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Intravenous iloprost in systemic sclerosis and its effect in cardiopulmonary function: a retrospective observational study

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Abstract. – OBJECTIVE: This study aims at evaluating the disease progression, specifically in terms of cardiopulmonary function, in a group of consecutively enrolled systemic sclerosis (SSc) patients treated with the approved iloprost regimen.

PATIENTS AND METHODS: A retrospective observational study was performed on 68 SSc patients treated with 5-6 infusions of iloprost per month for 6 hours per day at a dosage of 0.5-2.0 ng/kg/min through a portable syringe pump. All patients were evaluated for modified Rodnan skin score, systolic pulmonary arterial pressure, tricuspid annular plane systolic excursion, diffusing capacity of the lungs for carbon monoxide, forced vital capacity, alveolar volume, diffusing capacity of the lungs for carbon monoxide/alveolar volume, pro-brain natriuretic peptide (pBNP), New York Heart Association class, and the presence or absence of digital ulcers (DUs).

RESULTS: After a follow-up period of 9.9±2.9 years, all patients improved in frequency and severity of the Raynaud phenomenon and showed a stabilization or improvement of cardiopulmonary parameters. The pulmonary arterial pressure and pBNP improved significantly from baseline (30.91±6.4 mmHg *vs*. 27.36±7.1 mmHg, and 97.20±69.3 pg/ml *vs*. 66.65±44.3 pg/ml, respectively; $p<0.0001$ for both). A significant improvement was observed in the modified Rodnan skin score in 57 patients who continued the treatment during the entire follow-up (5.09±5.7 *vs*. 3.30±4.2, $p<0.0001$).

CONCLUSIONS: Despite the retrospective design and the lack of a control group, the regular and continued administration of iloprost maintained the stability of the cardiopulmonary and cutaneous parameters in SSc. It significantly reduced pBNP levels, a prognostic cardiac biomarker of SSc. Future research should be addressed to demonstrate a stronger causality of this effect.

Key Words:
Systemic sclerosis, Iloprost, Cardiopulmonary function.

Introduction

Systemic sclerosis (SSc) is a rare autoimmune disease of still not fully understood pathogenesis with an incidence of 1 in 100,000[1]. It is a chronic connective tissue disease characterized by endothelial dysfunction and widespread fibrosis of the skin and/or internal organs[2,3]. SSc is more prevalent in females than males[4].

Primary myocardial involvement and pulmonary hypertension represent severe organ damage that is likely responsible for 20-30% of all premature deaths in SSc. Therefore, stabilizing these conditions may represent an important therapeutic goal[5,6]. The mortality rate of patients with SSc is 1.5-7.2-times higher than that of the general population. This is mainly due to the involvement of the internal organs. In particular, cardiac involvement appeared to increase the death rate by 2.8-times, with no difference between the diffuse and limited forms. An increased NT-proBNP predicts pulmonary arterial hypertension (PAH) in SSc. The use of these markers should improve PAH risk stratification[7]. Currently, a disease-modifying drug that tackles the natural evolution of the disease itself is yet to be discovered[8]. Although vascular abnormalities are the key features of SSc and play a crucial role in developing disease complications, including cardiovascular involvement, only a few drugs directed at endothelial dysfunction have been approved to treat the vascular pathology in patients with SSc[5,9].

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Different pathophysiological steps associated with progressive fibrotic involvement of skin and internal organs have been identified, and new target treatments are under evaluation. Early systematic combination therapy of SSc patients with vasodilators, immunosuppressive and antifibrotic drugs may be required to reduce the disease progression[10]. Studies[11] using prostacyclin and its analogs as iloprost in lungs and pulmonary endothelial cells support the benefits of using these drugs in patients with PAH. It has been demonstrated that the protective barrier effect of iloprost in SSc endothelial cells is mediated by enhancing vascular endothelial-cadherin adherens junctions. In human pulmonary artery endothelial cells, iloprost attenuates the disruption of the endothelial monolayer.

The European League Against Rheumatism (EULAR) guidelines recommend intravenous (IV) iloprost for the treatment of Raynaud's phenomenon (RP) and the healing and prevention of ulcers. Despite the demonstrated benefits in randomized clinical trials[9,12] with the approved scheme, dissimilar therapeutic iloprost administration schemes are frequently adopted among different tertiary centers.

The present study aimed at evaluating cardiopulmonary parameters and pro-brain natriuretic peptide (pBNP) in a group of consecutively enrolled SSc patients treated with the approved iloprost regimen for RP in a long-term follow-up.

Patients and Methods

A retrospective observational study was performed on SSc patients diagnosed according to 2013 ACR/EULAR (American College of Rheumatology/European League Against Rheumatism) criteria. All the patients in charge at the rheumatology unit at Catania hospital, in Italy, from 2011 to 2020, with RP of any degrees of severity, were included in the analysis. They were treated with iloprost with a schedule of 5-6 consecutive daily infusions per month (6 h/day, 0.5-2.0 ng/kg/min).

All the patients received iloprost with the conventional IV administration and subsequently, from 2014, by the portable infusion pump, Infonde® (Italfarmaco S.p.A, Milan, Italy).

Infonde® is a portable syringe pump with reduced dimensions (84.9 × 49.3 × 32.1 mm) and a weight of 118 g specifically designed for controlled administration of IV iloprost and uses dedicated 25.5 ml syringes. The frequency and severity of the RP attacks were clinically evaluated at each monthly visit. The assessed parameters included the modified Rodnan skin score (mRSS), systolic pulmonary arterial pressure (PASP), tricuspid annular plane systolic excursion (TAPSE), ejection fraction (EF), left atrium (LA) volume, diffusing capacity of the lung for carbon monoxide (DLCO), forced vital capacity (FVC), alveolar volume (VA), DLCO/VA, pBNP, New York Heart Association (NYHA) class, and the presence or absence of DUs. These parameters were assessed for all patients annually.

A sub-analysis was performed on the mRSS of 57 patients who continued iloprost treatment for the entire follow-up and 11 patients who discontinued the treatment early.

The study was conducted under the Declaration of Helsinki and the current ethical standards. The Local Ethical Committee (Comitato Etico Catania 1, Azienda Ospedaliero-Universitaria Policlinico "G. Rodolico-San Marco", Catania, Italy) has approved the study protocol and all patients signed an informed consent for the use of their data for research purposes.

Statistical Analysis

Descriptive statistical analyses were performed by calculating the mean and standard deviation (SD) for continuous variables and the percentage for discrete variables. Statistical comparisons between post-baseline and baseline data were made using the Student's *t*-test or the Mann-Whitney U test (depending on the distribution of these variables) and applying the two-proportion z-test when categorical variables were considered. A p-value less than 0.05 was considered statistically significant. The statistical analyses were performed through standard procedures using the R statistical program, version 3.5.0 (The R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 68 consecutive female patients were evaluated in the study. At baseline, the mean age was 52.88±12.6 years. Patients were followed up for 9.9±2.9 years, during which they were treated regularly with intravenous iloprost for 5-6 consecutive days per month. Interstitial lung disease was present in 20.6% of patients, and the limited pattern was the most prevalent.

Table I. Characteristics of the study population.

Characteristics	%/mean ± SD
Patients (n)	68
Age (years)	52.88 ± 12.6
Age of onset of Raynaud's phenomenon (years)	46.6 ± 13.7
Time to diagnosis (years)	6.72 ± 10
Sex (female)	100%
BMI	24.3 ± 5.2
Interstitial lung disease	20.6
Type:	
• Limited	67.6
• Diffuse	25.0
• Early	5.9
Pattern:	
• Early	27.9
• Active	55.9
• Late	23.5
Antibodies:	
• ANA	92.6
• ACA	48.5
• SCL70	20.6
Duration of treatment with IV iloprost (years)	9.9 ± 2.9
Bosentan	54.4
Sildenafil	2.9
Losartan	76.5
Hydroxychloroquine	25.0
Azathioprine	23.5
Mycophenolat	22.1
Cyclosporine	1.5

BMI, body mass index; ANA, antinuclear antibodies; ACA, anticentromere antibodies; SCL70, Scl 70 antibodies; IV, intravenous; SD, standard deviation; F, Female.

The mean age of onset of RP was 46.6±13.7 years, and the mean time to diagnosis was 6.72±10 years (Table I).

Overall, the frequency and severity of RP attacks were reduced in all patients and were kept under control during the entire follow-up period.

At the end of the follow-up, all patients showed a significant reduction in the PASP levels from 30.9l±6.4 mmHg to 27.36±7.1 mmHg, as well as a significant reduction in the pBNP from 97.20±69.3 pg/ml to 66.65±44.3 pg/ml and LA volume from 38.94±18.7 to 26.19±4.4 (p<0.001). Over time, no significant variations in the NYHA class, TAPSE, FVC, DLCO, VA, DLCO/VA, EF, and mRSS were observed.

The prevalence of DUs decreased from 44.11% to 19.11% (p<0.01). Upon dividing the patients according to concurrent treatment, we found that bosentan with iloprost reduced the prevalence of DUs from 54.05% to 16.21% (p<0.01). In contrast, iloprost alone did not induce significant improvement in this parameter.

Of the 68 patients included in the analysis, 11 discontinued the treatment after a mean follow-up period of 8±1.7 years. The reasons for discontinuation of treatment were related to difficulty reaching the hospital in 9 cases, the development of esophageal varices in one case, and arrhythmia in another.

The 57 patients who continued the treatment for the entire follow-up period exhibited a significant reduction in the mRSS that ranged from 5.09±5.7 to 3.30±4.2 (p<0.0001), PASP from 30.82±6.0 mmHg to 26.30±6.1 mmHg (p<0.0001), pBNP from 100.11±72.1 pg/ml to 58.80±39.3 pg/ml (p<0.0001), and LA volume from 38.66±18.9 to 26.21±4.6 (p<0.0001). The remaining 11 patients experienced a significant increase in the mRSS (from 2.60±2.3 to 6.90±3.0; p<0.01) and DLCO (from 84.27±16.6% to 62.45±17.9%; p<0.05) after discontinuing the iloprost treatment at the end of the follow-up. Lastly, patients who discontinued the treatment exhibited a worsening of skin thickness, with an increase in the mRSS from 2.0±1.4

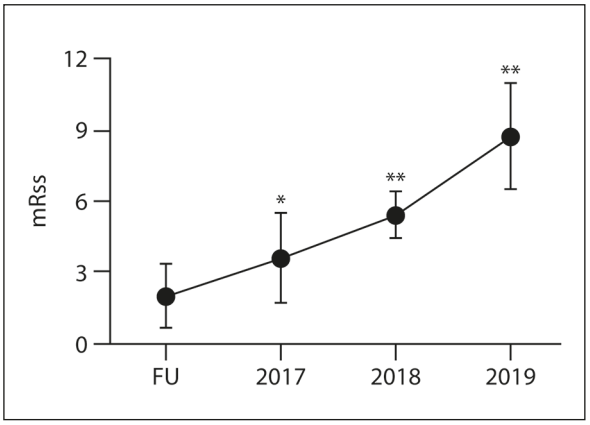

Figure 1. Modified Rodnan skin score values of 11 patients after treatment discontinuation. The mRSS significantly worsened after 1, 2 and 3 years of treatment drop-out; asterisks denote statistically significant differences compared to the last visit (*$p < 0.05$; **$p < 0.01$). FU: Follow-up; mRSS: Modified Rodnan skin score.

to 3.7±1.9 ($p<0.05$) in the first year and to 5.5±1.0 and 8.8±2.3 after 2 years and 3 years of discontinuing therapy, respectively ($p<0.01$) (Figure 1). Meanwhile, no statistical differences were found for all the other parameters.

Discussion

In our study, the approved regimen of iloprost for treating RP of all degrees of severity induced control of the frequency and severity of RP symptoms. It caused stabilization of cardiopulmonary parameters in all patients during a long-term follow-up, as indicated by the improvement or non-worsening of the assessed parameters. In these patients, we witnessed a control of the cardiopulmonary disease, suggesting a possible favorable effect of the treatment against the development of PAH. These conclusions are supported by the non-progression of the NYHA class and a significant reduction in the PASP and pBNP levels.

Our results showed a significant reduction in PASP values in the main group of patients who continued treatment throughout the follow-up period. At baseline, only 7 patients had a PASP > 40 mmHg. In our clinical practice, right heart catheterization was not performed in our patients at baseline. Follow-up and PAH detection were based on DETECT algorithm[13].

In patients with SSc, cardiopulmonary dysfunction is considered one of the leading life-threatening complications. This condition has probably already been underdiagnosed. Cardiac biomarkers, such as BNP and NT-proBNP, could be used to detect cardiac involvement and, in particular, as prognostic predictors at baseline in PAH[14,15]. High levels of this hormone are indicators of diastolic dysfunction and cardiac overload[16,17], and predictors of atrial fibrillation[18] or pulmonary hypertension[19,20]. NT-proBNP may be elevated in SSc in the absence of pulmonary hypertension due to left ventricular disease and primary myocardial involvement. Despite this, it may be an adjunct to other screening tools, such as transthoracic echocardiography and pulmonary function tests. The change in NT-proBNP levels after therapy was shown to be a powerful independent predictor of survival[21]. In our study, we found that 9 patients had an NT-proBNP level > 125 pg/ml, and regular treatment with iloprost significantly reduced the NT-proBNP.

Despite the significant reduction, PASP and NT-proBNP decreased levels remained in the normal range. Furthermore, the prevalence of PAH in our patient's cohort at baseline was 10.4% (7/68) and reached 4.4% (3/68) at the end of follow-up. These findings are in line with those of the EUSTAR study[22]: this included patients with early-stage SSc with an incidence rate of PASP increase > 40 mmHg of 14%, which remained low in the follow-up compared to other organ involvement, such as DLCO.

An impairment of the LA mechanics is an early sign of myocardial involvement in SSc[23]. Our results showed significant improvements in the LA size in patients who continued the iloprost regimen until the end of the follow-up period. It has previously been shown[24] that LA remodeling might be due to a physiological response to pressure overload in hypertensive patients. None of the hypertensive patients had increased atrial volume at baseline and follow-up in our study.

According to the current guidelines for diagnosing and treating pulmonary hypertension, the TAPSE value has well-established importance in assessing PAH patients' disease severity, stability, and prognosis. A cut-off value > 20 mm indicates a satisfactory patient status[25]. In this study, the mean TAPSE values remained > 20 mm during the entire study period.

Despite being less sensitive and specific than right heart catheterization, pulmonary function tests, such as the DLCO, FVC, VA, and DLCO/VA, are important means for lung impairment monitoring and early interstitial lung disease detection[26]. We observed stabilization of the in-

terstitial lung disease markers in the entire population without any clinically meaningful decline at the end of follow-up.

Regarding skin involvement, a statistically significant improvement in mRSS was observed in patients who continued the treatment for the entire follow-up period *vs.* baseline (5.09±5.7 *vs.* 3.30±4.2; $p<0.0001$). These results highlight that good treatment compliance and close follow-up of patients are essential to maintain the beneficial effects achieved. Although a progression of skin involvement is not expected in individuals with such a long disease duration, it seems like in anticentromere antibody (ACA)-positive patients (almost half of our population) worsening skin involvement may be detected at long-term follow-up[27]. Moreover, our results demonstrated that the administration of an intensive IV iloprost regimen, in combination with bosentan when indicated, improved the healing of pre-existing ulcers, and prevented the occurrence of new DUs, confirming the importance of these two therapeutic options in the management of SSc vasculopathy[12].

Following the approved label of iloprost, the drug was administered at the maximally tolerated dose of 0.5-2.0 ng/kg/min by a syringe pump. In clinical practice, a standard protocol for treating SSc-related vasculopathy is lacking. The PROSIT study[28] identified different therapeutic schemes adopted by Italian tertiary centers as well as various approaches to managing side effects. In our study, iloprost infusions were generally well-tolerated, and individual cases required a temporary dose reduction during iloprost infusion and adequate premedication. Side effects, mainly flushing, hypotension, and nausea, were limited to the titration phase until reaching the maximum tolerated dose and disappeared immediately after the infusion. After the identification of maximum tolerated dose, this was maintained for the subsequent infusions. Our data agree with those reported in the literature, where the most common side effects were managed by reducing/modulating the infusion rate and with premedication[29]. Discontinuation of the treatment during warmer seasons is not recommended, as it may result in the loss of the beneficial effects of therapy on microcirculation despite improvement in RP[30]. The feasibility and satisfaction of patients and healthcare professionals in using the Infonde® portable syringe pump have been previously demonstrated, showing it to be an efficient alternative to the traditional method. Indeed, it can reduce the time nurses spend monitoring patients and is useful for improving the human resource management in hospital settings[31,32].

In our study, the use of the Infonde® pump allowed us to treat all our patients regularly and ensured good treatment adherence in the hospital setting during long-term follow-up.

Limitations

The present study has some limitations, mainly due to the study design. Being a retrospective analysis of a patient database, it did not include a control group; furthermore, the number of patients was relatively small and limited the correlation between variables. However, the retrospective analysis showed that cardiopulmonary parameters remained stable and pro-BNP reduced significantly in all patients. A prospective and controlled trial could be useful to confirm and validate our observations.

Conclusions

Cardiopulmonary dysfunction is the main cause of mortality in patients with SSc. Stabilizing the cardiopulmonary parameters is one of the major therapeutic goals in the management of SSc, as well as the improvement of the skin pathology grade. In this study, discontinuation of the treatment for logistic or compliance reasons worsened the clinical condition of patients. In contrast, strict monitoring and follow-up significantly improved the skin and pulmonary symptoms. Regular and continuous administration of iloprost with the approved and recommended regimen may play a key role in cardiopulmonary and cutaneous functions in SSc during a long-term follow-up period and significantly reduce the pBNP levels, an independent predictor of survival.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Authors' Contribution

Conceptualization: RF, EV; Data curation: EV, GA; Formal analysis: GA; Investigation: CG; Methodology: SB; Supervision: RF; Visualization YDB, AB Roles/Writing - original draft EV; RF, RP. Writing - review & editing: All; Approval for submission: All.

Ethics approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the Local Ethics Committee (Comitato Etico Catania 1, Azienda Osperaliero-Universitaria Policlinico "G.Rodolico-San Marco", Catania, Italy).

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