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

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Article Info

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. 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. 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 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. 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.

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. It should also be considered that treatment with iloprost may offer greater efficacy than calcium antagonists. 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. The synthetic prostacyclin analogue iloprost closely mimics the whole range of endogenous prostacyclin’s physiological effects, 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.

**Figure 1:** Mode of action of iloprost

ATP: Adenosine triphosphate; AMP: adenosine monophosphate; cAMP: Cyclic adenosine monophosphate; PDE: Phosphodiesterase; PPAR: peroxisome proliferator-activated receptor.

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
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

![Diagram of altered microcirculation](image1)

![Diagram of restored microcirculation](image2)
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>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Patients</th>
<th>Infusion length</th>
<th>Rate</th>
<th>Treatment start</th>
<th>Treatment repetition</th>
<th>Main outcome</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yardumian, 1988(^{16})</td>
<td>RCT</td>
<td>12</td>
<td>5h</td>
<td>1.0-3.0 ng/kg/min</td>
<td>3 days</td>
<td>-</td>
<td>Improvement of RP symptomatology; Digital and nail bed flow increased</td>
<td>6 weeks</td>
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<tr>
<td>McHugh, 1988(^{17})</td>
<td>RCT</td>
<td>29</td>
<td>3-6h</td>
<td>0.5-2.0 ng/kg/min</td>
<td>3 days</td>
<td>-</td>
<td>Reduction in number and severity of RP-attacks compared with placebo;</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Rademaker, 1989(^7)</td>
<td>RCT</td>
<td>23</td>
<td>8h</td>
<td>0.5-2.0 ng/kg/min</td>
<td>3 days</td>
<td>1 day / 8 weeks</td>
<td>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</td>
<td>4 months</td>
</tr>
<tr>
<td>Constans, 1991(^{18})</td>
<td>RCT</td>
<td>12</td>
<td>6h</td>
<td>0.5-2.0 ng/kg/min</td>
<td>11±7 days</td>
<td>-</td>
<td>No substantial increase in Transcutaneous pO2; Clinical improvement</td>
<td>11±7 days</td>
</tr>
<tr>
<td>Torley, 1991(^{19})</td>
<td>RCT</td>
<td>55</td>
<td>6h</td>
<td>0.5 or 2.0 ng/kg/min</td>
<td>3 days</td>
<td>-</td>
<td>Reduction in frequency, duration, and severity of attacks of RP; Ulcer healing in 44% (High dose) and 39% (Low dose) of patients</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Kyle, 1992(^{20})</td>
<td>RCT</td>
<td>13</td>
<td>6h</td>
<td>0.5-2.0 ng/kg/min</td>
<td>3 days</td>
<td>-</td>
<td>Reduction in frequency of Raynaud’s attacks</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Wigley, 1992(^{21})</td>
<td>RCT</td>
<td>35</td>
<td>6h</td>
<td>0.5-2.0 ng/kg/min</td>
<td>5 days</td>
<td>-</td>
<td>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</td>
<td>10 weeks</td>
</tr>
<tr>
<td>Wigley, 1994(^{22})</td>
<td>RCT</td>
<td>131</td>
<td>6h</td>
<td>0.5-2.0 ng/kg/min</td>
<td>5 days</td>
<td>-</td>
<td>Reduction of mean number of RP attacks; improvement in a global Raynaud severity score; Effective in healing of cutaneous lesions</td>
<td>9 weeks</td>
</tr>
<tr>
<td>Zachariae, 1996(^{23})</td>
<td>O</td>
<td>12</td>
<td>6h</td>
<td>0.5-2.0 ng/kg/min</td>
<td>8-13 days</td>
<td>-</td>
<td>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.</td>
<td>13 days</td>
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<tr>
<td>Study</td>
<td>Type</td>
<td>Patients</td>
<td>Dose</td>
<td>Duration</td>
<td>Outcome</td>
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<td>Biasi, 1998</td>
<td>O</td>
<td>20</td>
<td>6h</td>
<td>0.5-2.0 ng/kg/min</td>
<td>Decrease in scleroderma skin lesion score; ischemic lesion improvement; No difference in VAS and DLCO</td>
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<tr>
<td>Filaci, 1999</td>
<td>RCT</td>
<td>20</td>
<td>6h</td>
<td>1.0 ng/kg/min</td>
<td>Improvement of skin, microvascular and esophageal morphological and functional parameters; Reduction of IL-6 serum concentration</td>
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<td>Scorza, 2001</td>
<td>RCT</td>
<td>46</td>
<td>8h</td>
<td>0.5-2.0 ng/kg/min</td>
<td>Reduction of skin score; DLCO remained stable</td>
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<td>Bettoni, 2002</td>
<td>O</td>
<td>30</td>
<td>6h</td>
<td>0.5-2.0 ng/kg/min</td>
<td>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%</td>
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<td>Milio, 2006</td>
<td>RCT</td>
<td>60</td>
<td>6h</td>
<td>0.5-2.0 ng/kg/min</td>
<td>Reduction in the number, duration and severity of attacks of RP; Improvement of Quality of Life</td>
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<tr>
<td>Caramaschi, 2006</td>
<td>O</td>
<td>81</td>
<td>6h</td>
<td>0.5-2.0 ng/kg/min</td>
<td>None of patients developed severe isolated pulmonary hypertension; None of patients developed scleroderma renal crisis.</td>
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<td>Balbir Gurman, 2007</td>
<td>O</td>
<td>12</td>
<td>8h</td>
<td>0.5-2.0 ng/kg/min</td>
<td>Reduction of malondialdehyde levels; Increase in Catalase and Superoxide dismutase levels</td>
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<tr>
<td>Airò, 2007</td>
<td>O</td>
<td>112</td>
<td>6h</td>
<td>0.5-2.0 ng/kg/min</td>
<td>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;</td>
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<td>Scarsi, 2008</td>
<td>O</td>
<td>59</td>
<td>6h</td>
<td>0.5-2.0 ng/kg/min</td>
<td>Improvement of RP symptomatology; Reduction in mean number of DUs; Decrease of the modified Rodnan Skin thickness score</td>
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<tr>
<td>Kawald, 2008</td>
<td>RCT</td>
<td>50</td>
<td>6h</td>
<td>0.5-2.0 ng/kg/min</td>
<td>Reduction in the number, duration and severity of attacks of RP; DLCO and FVC remained stable</td>
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<tr>
<td>Caramaschi, 2009</td>
<td>O</td>
<td>85</td>
<td>6h</td>
<td>0.5-2.0 ng/kg/min</td>
<td>Delay in beginning iloprost therapy (&gt;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)</td>
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<td>Bali, 2011</td>
<td>RCT</td>
<td>17</td>
<td>3h</td>
<td>0.5-2.0 ng/kg/min</td>
<td>No significant reduction in the number, duration and severity of attacks of RP</td>
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<tr>
<td>Caravita, 2011</td>
<td>O</td>
<td>14</td>
<td>6h</td>
<td>0.5-2.0 ng/kg/min</td>
<td>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)</td>
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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.

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 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. It was also observed a stabilization of interstitial lung disease markers, such as Diffusing capacity of the Lung for Carbon Monoxide (DLCO), 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 interest of interest.

**References**


