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Practice pattern for the use of intravenous iloprost for the treatment of peripheral vasculopathy in systemic sclerosis: A case-control study from the Italian national multicenter "SPRING" (Systemic Sclerosis Progression InvestiGation) Registry

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1       **PRACTICE PATTERN FOR THE USE OF INTRAVENOUS ILOPROST**  
2       **FOR THE TREATMENT OF PERIPHERAL VASCULOPATHY IN**  
3       **SYSTEMIC SCLEROSIS: A CASE-CONTROL STUDY FROM THE**  
4       **ITALIAN NATIONAL MULTICENTER “SPRING” (Systemic Sclerosis**  
5       **Progression InvestiGation) REGISTRY**  
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8       Valeria Ricciari\*<sup>1</sup>, Greta Pellegrino\*<sup>1,2</sup>, Edoardo Cipolletta<sup>3</sup>, Dilia Giuggioli<sup>4</sup>, Gianluigi Bajocchi<sup>5</sup>, Silvia  
9       Bellando-Randone<sup>6</sup>, Lorenzo Dagna<sup>7</sup>, Giovanni Zanframundo<sup>8</sup>, Rosario Foti<sup>9</sup>, Fabio Cacciapaglia<sup>10</sup>, Gio-  
10       vanna Cuomo<sup>11</sup>, Alarico Ariani<sup>12</sup>, Edoardo Rosato<sup>13</sup>, Gemma Lepri<sup>6</sup>, Francesco Girelli<sup>14</sup>, Elisabetta Zanatta<sup>15</sup>,  
11       Silvia Laura Bosello<sup>16</sup>, Iliara Cavazzana<sup>17</sup>, Francesca Ingegnoli<sup>18</sup>, Maria De Santis<sup>19</sup>, Giuseppe Murdaca<sup>20</sup>,  
12       Giuseppina Abignano<sup>21</sup>, Nicoletta Romeo<sup>22</sup>, Alessandra Della Rossa<sup>23</sup>, Maurizio Caminiti<sup>24</sup>, Annamaria Iu-  
13       liano<sup>25</sup>, Giovanni Ciano<sup>26</sup>, Lorenzo Beretta<sup>27</sup>, Gianluca Bagnato<sup>28</sup>, Ennio Lubrano<sup>29</sup>, Ilenia De Andres<sup>30</sup>,  
14       Alessandro Giollo<sup>31</sup>, Marta Saracco<sup>32</sup>, Cecilia Agnes<sup>33</sup>, Federica Lumetti<sup>4</sup>, Amelia Spinella<sup>4</sup>, Luca Magnani<sup>5</sup>,  
15       Corrado Campochiaro<sup>7</sup>, Giacomo De Luca<sup>7</sup>, Veronica Codullo<sup>8</sup>, Elisa Visalli<sup>9</sup>, Claudio Di Vico<sup>11</sup>, Antonietta  
16       Gigante<sup>13</sup>, Francesca Saccon<sup>34</sup>, Maria Grazia Lazzaroni<sup>17</sup>, Franco Franceschini<sup>17</sup>, Elena Generali<sup>19</sup>, Gianna  
17       Mennillo<sup>21</sup>, Simone Barsotti<sup>23</sup>, Giuseppa Pagano Mariano<sup>24</sup>, Francesca Calabrese<sup>24</sup>, Federica Furini<sup>35</sup>, Licia  
18       Vultaggio<sup>35</sup>, Simone Parisi<sup>36</sup>, Clara Lisa Peroni<sup>36</sup>, Gerolamo Bianchi<sup>37</sup>, Fabrizio Conti<sup>1</sup>, Franco Cozzi<sup>34</sup>, Sal-  
19       vatore D’Angelo<sup>21</sup>, Andrea Doria<sup>15</sup>, Enrico Fusaro<sup>36</sup>, Marcello Govoni<sup>35</sup>, Serena Guiducci<sup>6</sup>, Florenzo Ian-  
20       none<sup>10</sup>, Carlo Salvarani<sup>4</sup>, Gian Domenico Sebastiani<sup>25</sup>, Clodoveo Ferri<sup>4</sup>, Marco Matucci-Cerinic<sup>6</sup> and Ros-  
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22       Italian Society of Rheumatology).

23       \* first co-authors  
24

25       <sup>1</sup> Department of Internal Medicine, Anesthesiology and Cardiovascular Sciences, Sapienza University of Rome, Rome,  
26       Italy, Rome, Italy.

27       <sup>2</sup> Rheumatology Department, IRCCS Ospedale Galeazzi- Sant’Ambrogio, Milan, Italy.

28       <sup>3</sup> Rheumatology Unit, Department of Clinical and Molecular Sciences, Polytechnic University of Marche, Ancona, Italy.

29       <sup>4</sup> Rheumatology Unit, School of Medicine, University of Modena and Reggio Emilia, Modena, Italy, Modena, Italy.

30       <sup>5</sup> Rheumatology Unit, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy, Reggio Emilia, Italy.

31       <sup>6</sup> Department of Experimental and Clinical Medicine, Division of Rheumatology, University of Florence & Division of  
32       Rheumatology AOUC, University of Florence, Florence, Italy.

33       <sup>7</sup> Unit of Immunology, Rheumatology, Allergy and Rare Diseases (UnIRAR), IRCCS San Raffaele Scientific Institute,  
34       Vita-Salute San Raffaele University, Milan, Italy, Milano, Italy.

35       <sup>8</sup> Department of Rheumatology, Policlinico San Matteo, Pavia, Italy.

36       <sup>9</sup> Rheumatology Unit, A.O.U Policlinico S. Marco, Catania, Italy, Catania, Italy.

37       <sup>10</sup> Rheumatology Unit, Department of Precision and Regenerative Medicine-Ionian Area, University of Bari "Aldo Moro",  
38       Bari, Italy.

39       <sup>11</sup> Department of Precision Medicine - University of Campania "Luigi Vanvitelli", Naples, Italy, Caserta, Italy.

40       <sup>12</sup> Department of Medicine, Internal Medicine and Rheumatology, Azienda Ospedaliero Universitaria di Parma, Parma,  
41       Italy, Parma, Italy.

42       <sup>13</sup> Department of Translational and Precision Medicine, Sapienza University of Rome, Italy, Roma, Italy.

43       <sup>14</sup> Department of Medicine, Rheumatology Unit, Ospedale GB Morgagni - L Pierantoni, Forlì, Italy, Forlì, Italy.

44       <sup>15</sup> Rheumatology Unit, Department of Medicine (DIMED), University of Padua, Padua, Italy.

45       <sup>16</sup> Institute of Rheumatology and Affine Sciences, Division of Rheumatology, Catholic University of the Sacred Heart,  
46       Rome, Italy, Rome, Italy.

- 47 <sup>17</sup> Rheumatology and Clinical Immunology, ASST Spedali Civili of Brescia; Department of Clinical and Experimental  
48 Sciences, University of Brescia, Brescia, Italy, Brescia, Italy.  
49 <sup>18</sup> Division of Clinical Rheumatology, ASST Pini, Dept. of Clinical Sciences & Community Health, Research Center for  
50 Adult and Pediatric Rheumatic Diseases, Research Center for Environmental Health, Università degli Studi di Milano,  
51 Milan, Italy, Milano, Italy.  
52 <sup>19</sup> Rheumatology and Clinical Immunology, IRCCS Humanitas Research Hospital, Rozzano, and Humanitas University,  
53 Pieve Emanuele, Milan, Italy, Rozzano, Italy.  
54 <sup>20</sup> Department of Internal Medicine, University of Genoa, IRCCS Ospedale Policlinico San Martino, Genoa, Italy.  
55 <sup>21</sup> Rheumatology Institute of Lucania (IReL) and Rheumatology Department of Lucania, San Carlo Hospital, Potenza,  
56 Italy, Potenza, Italy.  
57 <sup>22</sup> Rheumatology Unit ASO Santa Croce e Carle, Cuneo, Italy.  
58 <sup>23</sup> Department of Rheumatology, University of Pisa, Pisa, Italy, Italy.  
59 <sup>24</sup> Departmental Rheumatology Unit, Grande Ospedale Metropolitano, Reggio Calabria, Italy, Italy.  
60 <sup>25</sup> Rheumatology Unit, San Camillo - Forlanini Hospital, Rome, Italy, Italy.  
61 <sup>26</sup> Hospital of Ariano Irpino, Local Health Department, Ariano Irpino, Avellino, Italy.  
62 <sup>27</sup> Referral Center for Systemic Autoimmune Diseases, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico  
63 di Milano, Milan, Italy.  
64 <sup>28</sup> Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy.  
65 <sup>29</sup> Department of Rheumatology, University of Molise, Campobasso, Italy.  
66 <sup>30</sup> Rheumatology Unit, Azienda Ospedaliera di Rilievo Nazionale ed Alta Specializzazione "Garibaldi", Catania, Italy.  
67 <sup>31</sup> Rheumatology Section, Department of Medicine, University of Verona, Verona, Italy.  
68 <sup>32</sup> Ospedale Mauriziano, Torino, Italy.  
69 <sup>33</sup> San Lorenzo Hospital, Carmagnola, Turin, Italy.  
70 <sup>34</sup> Department of Medicine, Villa Salus Hospital, Venice, Italy.  
71 <sup>35</sup> Rheumatology Unit, Department of Medical Sciences, University of Ferrara and Azienda Ospedaliera-Universitaria S.  
72 Anna di Ferrara, Ferrara, Italy.  
73 <sup>36</sup> Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Turin, Italy.  
74 <sup>37</sup> Rheumatology Unit, Department of Musculoskeletal Sciences, Local Health Trust 3, La Colletta Hospital, Genoa, Italy.  
75

## 76 **Key words**

77 Systemic sclerosis

78 Therapy

79 Intravenous Iloprost

## 86 **Corresponding author:**

87 Valeria Ricciari

88 [valeria.ricciari@uniroma1.it](mailto:valeria.ricciari@uniroma1.it)

89 Associate Professor of Rheumatology

90 Department of Internal Medicine, Anesthesiology and Cardiovascular Sciences, Sapienza University of Rome, Rome,  
91 Italy, Rome, Italy.

92 0039 06 49974641

93 0039 06 49974642 (Fax)

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95  
96  
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98  
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104 **ABSTRACT**

105 **Background.** Intravenous(IV) iloprost(ILO) has been widely used for the treatment of  
106 Systemic Sclerosis (SSc) peripheral vasculopathy. No agreement has been found on the  
107 regimen and the dosage of IV ILO in different scleroderma subset conditions.

108 This study aimed to evaluate the modalities of IV ILO administration within a large cohort  
109 of SSc patients from the SPRING Registry and to identify any associated clinical-  
110 demographic, instrumental or therapeutic data.

111 **Patients and methods.** Data of SSc patients treated with IV ILO for at least one year (case  
112 group) were retrospectively analyzed, including different timing and duration of IV ILO  
113 session, and compared with those of untreated patients (control group).

114 **Results.** Out of 1895 analyzed patients, 937(49%) received IV ILO treatment while 958(51%)  
115 were assigned to the control group. Among cases, about 70% were treated every four weeks,  
116 24% with an interval of more than four weeks, and only 6% of less than four weeks.

117 Most patients receiving the treatment every four weeks, or less, underwent infusion cycle  
118 for one day only, while if it was scheduled with an interval of more than 4 weeks, a total  
119 number of 5 consecutive days of infusions was the preferred regimen. The comparison  
120 between the two groups revealed that patients treated with IV ILO had a higher frequency  
121 of DUs( $p<0.001$ ), pitting scars( $p<0.001$ ), diffuse cutaneous involvement( $p<0.001$ ), interstitial  
122 lung disease( $p<0.002$ ), as well as higher rates of anti-Topoisomerase I, "late" scleroderma  
123 pattern at nailfold videocapillaroscopy. These findings were confirmed by multivariate  
124 analysis.

125 **Conclusions.** Our data provide a picture on the Italian use of IV ILO among SSc patients  
126 and showed that it was usually employed in patients with a more aggressive spectrum of  
127 the disease. The disparity of IV ILO treatment strategies in the different centers suggests the  
128 need of a rational therapeutical approach based on the clinical characteristics of different  
129 patients' subsets.

130  
131 **BACKGROUND**

132 Systemic sclerosis (SSc) is a severe autoimmune disease characterized by a prominent  
133 vasculopathy with a wide range of clinical features, such as Raynaud's phenomenon (RP)  
134 and digital ulcers (DUs).(1)

135 Intravenous (IV) iloprost (ILO), is a stable synthetic analogue of prostacyclin used for the  
136 treatment of RP and ischemic complications in SSc. In the clinical practice, ILO in infusion  
137 cycles has obtained efficient and safe results. (2-5)

138 According to the EULAR recommendation on SSc, IV ILO is employed for severe RP after  
139 failure of oral vasoactive drugs and, as first line therapy, for the treatment of DUs.(6) These  
140 endorsements are supported by metaanalyses and Randomized Clinical Trials (RCTs)  
141 demonstrating that IV ILO reduces the frequency and severity of RP attacks (4,7,8), and may  
142 prevent the occurrence and boost the healing of DUs.(9) Moreover, ILO has been registered  
143 for the treatment of severe pulmonary arterial hypertension (PAH) associated to SSc,

144 although it has a strength of recommendation “B”, since data are obtained from one RCT  
145 including patients with SSc and other connective tissue diseases.(6)  
146 A systematic review of the literature on IV ILO in SSc, enriched by a Delphi consensus  
147 exercise, confirmed its efficacy, without identifying accurately the most appropriate  
148 regimens, as for dosage, duration, and/or frequency. It should be also considered that all the  
149 existing published studies have been conducted on limited numbers of patients.(10)  
150 Indeed, there is a great variability on its use in daily clinical practice and therapeutic  
151 indications differ among countries: overall, the recommended dosage varies between 0.5  
152 to 2.0 ng/kg/min for an infusion of 6h/per day, depending on patient’s tolerance (as reported  
153 in the technical data sheet).(11) In some countries, IV ILO is available with the approved  
154 indication for RP secondary to SSc for 3-5 days and in Italy also for Buerger’s disease.(10,11)  
155 Data derived from expert opinion suggested a 1-3-day monthly regimen for RP and DUs  
156 healing, and 1 day monthly for DUs prevention. (10) Therefore, the lack of uniformity on  
157 the type of regimen, dosage, frequency, and duration, prompts in practice the use of IV ILO  
158 mainly based on personal experience and convenience.  
159 Thus, the aim of our study was to evaluate how IV ILO therapy is used and administered  
160 by rheumatologists within a large national cohort of SSc patients, included in the Italian  
161 “SPRING” (Systemic Sclerosis Progression InvestiGation) Registry, to investigate the  
162 association between clinical-demographic, instrumental, and therapeutic data, and to  
163 understand whether there were features that could drive its specific timing and dosage.  
164

## 165 **PATIENTS AND METHODS**

166 In this case-control study we retrospectively evaluated clinical-demographical, instrumental  
167 and therapeutical data from patients affected by definite SSc, classified according to the 2013  
168 European League Against Rheumatism (EULAR)/ American College of Rheumatology  
169 (ACR) criteria,(12) enrolled in the SPRING registry.  
170 SPRING project is a prospective cohort study, with a consecutive recruitment of SSc-  
171 spectrum cases, promoted by the Italian Society for Rheumatology-SIR in 2015, as a strategic  
172 no-profit project involving 37 Italian centers (the reference number of the Coordinating  
173 Centre is OSS 15.010, AOU Careggi-Firenze). All patients gave their written informed  
174 consent to participate. Study data were collected and managed using Research Electronic  
175 Data Capture (REDCap), a web-based application to support data collection. As previously  
176 described (13), the cohorts were categorized as RP (primary and suspected secondary), Very  
177 Early Diagnosis of SSc (VEDOSS)(14) and definite SSc.(12)  
178 At baseline and at yearly follow-up visit, demographic, clinical, instrumental and laboratory  
179 features of each patient, aged >18, were collected, together with the disease history, lifestyles,  
180 and comorbidities. Information included age, sex, age of disease onset, as well as the  
181 following clinical variables: skin signs (sclerodactyly, puffy fingers, calcinosis, and

182 telangiectasia), peripheral vascular signs (digital pitting scars, DUs, gangrene), presence of  
183 comorbidities (smoking habit, arterial hypertension, dyslipidaemia, diabetes).

184 Among instrumental features, non-invasive cardiac diagnostic testing was performed by  
185 electrocardiogram (ECG) and trans-thoracic echocardiography (including pulmonary  
186 arterial pressure-PAPs estimation). Investigations for lung involvement consisted of  
187 pulmonary function tests (total lung capacity-TLC, forced vital capacity-FVC), with  
188 diffusion capacity for carbon monoxide (DLCO) and high-resolution computed  
189 tomography-HRCT (to detect interstitial lung disease-ILD). Nailfold videocapillaroscopic  
190 (NVC) data were collected, using the classification proposed by Cutolo et al.(15)

191 Previous and current treatments were also reported, including both vasodilators/vasoactive  
192 drugs (calcium-channel blockers-CCB, prostanoids, endothelin receptor antagonists-ERAs,  
193 phosphodiesterase-5 inhibitors-PDE5i, angiotensin converting enzyme inhibitors-ACEi,  
194 anti-platelets).

195 For the study, only patients classified as definite SSc were evaluated, while VEDOSS and RP  
196 patients were excluded. **The sample selection process is illustrated in Figure 1.**

197 From the cohort of definite SSc, those treated with IV ILO were selected, evaluating the  
198 different timing of ILO infusions and in details the frequency and duration of infusion itself.

199 The second step was to collect and stratify patients based to the type of IV ILO regimens.

200 Additionally, clinical, demographic and instrumental features, as well as therapies, were  
201 compared between SSc patients treated with IV ILO (case group) and those without (control  
202 group). Besides, we evaluated if there was any difference among patients treated with  
203 different frequency of IV ILO infusion, and among their characteristics, such as the presence  
204 of DUs and/or pitting scars, SSc-specific autoantibodies (anti-Topoisomerase 1/Topo 1, anti-  
205 centromere/ACA, anti-RNA polymerase), organ involvement, severity of RP, NVC patterns  
206 or presence of limited (lcSSc)/diffuse (dcSSc)/sine SSc (ssSSc) subsets of the disease.(13,16)

207

## 208 STATISTICAL ANALYSIS

209 Descriptive analyses were reported as absolute and relative frequencies for categorical  
210 variables, mean and SD for continuous ones. Median (IQR) has been provided in place of  
211 mean (SD) when significant asymmetry of distributions was present.

212 The chi-square test was used to compare categorical variables, while quantitative variables  
213 were compared using the Student's t test or Mann-Whitney U test depending on their  
214 distribution, as appropriate.

215 Multivariable logistic regression analysis was also performed to examine the strength of the  
216 association between demographic and clinical variables and the use of IV ILO. The  
217 regression model was adjusted for the covariates with a  $p < 0.05$  in univariate models. Odds  
218 ratio (OR) values were reported with their 95% confidence intervals (95%CI).

219 The level of significance was set at  $< 0.05$ . Data were analyzed using Stata v.14.

220

## 221 RESULTS

222 The analysis of SPRING database showed that 1895 out of 2378 patients were classified as  
223 definite SSc. Of them 937/1895 (49,45%) were treated (cases) and 958/1895 (50,55%) were not  
224 treated (control group) with IV ILO.

225 The case group was analyzed from a geographical perspective by sorting the overall number  
226 of SSc patients enrolled in the entire database, based on their Italian macro-area of origin,  
227 which included 911 patients from the North, 339 patients from the Center, and 565 from the  
228 South. The IV ILO treatment was found to be more frequently used in Central Italy (189/339-  
229 55.7%) compared to the Northern (397/911-43,6%) and Southern macro-areas (269/565-47.6%)  
230 (p-value=0.006). A subgroup analysis was conducted to assess differences among patients  
231 undergoing IV ILO therapy across the Northern, Central and Southern Italy. It revealed that  
232 patients receiving IV ILO in Central Italy exhibited a higher prevalence of pitting scars  
233 (141/189-74.6% vs Northern: 244/397-61.5% and Southern: 155/269-57.6%; p-value=0.0001),  
234 of dcSSc subset of disease (70/189-37%vs Northern: 95/397-23.9% and Southern: 67/269-  
235 27.9%; p-value=0.002) and of a *scleroderma late pattern* at NVC (76/189-40.2% vs Northern:  
236 103/397-25.9% and Southern: 71/269-26.4%; p-value=0.0008) than patients from Northern  
237 Central and Southern regions. No statistically significant differences were observed in other  
238 clinical manifestations, except for ILD at HRCT, that was more frequently encountered  
239 among patients in Northern Italy (117/397-29.5% vs Central: 36/189-19% and Southern  
240 67/269-27.9%; p-value=0.0008).

241 The main clinical and demographic data of all patients at baseline, including laboratory, and  
242 instrumental findings, are shown in Table 1.

243 The comparison between the two groups revealed that the median age of the controls was  
244 significantly higher than that of the cases (61±14 vs 57±14 years ±SD; p-value=0.0001).

245 However, the two groups were well-matched in terms of gender and disease duration.

246 Almost all patients (99%) in both groups had RP. Regarding other clinical signs of peripheral  
247 vasculopathy, patients treated with IV ILO showed a higher frequency of DUs (cases vs  
248 controls: 275/934-29.4% vs 132/939-14.0%; p<0.001) and pitting scars (cases vs controls:  
249 584/933-62.5% vs 296/934- 31.7%; p<0.001). Baseline NVC showed a normal or non-specific  
250 pattern in 31/921 (3.4%) cases and 59/910 (6.5%) controls, while a NVC *scleroderma pattern*  
251 was significantly more frequent among cases (824/921- 89.4%) than controls (775/910- 85.1%;  
252 p<0.0001). In addition, cases more frequently presented a "late" *scleroderma pattern* than  
253 controls (cases vs controls: 272/921- 29.5% vs 162/910- 17.8% p<0.0001).

254 In all the Italian SPRING centers, IV ILO was administered between 0.5-2.0 ng/Kg/min for  
255 six hours, according to manufacturer indication and patient tolerability.

256 A detailed description of the differently available regimens of IV ILO treatment in SSc  
257 patients, including frequency (<, > or = 4 weeks) and number of days of infusion (from 1 to



258 6 days) for each cycle, is shown in Table 2. Most of the patients (602/861- 69.9 %) were on IV  
259 ILO every 4 weeks, 49/861 (5.7 %) with an interval less than four weeks, and 210/861 (24.4%)  
260 with an interval of more than four weeks. Most patients (311/602-51.6 %) on treatment every  
261 four weeks, underwent IV ILO infusion for only one day. The single-day cycle was also  
262 preferred for patients receiving IV ILO for less than 4 weeks (35/49, 71.4%). When IV ILO  
263 was scheduled with an interval of more than four weeks, most of the patients received a  
264 total number of 5 consecutive days of infusions (125/210, 59.5%).

265 Patients who received an IV ILO infusion with an interval of less than every 4 weeks had  
266 significantly more DUs (27/49-55.1% of cases) than patients treated every 4 weeks (178/602-  
267 29.5 %) or with an interval of more than 4 weeks (63/210-30%) ( $p=0.002$ ). Similarly, patients  
268 on IV ILO infusion more often over 4 weeks reported more severe RP than subjects treated  
269 with other infusion schedules (IV ILO<4 weeks  $N=22/49$ -44.8%, IV ILO every 4 weeks  
270  $N=136/602$ -22.5%, IV ILO>4 weeks  $N=42/210$ -20%;  $p<0.002$ ).

271 No difference was found for other clinical features, NVC patterns or other concomitant  
272 vascular therapies based on the different IV ILO regimens.

273 It should be noted that 129 controls were previously treated with IV ILO. The reasons for  
274 withdrawal included: toxicity (36%), recovery of symptoms (21%), presence of  
275 comorbidities (8%), and inefficacy (7%).

276 Besides, patients receiving IV ILO therapy showed a more aggressive disease (Table 1): a  
277 significantly higher proportion of cases were dcSSc (25.5% vs 13.1%,  $p<0.0001$ ), showed ILD  
278 on HRCT (38.2% vs 31.5%  $p=0.002$ ), DUs and pitting scars (62.5% vs 31.7%  $p<0.0001$ , for  
279 both. This observation is also consistent with the serological findings (Table 1), as patients  
280 on IV ILO therapy were more frequently anti-Topo (40.3% vs 28.9%  $p$ -value  $<0.0001$ ), while  
281 controls were more frequently ACA positive (24.4% vs 36.7%,  $p$ -value  $<0.0001$ ). In contrast,  
282 controls showed a higher percentage of patients with ssSSc (18.7% vs 5.9%  $p<0.0001$ ).

283 A detailed description of previous or ongoing treatments in 937 patients on IV ILO therapy,  
284 and in 958 controls is reported in Table 3; as expected ERA (290/937-30.9% vs 110/958-11.5%;  
285  $p$ -value  $<0.0001$ ) and anti-platelet agents (446/937-47.6% vs 385/958-40.2%;  $p$ -value 0.001)  
286 were prescribed more frequently in cases while there was no significant difference in the  
287 use of CCBs-and PDE5-inhibitors between the two groups.

288 The multivariate analysis revealed that patients' age ( $p<0.0001$ ), presence of pitting scars ( $p$   
289  $<0.0001$ ), and therapy with ERAs ( $p<0.0001$ ) and/or antiplatelet agents ( $p=0.049$ ) were  
290 significantly associated with the IV ILO use (Table 4).

291 An overall overview of the IV ILO regimens as detected from our study is given in Table 5.

292

## 293 **DISCUSSION**

294 Our data show that, in Italian centers, IV ILO is employed in patients with a more aggressive  
295 spectrum of the disease, **namely those patients with clinical features defined by previous**

296 studies (17) as risk factors for disease worsening (i.e. DUs, interstitial lung disease, diffuse  
297 cutaneous involvement). Thus, it is partly in agreement with the recent EULAR  
298 recommendations. (6) Usually, IV ILO is employed for 3-5 days of infusion, but our study  
299 found that different treatment regimens were employed in a large SSc Italian national cohort.  
300 The clinical-demographic, laboratory, and instrumental features, as well as other vascular  
301 therapies were investigated to identify whether there was a preferential regimen, given the  
302 absence of well-defined guidelines on the use of IV ILO in SSc.

303 Almost half of all the SSc cases, amounting to 1895, were on IV ILO, and up to date no study  
304 on such a large population has been reported in the literature.

305 A different geographical distribution of the IV ILO was recorded among the main Italian  
306 macro-areas, as a significant higher percentages of SSc patients treated with IV ILO were  
307 resident in Central and Southern Italy, rather than Northern Italy. This finding may result  
308 quite paradoxical because Northern regions have a colder average annual climate and  
309 therefore patients should be affected with a more severe RP and DUs.(5) Indeed, our  
310 analysis showed that patients from Central Italy more frequently have some disease features  
311 indicating typical of a more severe form of disease, especially regarding peripheral vascular  
312 microangiopathy (pitting scars, scleroderma late pattern) similarly to what was found in a  
313 previous clinical-demographical analysis of Spring Registry that have shown as patients  
314 from Southern Italy were characterized by a more aggressive disease, accounting for a  
315 greater need of IV ILO treatment(18). The different geographical distribution of SSc subsets  
316 has been previously emphasized, and may probably be related to referral bias as well to  
317 different environmental and/or genetic factors .(18)

318 According to the 2017 EULAR recommendations for the treatment of SSc, IV ILO is  
319 indicated for RP management after failure of oral vascular therapies such as CCB and PDE5i  
320 or as first choice for DU healing(6). Almost all cases (99%) complained about RP, while only  
321 one third presented DUs. However, as this study is a cross sectional analysis, it was not  
322 possible to clearly identify the reason for prescribing IV ILO, although we can hypothesize  
323 that the presence of RP was the main indication, in agreement with the results of expert  
324 consensus.(10) Moreover, the comparison of the clinical characteristics of cases and controls  
325 showed that IV ILO is prescribed to those SSc patients presenting a more severe vascular  
326 involvement, as cases were more frequently affected by DUs and pitting scars and exhibited  
327 a higher incidence of a "late" scleroderma pattern at NVC. Additionally, ERA and anti-platelet  
328 treatments were prescribed more frequently in cases than controls. In our SSc cases, it is  
329 clear that the manifestations of SSc vasculopathy seem to drive the prescription of IV ILO,  
330 in line with EULAR recommendations.(6)

331 In addition, cases treated with IV ILO were more frequently dcSSc, anti-Topo I positive and  
332 affected by ILD in respect to controls. This observation highlights that in the real life the  
333 prescription of IV ILO is also guided by the whole SSc severity. A similar finding was

334 observed in previous studies .(19,20) In our IV ILO treated patients the higher ILD  
335 prevalence is not surprising, as DUs and anti-Topo I are present in more severe patients,  
336 including those with ILD (21,22) . It is interesting to note that, despite the lack of RCTs, ILO  
337 seemed able to improve skin thickness and pulmonary arterial systolic pressure in  
338 observational studies (23,24,25), again suggesting its use in the more aggressive subsets of  
339 the disease.

340 The very recent 2023 update of EULAR recommendations for the treatment of SSc still do  
341 not specify the dose or the therapeutic regimen for IV ILO.(26) Currently, no trials are  
342 available providing guidance on the regimen. In some countries, IV ILO is available and  
343 approved for RP secondary to SSc, for 3-5 consecutive days cycle, with no indication on the  
344 infusion frequency. Thus, according to patients characteristics(10) and the organization of  
345 the hospital center, the physician may consequently choose the best regimen, which  
346 includes dosage, duration and frequency.(10) In the future, portable infusion pumps might  
347 be applied to selected subjects with a remote monitoring system, managed by expert  
348 physician or nurse, thus sparing costs for the patients and the centers.(27)

349 As regards concomitant vascular therapies, a combination strategy with IV ILO is  
350 considered the best therapeutic option for RP refractory to oral therapies as well as for  
351 DUs.(28) Antiplatelet drugs, used by nearly 50% of our cases, are possibly prescribed with  
352 IV ILO in preventing DUs, as recommended in the PROSIT study (28). The combination of  
353 ILO+ERAs is believed to be aimed to increase the rate of healing for DUs(18), and prevent  
354 the development of new DU(29). In fact, in a long-term follow-up, ILO+ERAs has proven to  
355 increase fingertip blood perfusion and the absolute nailfold capillary number/mm, reducing  
356 of 80% the incidence of new DU (30).

357 One of the greatest concerns for the use of IV ILO is represented by the choice of its  
358 administration regimen.(10) Neither in the EULAR recommendations nor in the  
359 manufacturer datasheet a specific dosage, duration or frequency of infusion are indicated,  
360 the latter only suggesting that the drug should be administered at a dose of 0.5-2  
361 ng/kilogram of body weight (kg)/min. This was also the most frequent dosage employed in  
362 our cohort. In a prospective RCT on 46 SSc subjects, an 8-hour IV ILO infusion was used as  
363 a daily dose of 2 ng/kg/min for 5 days.(8) Another placebo controlled double-blind study on  
364 131 SSc patients, showed IV ILO efficacy in reducing severity, frequency, and duration of  
365 RP at a dosage of 2 ng/kg/min over 6 hours a day for 5 consecutive days.(4) In 28 SSc patients,  
366 Auriemma et al. showed an amelioration of RP severity and number of RP attacks reduction  
367 using a median lower dosage (0.5-2 ng/kilogram of body weight (kg)/min) for 1-3 days every  
368 30 days.(31) However, similar results were detected also with different approaches  
369 including higher or lower dosages of ILO (32).

370 In most of our patients, the treatment regimen was one-day IV ILO every 4 weeks. This  
371 result is in agreement with the report suggesting that IV ILO could be administered 1-3 days  
372 monthly to treat RP and DUs healing and one day per month for DU prevention.(10)

373 Thus, in our study the reason for driving the choice of a more frequent infusion may mainly  
374 be due to a more severe vascular disease characterized by RP, DUs and pitting scars of the  
375 extremities.

376 Attention was also focused on the number of infusions per cycle ranging from a single-day  
377 dose or cycles of 2 to 5 consecutive days. A single-day infusion was used for treatment  
378 regimens every 4 weeks or less, while when IV ILO was scheduled for infusions with an  
379 interval of more than 4 weeks, 5 consecutive days of infusions were the most frequently  
380 used regimen.

381 The strength of the current study is represented by the extensive data obtained from a  
382 nationwide registry, which provides insights into the real-life IV ILO regimens of tertiary-  
383 rheumatology referral centers. At the same time, this type of data collection may have some  
384 limitations, including the heterogeneity of the involved centers from different areas of the  
385 country with potential geographical referral bias (18).

386 In conclusion, the observed data indicate that the choice of the IV ILO dosage and duration  
387 of a single infusion are generally made according to the main recommendations suggested  
388 in the datasheet. In particular, the following regimens have been most frequently detected  
389 in the Italian centers:

- 390 • dosage range = 0.5-2 ng/kg/min (tapered according to patient's needs);
- 391 • infusion duration = six consecutive hours for each cycle (as reported in the  
392 manufacturer datasheet);
- 393 • infusion frequency = more often than 4 weeks in the presence of severe vascular  
394 features; every 4 weeks or more in stable RP;
- 395 • cycle frequency = single-day infusion, if repeated within 4 weeks; from 2 to 5  
396 consecutive days, for intervals longer than 4 weeks.

397 Overall, the frequency and dosage of IV ILO administration depends on the severity of both  
398 peripheral vascular involvement (i.e., RP and DUs) and SSc variants. For a shared  
399 therapeutical approach, appropriate RCTs should be planned, allowing to elaborate the  
400 most effective and well-tailored IV ILO treatment modalities for different SSc patients'  
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407

408 *Convenors*  
409 Clodoveo Ferri, University of Modena & Reggio Emilia, Italy; clodoveo.ferri@unimore.it  
410 Marco Matucci-Cerinic, University of Florence, Italy; marco.matuccicerinic@unifi.it  
411  
412 *Investigators (in alphabetical order)*  
413 Abignano Giuseppina, AOR San Carlo di Potenza; g.abignano@hotmail.com  
414 Agnes Cecilia, Ospedale San Lorenzo, Carmagnola (TO), ASL-TO5  
415 Amato Giorgio, AOU Policlinico – Vittorio Emanuele, Catania; giorgioamato@hotmail.it  
416 Ariani Alarico, AOU Parma; dott.alaricoariani@libero.it  
417 Bagnato Gianluca, Università degli Studi di Messina; gianbagnato@gmail.com  
418 Bajocchi Gianluigi, Arcispedale S. Maria Nuova, Reggio Emilia; gianluigi.bajocchi@asmn.re.it  
419 Barsotti Simone, AOU Santa Chiara, Pisa; simone.barsotti@outlook.com  
420 Bellando-Randone Silvia, University of Florence; s.bellandorandone@gmail.com  
421 Benenati Alessia, AOU ‘Policlinico - Vittorio Emanuele, Catania; alessia.benenati@libero.it  
422 Beretta Lorenza, Fondazione IRCCS Ca’ Granda Ospedale Maggiore Policlinico, Milano; lorberimm@hotmail.com  
423 Bianchi Gerolamo, ASL3 Genova; gerolamo.bianchi@asl3.liguria.it  
424 Bosello Silvia, Policlinico “A. Gemelli” –IRCCS – UOC di Reumatologia; Roma; silvia.bosello@libero.it  
425 Cacciapaglia Fabio, UO Reumatologia – DETO, Università di Bari; fabio.cacciapaglia79@gmail.com  
426 Calabrese Francesca, SSD Reumatologia, Reggio Calabria; francescacalabrese81@virgilio.it;  
427 Caminiti Maurizio, Ospedale Bianchi-Melacrino-Morelli, SSD Reumatologia, Reggio Calabria; mauriziocaminiti@tin.it  
428 Campochiaro Corrado, Ospedale S. Raffaele, Milano; corradocampochiaro@gmail.com  
429 Carignola Renato, AOU San Luigi Gonzaga, Orbassano (TO); renatocarigno@gmail.com  
430 Cavazzana Ilaria, Spedali Civili di Brescia; ilariacava@virgilio.it  
431 Ciano Giovanni, Ospedale Ariano Irpino, ASL Avellino; giovanni.ciano55@gmail.com;  
432 Cipolletta Edoardo, Clinica Reumatologica, Università Politecnica delle Marche, Ancona; edo.cipo@hotmail.it  
433 Codullo Veronica, Policlinico San Matteo, Pavia; veronicacodullo@yahoo.it  
434 Cozzi Franco, Villa Salus, Mestre; franco.cozzi@unipd.it  
435 Cuomo Giovanna, Università degli Studi della Campania - Luigi Vanvitelli, Napoli; giovanna.cuomo@unicampania.it  
436 D’Angelo Salvatore, AOR San Carlo di Potenza; saldangelo@katamail.com  
437 Dagna Lorenzo, Ospedale S. Raffaele, Milano; dagna.lorenzo@hsr.it  
438 Dall’Ara Francesca, UO Medicina Interna-Ambulatorio Reumatologia, Ospedale di Lodi; francesca.dallara@gmail.com  
439 De Andres Ilenia, AO ARNAS Garibaldi, Catania; ilenia.deandres@gmail.com  
440 De Angelis Rossella, Clinica Reumatologica, Università Politecnica delle Marche, Ancona; r.deangelis@staff.univpm.it  
441 De Cata Angelo, Ospedale Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG); a.decata@operapadrepio.it  
442 De Luca Giacomo, Ospedale S. Raffaele, Milano; deluca.giacomo@hsr.it  
443 De Santis Maria, Istituto Clinico Humanitas, Rozzano, Milano; maria.desantis@humanitas.it  
444 Della Rossa Alessandra, AOU Santa Chiara, Pisa; [a.dellarossa69@gmail.com](mailto:a.dellarossa69@gmail.com)  
445 Di Vico Claudio, Università degli Studi della Campania “Luigi Vanvitelli”; claudio.divico@unicampania.it  
446 Doria Andrea, Università degli Studi di Padova; adoria@unipd.it  
447 Doveri Marica, ASL3 Genova; marica.doveri@asl3.liguria.it  
448 Foti Rosario, AOU Policlinico San Marco, Catania; rosfoti5@gmail.com  
449 Furini Federica, Department of Medical Sciences, University of Ferrara; fefe.furini@gmail.com  
450 Fusaro Enrico, AOU Città della Salute e della Scienza di Torino; fusaro.reumatorino@gmail.com  
451 Generali Elena, Istituto Clinico Humanitas, Rozzano, Milano; e.generali@gmail.com  
452 Gigante Antonietta, Università degli Studi “La Sapienza”, Roma; antonietta.gigante@uniroma1.it  
453 Giollo Alessandro, AOUI Verona; alessandro.giollo@univr.it  
454 Girelli Francesco, Ospedale GB Morgagni, Forlì; francesco.girelli@auslromagna.it  
455 Giuggioli Dilia, University of Modena/Reggio Emilia; dilia.giuggioli@unimore.it  
456 Govoni Marcello, AOU S. Anna, Ferrara; gvl@unife.it  
457 Guiducci Serena, University of Florence; s.guiducci@hotmail.com  
458 Iannone Florenzo, UO Reumatologia– DETO, Università di Bari; florenzo.iannone@uniba.it  
459 Ingegnoli Francesca, Università degli Studi di Milano; francesca.ingegnoli@unimi.it  
460 Iuliano Anna Maria, AO San Camillo Forlanini, Roma; annamariaiuliano@hotmail.it  
461 Lazzaroni Maria Grazia, Spedali Civili and University of Brescia; mariagrazialazzaroni@gmail.com  
462 Lepri Gemma, University of Florence; lepri.gemma@gmail.com  
463 Lubrano Ennio, Università del Molise, Campobasso; ennio.lubrano@unimol.it  
464 Lumetti Federica, University of Modena & Reggio Emilia; fedelumetti@gmail.com  
465 Magnani Luca, Arcispedale S. Maria Nuova, Reggio Emilia; luca.magnani@ausl.re.it  
466 Mennillo Gianna, AOR San Carlo di Potenza; giannaangelamennillo@virgilio.it  
467 Murdaca Giuseppe, Department of Internal Medicine, University of Genoa, IRCCS Ospedale Policlinico San Martino,  
468 Genoa, Italy; giuseppe.murdaca@unige.it  
469 Pagano Mariano Giuseppa, Ospedale Bianchi-Melacrino-Morelli, Reggio Calabria; giusypaganomariano@libero.it

470 Parisi Simone, AOU Città della Salute e della Scienza, Torino; simone.parisi@hotmail.it  
471 Pellegrino Greta, Sapienza, Università di Roma; greta.pellegrino01@gmail.com  
472 Peroni Clara Lisa, AOU Città della Salute e della Scienza, Torino; claralisaperoni@gmail.com  
473 Pigatto Erika, UOC Medicina Interna, Ospedale San Bassiano, Bassano del Grappa, Vicenza; erika.pigatto@gmail.com  
474 Ricciari Valeria, Sapienza Università di Roma; valeria.ricciari@uniroma1.it  
475 Romeo Nicoletta Rheumatology Unit ASO Santa Croce e Carle, Cuneo; romeo.n@ospedale.cuneo.it  
476 Rosato Edoardo, Università degli Studi di Roma "La Sapienza" Policlinico Umberto I; edoardo.rosato@uniroma1.it  
477 Sambataro Gianluca, Azienda Ospedaliera Cannizzaro, Catania  
478 Saracco Marta, Ospedale Mauriziano, Torino; marta.saracco@gmail.com  
479 Sebastiani Giandomenico, AO San Camillo Forlanini, Roma; gsebastiani@scamilloforlanini.rm.it  
480 Spinella Amelia, University of Modena & Reggio Emilia; amelia.spinella@gmail.com  
481 Talotta Rossella, L. Sacco Hospital, Milan; talotta1@virgilio.it  
482 Visalli Elisa, AOU Policlinico San Marco, Catania; elivisa21@gmail.com  
483 Vultaggio Licia, AOU S. Anna, Ferrara, licia.vultaggio@unife.it  
484 Zanatta Elisabetta, Università degli Studi di Padova; elisabetta.zanatta@yahoo.it  
485 Zanframundo Giovanni, Policlinico San Matteo, Pavia; gio.zanframundo@gmail.com

486  
487

#### 488 **Study Center of the Italian Society of Rheumatology (SIR)**

489 Carlo Scirè, Università degli Studi, Milano-Bicocca, Milan; c.scire@reumatologia.it  
490 Greta Carrara, Epidemiology Unit, Italian Society for Rheumatology, Milan, Italy; g.carrara@reumatologia.it  
491 Gianpiero Landolfi, Epidemiology Unit, Italian Society for Rheumatology, Milan, Italy; g.landolfi@reumatologia.it  
492 Davide Rozza, Epidemiology Unit, Italian Society for Rheumatology, Milan, Italy; d.rozza@reumatologia.it  
493 Anna Zanetti, Epidemiology Unit, Italian Society for Rheumatology, Milan, Italy; a.zanetti@reumatologia.it

494  
495

#### 496 **Contributors**

497 VR and GP conceived the idea for the study, contributed to the study design, supervised data analysis, interpreted the  
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#### 517 **ORCID iDs**

518 Valeria Ricciari <http://orcid.org/0000-0002-7507-5483>

519 Greta Pellegrino <http://orcid.org/0000-0002-1762-0770>

520 Giovanni Zanframundo <http://orcid.org/0000-0001-5042-1282>

521 Fabio Cacciapaglia <http://orcid.org/0000-0001-7479-4462>

522 Alarico Ariani <http://orcid.org/0000-0003-1428-6102>

523 Edoardo Rosato <http://orcid.org/0000-0002-7417-8093>

524 Gemma Lepri <http://orcid.org/0000-0003-4141-6937>

525 Maria De Santis <http://orcid.org/0000-0002-3196-1336>

526 Lorenzo Beretta <http://orcid.org/0000-0002-6529-6258>  
527 Ennio Lubrano <http://orcid.org/0000-0003-1471-6467>  
528 Giacomo De Luca <http://orcid.org/0000-0002-5306-7714>  
529 Veronica Codullo <http://orcid.org/0000-0003-2557-8514>  
530 Simone Parisi <http://orcid.org/0000-0003-4496-8315>  
531 Anna Zanetti <http://orcid.org/0000-0001-8408-451X>  
532 Salvatore D'Angelo <http://orcid.org/0000-0002-7442-1110>  
533 Franco Cozzi <http://orcid.org/0000-0003-3627-3927>  
534 Fabrizio Conti <http://orcid.org/0000-0002-1897-049X>  
535 Andrea Doria <http://orcid.org/0000-0003-0548-4983>  
536 Marco Matucci-Cerinic <http://orcid.org/0000-0002-9324-3161>  
537 Rossella De Angelis <http://orcid.org/0000-0001-5169-3511>

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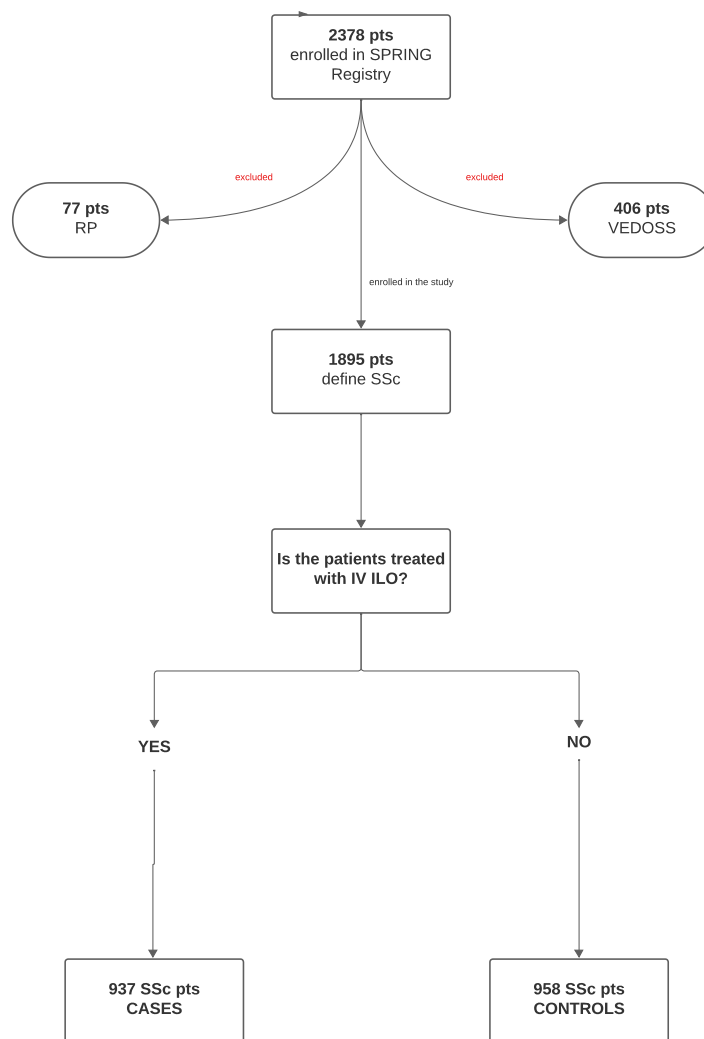
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611 patients from the national registry 'SPRING' of the Italian Society for Rheumatology.  
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641 **Figure 1. The selection process of the sample: from the SPRING Registry to the definition of**  
642 **case and control cohorts.**



643 Legend: pts: patients; RP: primary Raynaud's phenomenon; VEDOSS: Very Early Systemic Sclerosis; SSc: Systemic  
644 Sclerosis; IV ILO: intravenous iloprost.  
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**Table 1. Comparison of clinical, demographic, and instrumental characteristics between SSc patients treated (cases) and not treated (controls) with IV ILO**

Legend: SSc: Systemic Sclerosis; IV ILO: intravenous iloprost; lcSSc: limited cutaneous Systemic Sclerosis; dcSSc: diffuse cutaneous Systemic Sclerosis; ssSSC: sine scleroderma Systemic Sclerosis; ILD: interstitial lung disease; HRTC: High Resolution Computed Tomography; DLCO:diffusing capacity for carbon monoxide; FVC: forced vital capacity; PAH: pulmonary arterial hypertension;  
ANA: Antinuclear antibodies; ACA: anticentromere antibodies; ILD: interstitial lung disease; HRTC: High Resolution Computed Tomography  
SD: standard deviation  
ns: not significant  
[§] =missing data  
\*\*confirmed by right heart catheterization

**Table 2. Different regimens of IV ILO treatment in the cases group: frequency (<, > or = 4 weeks) and number of infusions (from 1 to 6 days) for each cycle**

		Frequency of IV ILO cycles			
		<4 weeks	=4 weeks	>4 weeks	Total N (%)
Length of each IV ILO cycle (days)	1	35 (71.4)	311 (51.6)	26 (12.4)	372 (43.2)
	2	1 (2.0)	104 (17.3)	8 (3.8)	113 (13.1)
	3	8 (16.4)	69 (11.5)	9 (4.3)	86 (10.0)
	4	5 (10.2)	27 (4.5)	38 (18.1)	70 (8.2)
	5	0 (0)	87 (14.4)	125 (59.5)	212 (24.6)
	6	0 (0)	4 (0.7)	4 (1.9)	8 (0.9)
	<b>Total N (%)</b>	49 (5.7)	602 (69.9)	210 (24.4)	861 (100)*

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Legend: IV ILO: intravenous iloprost  
\*Total number of patients with available data

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**Table 3. Concomitant vascular therapies carried out by cases and controls.**

	<b>Ssc pts under IV ILO N= 937</b>	<b>Ssc pts not under IV ILO N= 958</b>	<b>p-value</b>
Mean age $\pm$ SD	57 $\pm$ 14	61 $\pm$ 14	0.0001
Mean disease duration (years) $\pm$ SD	14.1 $\pm$ 10.1	13.4 $\pm$ 10.9	ns
Sex (female) <i>n</i> (%)	822 (87.7%)	859 (89.6%)	ns
lcSSc-dcSSc- ssSSc <i>n</i> (%) [§]	624 (68%) - 239 (25.5%)- 55 (5.9%) [19]	631 (68%) -126 (13.1%)- 174(18.7%) [27]	<0.0001
Raynaud's phenomenon <i>n</i> (%)	931 (99.3%)	948 (98.9%)	ns
Pitting scars <i>n</i> (%) [§]	584 (62.5%) [4]	296 (31.7%) [24]	<0.0001
Digital ulcers <i>n</i> (%) [§]	275 (29.4%) [3]	132 (14.0 %) [19]	<0.0001
Gangrene <i>n</i> (%) [§]	13 (1.4%) [5]	5 (0.5%) [23]	ns
Teleangiectasias <i>n</i> (%) [§]	598 (64.1%) [5]	537 (57.1%) [19]	0.002
Oesophageal involvement <i>n</i> (%) [§]	435 (46.41%) [139]	437 (45.61%) [164]	ns
Renal crisis <i>n</i> (%) [§]	13 (1.4%) [25]	9 (0.9%) [48]	ns
Cardio-pulmonary involvement			
Symptoms <i>n</i> (%) [§]	359 (38.3%) [93]	357 (37.2%) [115]	ns
ILD at HRCT <i>n</i> (%)	358 (38.2%)	302 (31.5%)	ns
Mean DLCO (%) $\pm$ SD	66.45 $\pm$ 18.4 [262]	70.9 $\pm$ 20.3 [299]	<0.0001
Mean FVC (%) $\pm$ SD	99.8 $\pm$ 22 [228]	102.6 $\pm$ 22 [264]	0.001
PAH** <i>n</i> (%)	12 (1.3%)	19 (2.0%)	ns
<b>Traditional risk factors</b>			
Smokers <i>n</i> -(%)	96 (10.2%)	106 (11.0%)	ns ns ns
Arterial hypertension <i>n</i> (%)	204 (21.8%)	248 (25.9%)	ns
Dyslipidemia <i>n</i> (%)	95 (10.1%)	114 (11.9%)	ns
Diabetes <i>n</i> (%)	22 (2.3%)	34 (3.5%)	ns ns
<b>Serological</b> [§]	[4]	[38]	
ANA positive <i>n</i> (%)	916 (98.2%)	890 (96.7%)	0.049
Anti-Topoisomerase1 antibody positive <i>n</i> (%)	376 (40.3%)	266 (28.9%)	<0.0001
ACA positive <i>n</i> (%)	228 (24.4%)	338 (36.7%)	<0.0001
Anti-RNA polymerase 3 antibody positive <i>n</i> (%)	13 (1.4%)	15 (1.6%)	ns
<b>NVC patterns</b> [§]	[16]	[48]	
Normal/non specific <i>n</i> (%)	31 (3.4%)	59 (6.5%)	<0.0001

Scleroderma pattern <i>n</i> (%)	824 (89.4%)	775 (85.1%)	<0.0001
Early <i>n</i> (%)	142 (15.4%)	223 (24.5%)	
Active <i>n</i> (%)	410 (44.5%)	390 (42.8%)	<0.0001
Late <i>n</i> (%)	272 (29.5%)	162 (17.8%)	

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Treatment	SSc pts under IV ILO N= 937	SSc pts not under IV ILO N= 958	p-value
Calcium-channel blockers			
- ongoing <i>n</i> (%)	498 (53.1%)	478 (49.9%)	Ns
- past or never done therapy <i>n</i> (%)	439 (47.0%)	480 (50.1%)	
PDE5 inhibitors			
- ongoing <i>n</i> (%)	34 (3.6%)	36 (3.8%)	ns
- past or never done therapy <i>n</i> (%)	903 (96.5%)	922 (96.2%)	
Endothelin receptor antagonists			
- ongoing <i>n</i> (%)	289 (30.9%)	108 (11.3%)	<0.0001
- past or never done therapy <i>n</i> (%)	648 (69.2%)	850 (88.7%)	
Anti-platelet agents			
- ongoing <i>n</i> (%)	446 (47.6%)	381 (39.7%)	0.001
- past or never done therapy <i>n</i> (%)	491 (52.5%)	577 (60.2%)	

Legend: SSc: Systemic Sclerosis; IV ILO: intravenous iloprost; ns: not significant; PDE5: phosphodiesterase type 5.

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**Table 4. Univariate and multivariate analysis for variables associated with IV ILO treatment.**

	<b>Univariate analysis OR (95%CI)</b>	<b>p-value</b>	<b>Multivariate analysis OR (95%CI)</b>	<b>p-value</b>
Age	0.98 (0.97-0.99)	<0.0001	0.98 (0.97-0.99)	<0.0001
dcSSc	1.92 (1.50-2.44)	<0.0001	1.14 (0.85-1.53)	0.377
Digital ulcers	2.55 (2.02-3.21)	<0.0001	1.16 (0.87-1.55)	0.320
Pitting scars	3.60 (2.98-4.37)	<0.0001	2.70 (2.12-3.44)	<0.0001
Teleangiectasias	1.33 (1.11-1.61)	0.002	0.98 (0.78- 1.22)	0.837
Anti-Topo1 positive	2.08 (1.65-2.62)	<0.0001	1.25 (0.93-1.69)	0.133
Scleroderma pattern at NVC	2.02 (1.30-3.16)	0.002	1.50 (0.91-2.47)	0.109
ILD at HRCT	1.35 (1.12-1.64)	0.002	1.02 (0.81-1.29)	0.878
Ongoing therapy with ERAs	3.47 (2.73-4.43)	<0.0001	1.82 (1.37-2.42)	<0.0001
Ongoing therapy with anti-platelet agents	1.37 (1.14-1.64)	0.001	1.24 (1.00-1.53)	0.049

Legend: OR: Odd Ratio; CI: confidential interval; dcSSc: diffuse cutaneous systemic sclerosis; NVC: nailfold videocapillaroscopy; ILD: interstitial lung disease; HRCT: High Resolution Computed Tomography. ERAs: endothelin receptor antagonists

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**Table 5. Most frequent IV ILO regimens as detected from our study.**

<b>Regimen Information</b>	<b>Value</b>
Dosage range	0.5-2 ng/kg/min (tapered according to patient's need)
Infusion Duration	Six consecutive hours for each cycle (as reported in the manufacturer data sheet)
Infusion Frequency	More frequently than 4 weeks in the presence of severe vascular features; every 4 weeks or more in stable RP
N° sessions/Cycle	Single-day infusion, if IV ILO was repeated every 4 weeks or more often; between 2 and 5 consecutive days/each cycle for cycles interval longer than 4 weeks

Legend:IV ILO: intravenous iloprost; RP: Raynaud's phenomenon

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