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Sudden winter iloprost withdrawal in scleroderma patients during COVID-19 pandemic

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ABSTRACT

Introduction: Intravenous iloprost is currently recommended in the treatment of Raynaud's phenomenon (RP) refractory to oral therapy and of digital ulcers (DUs) related to systemic sclerosis (SSc). In real-life practice there is a huge heterogeneity about the Iloprost regimens used.

Methods: A survey was carried out on SSc patients that interrupted Iloprost infusion to compare acral vascular symptoms just before Iloprost withdrawal and just after the missed infusion. Severity, and frequency of RP, new DUs onset or aggravation of those pre-existing were reported. Last available capillaroscopic images were also evaluated.

Results: The analysis includes 50 patients. After iloprost withdrawal, 11 patients reported a RP worsening because of enhanced intensity ($p = 0.007$). Only 8 patients of them also complained of an increased frequency ($p = 0.07$). None of the patients experienced digital ulcers for the first-time during quarantine. Among the 27 patients with a history of digital ulcers, 9 reported worsening and 7 recurrence of DUs. Overall, 17 patients (34.0 %) complained of a worsening of SSc vascular acral manifestations, namely RP or DUs. Reduced capillary density was associated with RP worsening, in particular, each unit increase of capillary density corresponds to an average 44 % decrease in the odds of RP worsening (OR 0.56, CI 95 % 0.36–0.97, $p = 0.037$). As for RP worsening, the aggravation of DU was associated with a lower capillary density.

Conclusions: Low capillary density can predict a worsening of both RP and DUs in controlled quarantine conditions within a month after iloprost discontinuation in SSc patients.

1. Introduction

Intravenous iloprost is currently recommended in the treatment of Raynaud's phenomenon (RP) refractory to oral therapy and of digital ulcers (DU) related to systemic sclerosis (SSc) [1]. Despite its large use, in real-life practice there is a marked heterogeneity in the protocols used and the interval between administrations is chosen based on symptoms severity, tolerated dose, logistics needs, environmental barriers and experience of the single centre. Furthermore, there are no recommendations about the duration of SSc treatment throughout life and the treatment is typically continued until the development of contraindications or the deterioration in the general health conditions [2].

In the winter of 2020, Italy was the second country in the world for the number of reported Coronavirus disease 2019 (COVID-19) cases.

This unexpected emergency led to a sudden and synchronous withdrawal of programmed iloprost infusions for most SSc patients because of patients' concerns and the directive to postpone any non-urgent medical procedure. Moreover, the national lockdown measures house-bound most of our patients that were exceptionally protected from cold exposures. Both these unavoidable circumstances were close to experimental conditions and clearly non-replicable in routine conditions.

Given those premises, while we tele-monitored and reassured our patients, during the first Italian lockdown, we also investigated the course of vascular symptoms in this scenario in a standardized way through a constructing survey questionnaire. The aim of the survey was to evaluate the consequences related to a sudden and simultaneous iloprost discontinuation in a cohort of SSc patients.

Abbreviations: COVID-19, Coronavirus disease 2019; DU, digital ulcers; DUCAS, digital ulcer clinical assessment score; NRS, numeric rating scale; OR, odds ratio; Q-Q, quartile-quartile; RP, Raynaud's phenomenon; SSc, systemic sclerosis.

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2. Methods

A telephone survey was carried out at the time of rescheduling the periodic Iloprost infusion in April 2020 after national and hospital safety protocols had been properly defined. All the patients had been treated before pandemic at the standard dose of 1–2 ng/kg/min for a single day a month because of RP or DU not responsive or intolerant to oral vasoactive treatment. Patients were specifically asked to compare their condition in the week just after the last iloprost treatment in February and that just after the missed infusion in March. Severity and frequency of RP were reported on a verbal numeric rating scale (NRS) from 0 to 10. Patient reported new-onset or aggravation of DU in terms of number or dimensions were also recorded. Patients were also asked to compare the personal exposure to cold during daily activities in the two periods. Medical records were used to collect demographic and disease characteristics and the images of the last available annual capillaroscopic examination (VideoCap 3.0 capillaroscope, DS Medica, Milan, Italy), acquired according to a standardized protocol, were also evaluated to assess the capillary density, presence of giant capillaries, haemorrhages, avascular areas and signs of neovascularization and the overall capillaroscopy pattern, namely early, active or late scleroderma pattern [3]. A specialized VideoCap 3.0 tissue-contact type biomicroscope providing colour images at 200× magnification (DS Medica, Milan, Italy) with a dedicated software for image analysis (version 10.0) was used. Qualitative and semiquantitative data were extrapolated from four consecutive fields in the middle of the nailfold from the second to the fifth finger bilaterally. We reported the presence of giant capillaries, haemorrhages, avascular areas, signs of neovascularization and the overall capillaroscopy pattern, namely early, active or late scleroderma pattern. Capillary density was defined as the number of capillaries in a one-millimetre span of the distal row and a capillary loop will be considered as a distal loop if the angle between the apex of that capillary and the apex of its two adjacent capillaries is greater than $>90^\circ$ [4]. The study was approved by the Ethics Committees (Protocol no 0024185/20). Patients with unavailable capillaroscopy images in the previous year were excluded.

Data were analysed using SPSS Statistics v 26.0 for Windows (IBM Corp. Armonk, NY). Categorical variables were reported as number and percentage while continuous variables were reported as mean \pm SD after the verification of their normality by inspection of Q–Q (quantile-quantile) plots. Analysis of categorical variables was performed with the chi-square test or Fisher's exact test, as appropriate. Comparisons between groups of unpaired and paired continuous variables were performed with *t*-test after the verification of the homogeneity of variances by the Levene test. A binomial logistic regression was performed to ascertain the effects of on the likelihood that patients have a worsening of SSc vascular acral manifestations. Linearity of the continuous variables with respect to the logit of the dependent variable was assessed via the Box-Tidwell procedure. Results are expressed as the Odds Ratio (OR) and 95 % confidence interval (95 % CI). Statistical significance was defined as a $p < 0.05$ for all the statistical analyses, all the tests were two-tailed.

3. Results

A total of 62 patients were treated with monthly iloprost infusion in our centre in February 2020. Three patients did not discontinue iloprost because of active and persistent digital ulcers and 9 were not evaluated with a capillaroscopy in the previous year. Of the remaining patients, 50 were contacted by phone at the time of the survey and therefore included in the final analysis. The characteristics of the cohort are reported in Table 1.

Overall, 11 patients (22.0 %) reported a worsening of RP during iloprost withdrawal. While all these patients reported an enhanced intensity, only 8 (16.0 %) complained of an increased frequency, too. The rated RP intensity significantly raised during the during iloprost

Table 1

Characteristics of the enrolled patients (n = 50).

Female, n (%)	45 (90.0)
Age, years, mean \pm SD	54.9 \pm 13.4
Disease duration, year, mean \pm SD	11.3 \pm 6.7
Diffuse cutaneous, n (%)	15 (30.0)
Anticentromere antibodies, n (%)	13 (26.0)
Anti-Scl70 antibodies, n (%)	18 (36.0)
Scleroderma pattern early/active/late, n (%)	22 (44.0)/16 (32.0)/12 (24.0)
History of digital ulcers, n (%)	27 (54.0)
Active digital ulcers, n (%)	8 (16.0)
Calcium channel blockers, n (%)	33 (66.0)
Anti-endothelin treatment, n (%)	5 (10.0)
Anti-PDE-5 treatment, n (%)	4 (8.0)
ASA 100 mg/die, n (%)	30 (60.0)
Decreased reported cold exposure, n (%)	26 (52.0)

Abbreviations: SD standard deviation, ASA acetylsalicylic acid, PDE phosphodiesterase.

withdrawal (4.6 ± 2.1 vs 5.2 ± 2.3 , $p = 0.007$) while the trend toward worsening of frequency did not reach the statistical significance (4.5 ± 2.3 vs 5.0 ± 2.4 , $p = 0.07$). No SSc patient developed digital ulcers for the first time during iloprost withdrawal. In the subgroup of 27 SSc patients with history of digital ulcers, 9 (33.3 %) complained of their worsening. Of note, 7 patients (25.9 %) without active digital ulcers in February 2020 had a recurrence during iloprost withdrawal. Overall, 17 patients (34.0 %) overall complained of a worsening of SSc vascular acral manifestations, namely RP or DU.

Patients who experienced a worsening of RP did not statistically differ from the rest of the cohort for any demographic, disease-related characteristic, or ongoing vasoactive treatment. As regards capillaroscopy findings, the median time between the survey and the last capillaroscopy was 7.0 months (IQR 9.0–6.0). A RP worsening was associated with a reduced capillary density at the most recent evaluation. Of note, each unit increase of capillary density was associated with an average 44 % decrease in the odds of RP worsening (OR 0.56, CI 95 % 0.36–0.97, $p = 0.037$). Nevertheless, drug treatment for a depressive or anxious disorder was more common in patients who complained of a more severe RP after the iloprost withdrawal (Table 2).

With regard to DU severity, a history of DU - either active or former at the time of iloprost discontinuation - was the only clinical predictor of worsening. As for RP worsening, the aggravation of DU was associated with a lower capillary density (Table 3).

4. Discussion

Although iloprost is one of the most widely used treatments in SSc, data about the comparison of different regimens or drug discontinuation are poor. Moreover, given the clinical heterogeneity of SSc, it can be inferred that the actual iloprost need could also differ from one patient to another. The completely unexpected first COVID-19 wave has provided some unique conditions to evaluate the consequences of sudden iloprost discontinuation and given some clues on the ideal interval between administration and treatment duration.

One patient in three of our SSc cohort reported a worsening of the acral manifestation (including both RP and DU) after a synchronous discontinuation of their monthly iloprost in a context of overall reduction to cold exposure. Noticeably, only three studies have explored the consequences of iloprost discontinuation on RP or DU, all referred to a one-day monthly regimen. In particular, Bali and colleagues failed in demonstrating a RP worsening after iloprost monthly withdrawal in a randomized controlled trial, but the study showed consistent limitations related to the small size of the sample and the choice to carry out the study in summer [5]. Similarly, Auriemma and colleagues evaluated clinical and biological consequences of iloprost summer withdrawal and attested a deterioration in skin thermal properties and cytokine deregulation despite an improved RP [6]. It can be hypothesized that the lack

Table 2
Predictors of increased Raynaud's phenomenon intensity after monthly iloprost withdrawal.

	Worsened RP n = 11	Not worsened RP n = 39	p
Female, n (%)	11 (100.0)	34 (87.2)	0.211
Age, years, mean ± SD	54.6 ± 14.6	55.0 ± 13.2	0.942
Disease duration, year, mean ± SD	10.6 ± 8.0	11.4 ± 6.4	0.731
Diffuse cutaneous, n (%)	3 (27.3)	12 (30.8)	0.823
Anticentromere antibodies, n (%)	3 (27.3)	10 (25.6)	0.913
Anti-Scl70 antibodies, n (%)	4 (36.4)	14 (35.9)	0.977
History of digital ulcers, n (%)	20 (51.3)	7 (63.6)	0.468
Current digital ulcers, n (%)	8 (20.5)	0 (0.0)	0.101
Scleroderma pattern early, n (%)	4 (36.4)	18 (46.2)	0.563
Scleroderma pattern active, n (%)	4 (36.4)	12 (30.8)	0.725
Scleroderma pattern late, n (%)	3 (27.3)	9 (23.1)	0.774
Giant capillaries, n (%)	5 (45.5)	19 (48.7)	0.848
Haemorrhages, n (%)	5 (45.5)	11 (28.2)	0.279
Avascular areas, n (%)	6 (54.5)	16 (54.5)	0.425
Neovascularization, n (%)	4 (36.4)	9 (23.1)	0.375
Average capillary density, capillaries/mm, mean ± SD	5.4 ± 1.4	6.6 ± 1.7	0.028
Lower capillary density, capillaries/mm, mean ± SD	3.7 ± 1.2	4.6 ± 2.2	0.232
Calcium channel blockers, n (%)	6 (54.5)	27 (69.2)	0.364
Anti-endothelin treatment, n (%)	1 (9.1)	4 (10.3)	0.909
Anti-PDE-5 treatment, n (%)	0 (0.0)	4 (10.3)	0.268
ASA 100 mg/die, n (%)	6 (54.5)	24 (61.5)	0.676
Decreased reported cold exposure, n (%)	8 (72.7)	18 (46.2)	0.119
Mood disorder under medical treatment, n (%)	5 (45.5)	6 (15.4)	0.033

Abbreviations: RP Raynaud's phenomenon, SD standard deviation, ASA acetylsalicylic acid, PDE phosphodiesterase.

Table 3
Predictors of digital ulcers worsening after monthly iloprost withdrawal.

	Worsened DU n = 9	Not worsened DU n = 41	p
Female, n (%)	8 (88.9)	37 (90.2)	0.902
Age, years, mean ± SD	62.7 ± 13.5	53.2 ± 12.9	0.053
Disease duration, year, mean ± SD	12.9 ± 7.3	10.9 ± 6.6	0.425
Diffuse cutaneous, n (%)	2 (22.2)	13 (31.7)	0.574
Anticentromere antibodies, n (%)	3 (33.3)	10 (24.4)	0.580
Anti-Scl70 antibodies, n (%)	3 (33.3)	15 (36.6)	0.854
History of digital ulcers, n (%)	9 (100.0)	18 (43.9)	0.002
Current digital ulcers, n (%)	2 (22.2)	6 (14.6)	0.445
Scleroderma pattern early, n (%)	3 (33.3)	19 (46.3)	0.477
Scleroderma pattern active, n (%)	2 (22.2)	14 (34.1)	0.487
Scleroderma pattern late, n (%)	4 (44.4)	8 (19.5)	0.126
Giant capillaries, n (%)	4 (44.4)	20 (48.8)	0.814
Microhemorrhages, n (%)	1 (11.1)	15 (36.6)	0.138
Avascular areas, n (%)	5 (55.6)	17 (41.5)	0.441
Neovascularization, n (%)	2 (22.2)	11 (26.8)	0.775
Average capillary density, capillaries/mm, mean ± SD	5.2 ± 1.0	6.6 ± 1.7	0.026
Lower capillary density, capillaries/mm, mean ± SD	3.3 ± 1.2	4.6 ± 2.1	0.088
Calcium channel blockers, n (%)	7 (77.8)	26 (63.4)	0.410
Anti-endothelin treatment, n (%)	1 (11.1)	4 (9.8)	0.646
Anti-PDE-5 treatment, n (%)	1 (11.1)	3 (7.3)	0.704
ASA 100 mg/die, n (%)	8 (88.9)	22 (53.7)	0.051
Decreased reported cold exposure, n (%)	4 (44.4)	20 (48.8)	0.814
Mood disorder in medical treatment, n (%)	2 (22.2)	9 (22.0)	0.986

Abbreviations: DU digital ulcers, SD standard deviation, ASA acetylsalicylic acid, PDE phosphodiesterase.

of clinical worsening in the previous study, unlike our cohort, could be ascribed to a seasonal aspect. Lastly, Crisafulli and colleagues reported a DU worsening or relapse in one fifth of SSc patients evaluated by DU Clinical Assessment Score (DUCAS) who interrupted iloprost because of

the pandemic. It can be postulated that the lower rate of worsening compared to our cohort (18.0 % vs 33.3 %) could be ascribed to a different method of assessment and a larger bosentan exposure [7].

Moving to the predictors of clinical worsening, we observed a reduced capillary density in patients who experienced a worsening of both RP and DU after iloprost withdrawal. In addition, a concomitant mood disorder and a history of digital ulcers, represent further risk factors for a worsening of RP and DU, respectively. While the two last clinical associations have been already reported [8,9], to the best of our knowledge this is the first report of the association of capillaroscopy findings with clinical consequences of iloprost withdrawal. Consequently, it can be inferred that capillaroscopy could itself help the choice to increase or reduce iloprost dosage given the different possible regimens. In this context, capillaroscopy could be used not only for diagnostic and prognostic purposes but also to personalize iloprost posology in SSc patients. With reference to the association of a worse outcome with a mood disorder, the cross-sectional design of the study did not allow to clarify whether those patients were more prone to report negative outcome, or this psychological impairment promotes itself a vascular damage through abnormal neuro-hormonal activation.

The study has clearly some limitations. Firstly, we investigated a relatively small sample that does not allow adjusting the capillary density for other possible confounding as a predictor of clinical worsening. Moreover, the chosen outcome measures are based on patients' reports on the phone and not on direct physician evaluation although the RP, given its parossistic nature, is supposed to be assessed primarily by the patients. Furthermore, our observations are consistent with the reported association of low capillary density with DU [10,11].

5. Conclusion

Low capillary density can predict a worsening of both RP and DU within a month after iloprost discontinuation in SSc patients. Further studies are needed to assess whether the capillaroscopy could be used to personalize iloprost regiment in SSc patients.

CRedit authorship contribution statement

Enrico De Lorenzis: conceptualization, methodology, formal analysis, investigation and resources, data curation, writing original and revised draft, editing.

Gerlando Natalello: methodology, investigation, resources, data curation, writing original draft.

Lucrezia Verardi: investigation, resources, data curation, writing original draft.

Pier Giacomo Cerasuolo: investigation, resources, data curation, writing original draft.

Laura Gigante: investigation, resources, data curation, writing original draft.

Maria Antonietta D'Agostino: methodology, writing original draft, editing, supervision, project administration.

Silvia Laura Bosello: conceptualization, methodology, resources formal analysis, data curation, writing original and revised draft, editing, supervision, project administration.

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There are no competing interests for any author. All the authors gave substantial contributions to the conception or design of the work, acquisition, analysis or interpretation of data, drafting the work or

revising it critically for important intellectual content and final approval of the version published.

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