturbance promotes vasoconstriction via release of endothelium-derived constricting factor, endothelin, thromboxane A2, and serotonin, leukocyte adhesion, platelet adhesion and subsequent release of e.g. mitogens, and impairment of the fibrinolytic balance with inappropriate release of tissue-type plasminogen activator and its plasminogen activator inhibitor. Inflammatory factors are involved in these processes to a varying extent (Figure 2).

The overall effect is to cause occlusion of much of the microcirculation by platelet, white cell, fibrin or thrombotic plugs. Disordered vasomotion increases further the maldistribution of blood flow in the microcirculation. Correction of this imbalance is the

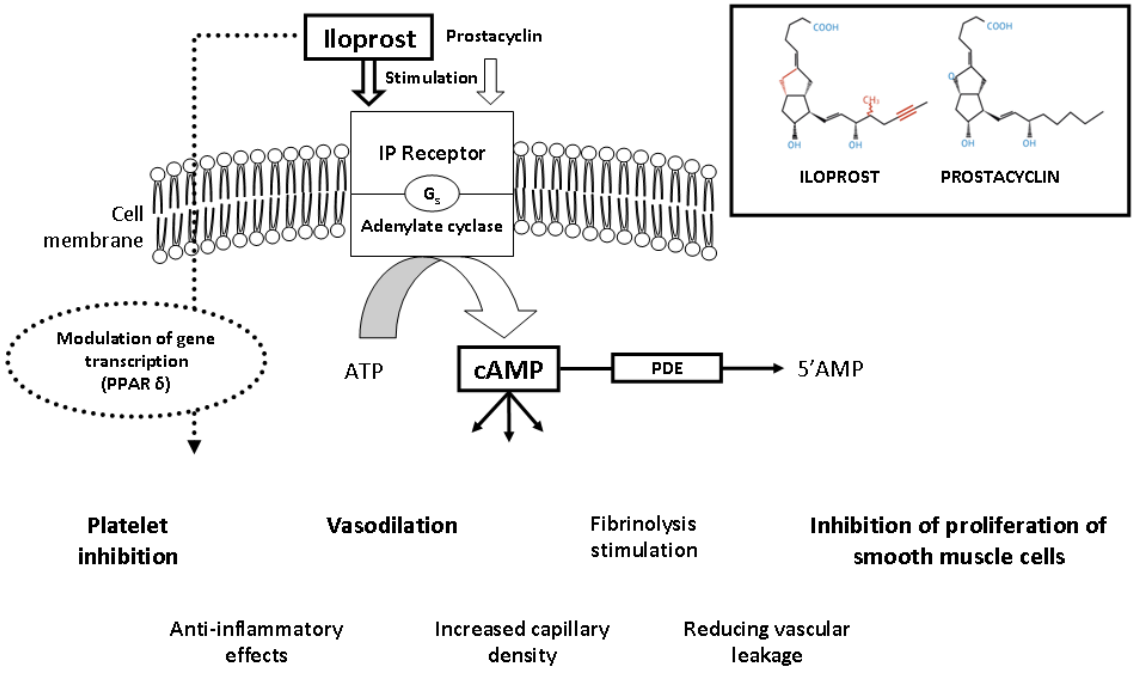

Figure 1: Mode of action of iloprost
ATP: Adenosine triphosphate; AMP: adenosine monophosphate; cAMP: Cyclic adenosine monophosphate; PDE: Phosphodiesterase; PPAR: peroxisome proliferator-activated receptor.

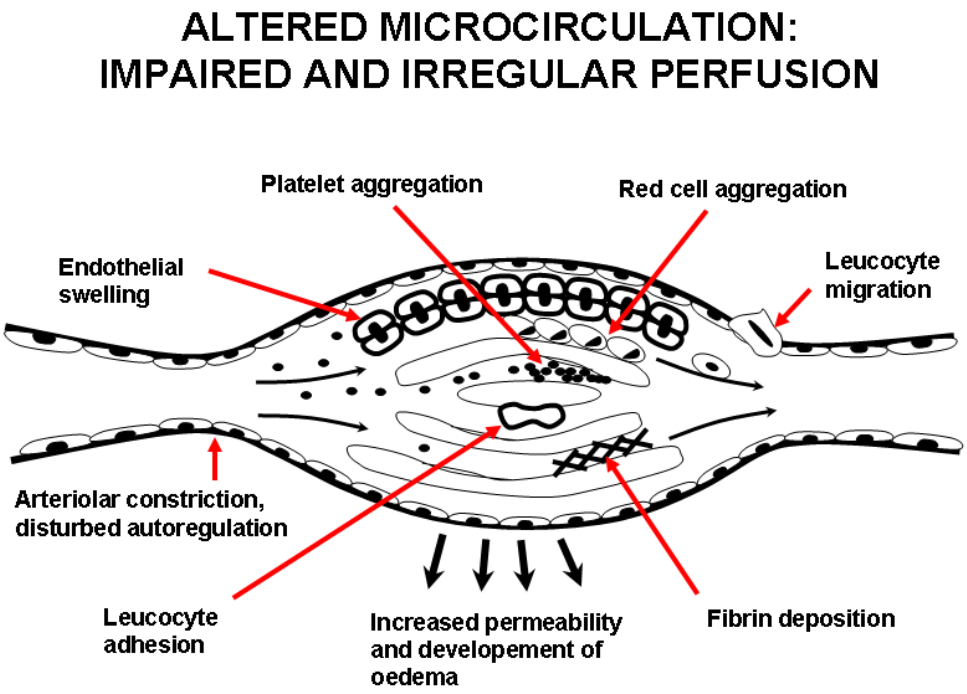

Figure 2

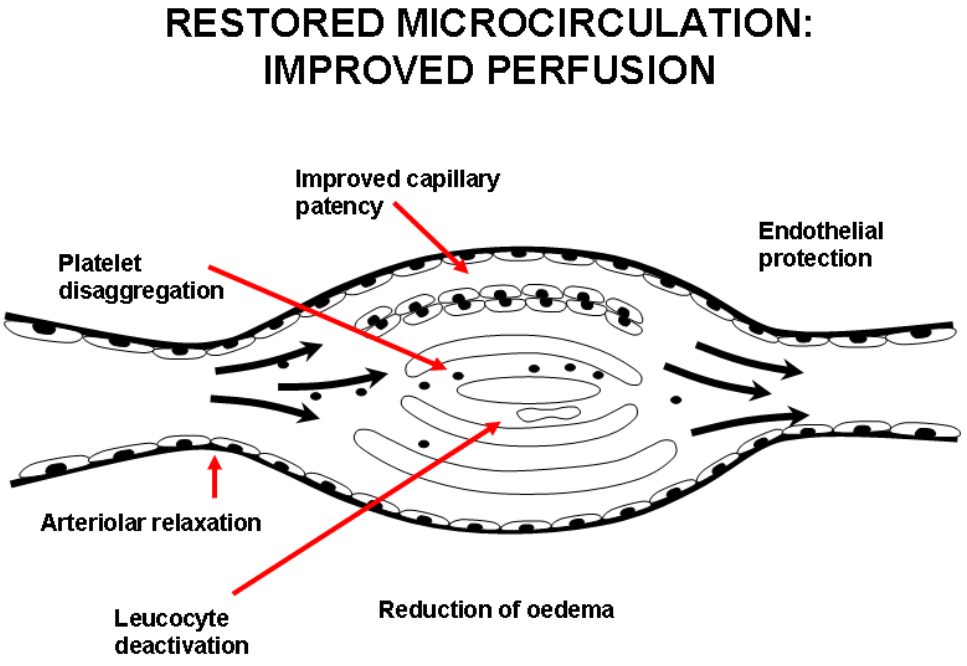

Figure 3

therapeutic approach for the administration of iloprost. The beneficial effects of iloprost in improving symptoms of ischemia such as Raynaud's phenomenon and digital ulcers in patients with SSc are largely due to modulating the disordered microcirculation. Iloprost restores the disturbed microcirculation by inducing vasodilatation, inhibiting platelet activation, repairing and protecting the endothelium, activating the endogenous fibrinolysis and by correcting cytokine network imbalances (Figure 3). The effects of iloprost are mediated by its binding to specific

prostaglandin I2 (PGI2) receptors and by a subsequent increase in cellular cyclic adenosine monophosphate (cAMP). More recently described, also peroxisome proliferator-activated receptor delta (PPARδ) activation plays a role in controlling the cell fate, i.e. apoptosis[14,15].

Clinical data on the use of iloprost in SSc

Clinical data from the literature show an improvement in the frequency, duration and intensity of ischemic episodes for up to at least 6 weeks after a short (3 to 5 days) course of intravenous iloprost. Improved healing of active digital ulcers was also reported. Table 1 summarizes the main studies reported in the literature on the use of iloprost in patients with SSc. The long-term studies show the maintenance of efficacy on the vascular symptoms over time. This is an important therapeutic goal since iloprost administration aims to correct vasculopathy and restore the function of microcirculation, which are key factors in the disease. Long-term treatment of vasculopathy may therefore represent a rational therapeutic approach: it has an impact on the quality of patient's life - since RP and DUs are two of the major causes of pain and disability in these patients - and may potentially have a favorable impact on the evolution of the disease. In fact, a low incidence of severe vascular complications, such as pulmonary arterial hypertension, or a stabilization of cardiopulmonary parameters was observed in long-term studies[7,8,25,26].

Recently, at the Rheumatology Unit of Policlinico Vittorio Emanuele, Catania, Italy, the disease progression, specifically in terms of cardiopulmonary function, was

Table 1. *Summary of the main clinical studies*

Study	Design	Patients	Infusion length	Rate	Treatment start	Treatment repetition	Main outcome	Follow-up
Yardumian, 1988[16]	RCT	12	5h	1.0-3.0 ng/kg/min	3 days	-	Improvement of RP symptomatology Digital and nail bed flow increased	6 weeks
McHugh, 1988[17]	RCT	29	3-6h	0.5-2.0 ng/kg/min	3 days	-	Reduction in number and severity of RP-attacks compared with placebo;	6 weeks
Rademaker, 1989[7]	RCT	23	8h	0.5-2.0 ng/kg/min	3 days	1 day / 8 weeks	Reduction in the number, duration and severity of attacks of RP; Reduction in mean number of DUs; increase in hand temperature and digital and microcirculatory blood flow	4 months
Constans, 1991[18]	RCT	12	6h	0.5-2.0 ng/kg/min	11±7 days	-	No substantial increase in Transcutaneous pO2; Clinical improvement	11±7 days
Torley, 1991[19]	RCT	55	6h	0.5 or 2.0 ng/kg/min	3 days	-	Reduction in frequency, duration, and severity of attacks of RP, Ulcer healing in 44% (High dose) and 39% (Low dose) of patients	8 weeks
Kyle, 1992[20]	RCT	13	6h	0.5-2.0 ng/kg/min	3 days	-	Reduction in frequency of Raynaud's attacks	6 weeks
Wigley, 1992[21]	RCT	35	6h	0.5-2.0 ng/kg/min	5 days	-	Complete healing of cutaneous lesions; Reduction of the number, duration and severity of attacks of PR; Decrease in critical ischemic temperature; Improvement in the rate of skin temperature recovery following cold challenge	10 weeks
Wigley, 1994[22]	RCT	131	6h	0.5-2.0 ng/kg/min	5 days	-	Reduction of mean number of RP attacks; improvement in a global Raynaud severity score; Effective in healing of cutaneous lesions	9 weeks
Zachariae, 1996[23]	O	12	6h	0.5-2.0 ng/kg/min	8-13 days	-	2 patients with RP noted a temporary improvement lasting several weeks; Imminent gangrene was arrested and followed by total healing; All ischemic ulcers healed in 4 of 6 patients, while the remaining 2 patients experienced partial healing.	13 days

Biasi, 1998[24]	O	20	6h	0.5-2.0 ng/kg/min	-	5 days / 3 Months	Decrease in scleroderma skin lesion score; Ischemic lesion improvement No difference in VAS and DLCO	1 year
Filaci, 1999[25]	RCT	20	6h	1.0 ng/kg/min	-	5 days / Month	Improvement of skin, microvascular and esophageal morphological and functional parameters; Reduction of IL-6 serum concentration	1 year
Scorza, 2001[8]	RCT	46	8h	0.5-2.0 ng/kg/min	5 days	1 day / 6 weeks	Reduction of skin score; DLCO remained stable	1 year
Bettoni, 2002[26]	O	30	6h	0.5-2.0 ng/kg/min	5 days	1 day / 3 weeks	Complete healing of digital ulcers in 90% of patients; Decrease of the RP-VAS and of Rodnan skin thickness score; DLCO/VA decreased from 71% to 62%	3 years
Milio, 2006[27]	RCT	60	6h	0.5-2.0 ng/kg/min	-	Group A: 10 days / 3 months Group B1: 1 day / month Group B: 20 days / 6 months	Reduction in the number, duration and severity of attacks of RP; Improvement of Quality of Life	18 months
Caramaschi, 2006[28]	O	81	6h	0.5-2.0 ng/kg/min	-	1 day / Month, or 5 days / 3 Months	None of patients developed severe isolated pulmonary hypertension; None of patients developed scleroderma renal crisis.	1-3 years
Balbir Gurman, 2007[29]	O	12	8h	0.5-2.0 ng/kg/min	5 days	-	Reduction of malondialdehyde levels Increase in Catalase and Superoxide dismutase levels	5 days
Airò, 2007[30]	O	112	6h	0.5-2.0 ng/kg/min	5 days	1 day / 3 weeks	Decrease in the Raynaud's phenomenon VAS and Rodnan skin thickness score compared to the pre-treatment point; No significant difference with regard to changes in lung function tests over time compared with a control group;	4 years
Scarsi, 2008[31]	O	59	6h	0.5-2.0 ng/kg/min	5 days	1 day / 3 weeks	Improvement of RP symptomatology Reduction in mean number of DUs; Decrease of the modified Rodnan Skin thickness score	4 years
Kawald, 2008[32]	RCT	50	6h	0.5-2.0 ng/kg/min	21 days	21 days once or twice a year	Reduction in the number, duration and severity of attacks of RP; DLCO and FVC remained stable	2 years
Caramaschi, 2009[33]	O	85	6h	0.5-2.0 ng/kg/min	-	1 day / Month, or 5 days / 3 Months	Delay in beginning iloprost therapy (>18 months from the SSc onset) is a potential modifiable risk factor associated with ischemic DUs OR= 5.70 (95% CI 1.96–16.59)	7 years
Bali, 2011[34]	RCT	17	3h	0.5-2.0 ng/kg/min	5 days	5 days / Month	No significant reduction in the number, duration and severity of attacks of RP	4 months
Caravita, 2011[35]	O	14	6h	0.5-2.0 ng/kg/min	-	5 days / 6 weeks	Pulmonary Arterial Systolic Pressure (PASP) significantly decreased; 6 Minute-Walk Distance (6MWD) increased; PASP resulted significantly correlated with N-terminal pro b-type natriuretic peptide (NT-proBNP)	8 months

Casigliani Rabl,l 2012[36]	O	73	-	1.0-1.5 ng/kg/min	-	1 day / 3 Months	Complete healing of DU in 25/28 patients; Improvement of RP symptomatology	1-8 years
Caramaschi, 2012[37]	O	115	6h	0.5-2.0 ng/kg/min	-	1 day / Month, or 5 days / 3 Months	Low incidence of digital gangrene requiring amputation;	8 years
Auriemma, 2013[38]	O	28	3h	0.5-2.0 ng/kg/min	1-3 days	1-3 days / 3 Months	Improvement of RP symptomatology; IL-23 modulation	12-16 weeks
De Cata, 2016[39]	O	34	6h	0.5-2.0 ng/kg/min	1 day	1 day / Month	Complete healing of DUs in 49,3% of patients; Partial healing of DUs in 26,1% of patients; 24,6% did not respond	6 months
Trombetta, 2016[40]	O	30	24h	0.5-2.0 ng/kg/min	-	5 days / 3 Months	Iloprost + bosentan Increase in fingertip blood perfusion and in absolute nail fold capillary number /mm Reduction (80%) in the incidence of new DU. DLCO and sPAP did not worsen	4 years
Colaci, 2016[41]	O	50	6h	0.8-1.0 ng/kg/min	-	1-3 days / Month	Reduction in mean number of DUs; 71% of DUs improved during the follow-up	10 years
Foti, 2016[42]	O	68	6h	0.5-2.0 ng/kg/min	-	5-6 days / Month	Reduction in the occurrence of DUs; None of the free-DUs patients at baseline presented DUs at the end of follow-up; Improvement in tricuspid annular plane systolic excursion, sPAP, and brain natriuretic peptide.	7 years
Cestelli, 2017[43]	O	95	-	2.0 ng/kg/min	1 month	1 day / Month	Reduction of the number of giant capillaries; increase of ramified capillaries in iloprost + bosentan group	1 year

Abbreviations: RCT: randomized clinical trial, O: observational study, SSc: systemic sclerosis, RP: Raynaud's phenomenon, DUs: digital ulcers, VAS: visual analogue scale, DLCO: diffusing capacity of the lung for carbon monoxide, VA: alveolar volume, FVC: forced vital capacity, OR: odds ratio, sPAP: systolic pulmonary artery pressure.

evaluated in a group of 68 consecutive SSc patients treated with iloprost with a schedule of 5–6 consecutive daily infusions per month (6 h/day, 0.5–2.0 ng/kg/min), during a 7 years follow-up[41].

Data show a stabilization of the cardiopulmonary disease, in particular in a very long-term follow-up and this results are first supported by NYHA class non-progression and a significant reduction of systolic pulmonary arterial pressure (sPAP), brain natriuretic peptide levels (BNP) and improvement of tricuspid annular plane systolic excursion (TAPSE) values in study population. In particular, a significant sPAP reduction was observed in the subgroup of patients with baseline sPAP ≥36 mmHg and after an average long-term follow-up. The EUSTAR working group recently showed the importance of sPAP considering that baseline values ≥36 mmHg were significantly associated with an increased risk of death up to 3-year follow-up[44] while BNP levels is an important diagnostic marker of early pulmonary artery hypertension and TAPSE is important for assessing disease severity, stability, and prognosis in PAH patients, with a cut-off value > 20 mm indicating a satisfactory patient status[45,46]. It was also observed a stabilization of interstitial lung disease markers, such as Diffusing capacity of the Lung for Carbon Monoxide (DLCO), Forced Vital Capacity (FVC), Alveolar Volume (VA), and DLCO/VA and favourable effect on skin involvement with a significant change of Rodnan skin score value. Finally, the long-term effectiveness of the therapy was confirmed since a significant reduction in the prevalence of digital ulcers was observed.

Concerning the safety profile, data from the literature show a satisfactory tolerability of the drug both in the short and long-term studies, the most common side effects, mainly due to the vasodilating properties of the drug, can be managed with the optimal titration of the individual dose at beginning of treatment.

Conclusions

SSc remains a disease characterized by a poor prognosis due to the occurrence of cardiopulmonary complications and the long-term disease stabilization represents an important therapeutic goal. Intravenous iloprost acts on small vessel vasculopathy, which is one of the key factors of the disease, with proven effectiveness in the treatment

of Raynaud's phenomenon and digital ulcers. Data from observational studies suggest that an intensive and chronic regimen of IV iloprost administration may lead to the stabilization of disease in SSc patients but randomized and controlled trials are needed to confirm these promising results.

Conflict of Interest

Alberto Farina is an employee of Italfarmaco S.p.A., the other authors report no conflict of interest.

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