ORIGINAL ARTICLE

The safety and persistence of intravenous iloprost in systemic sclerosis

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ABSTRACT

Introduction: Vasculopathy is a crucial feature of systemic sclerosis (SSc). It occurs in almost every patient with SSc, with Raynaud's phenomenon (RP) and digital ulcers (DU) having a great impact on the quality of patients' lives. Intravenous (IV) iloprost, a synthetic analogue of prostacyclin, is broadly used to treat RP and DU secondary to SSc. Currently, there is no standard protocol defined for the iloprost treatment of SSc-associated RP and DU, and, consequently, the management of this treatment is largely based on each centre's experience.
Objective: The objective of this study is to evaluate the safety profile of a particular scheme of IV iloprost used in our centre as the standard treatment of SSc-related vascular complications.
Methods: We retrospectively evaluated the clinical records of SSc patients, classified according to the 2013 European Alliance of Associations for Rheumatology (EULAR) criteria (31) with SSc-related DU and/or severe RP not responsive to calcium channel blockers (CCB), receiving or who have received IV iloprost infusions from January 1st 2011 to March 31st 2021
Results: Within this time frame, 60 patients (n=44 for DU; n=16 for severe RP) were treated with a monthly 10-hour IV iloprost perfusion with a dosing regimen adapted to individual tolerance. Forty-nine of these 60 patients (81.7%) were on iloprost for more than one year. Within 12 months of therapy, 40 patients have healed the DUs (90.9%), with only 4 patients maintaining active DUs. A significant clinical improvement in RP at 12 months was observed in 87.5% (n=14/16) of SSc patients with severe RP. Eleven AE implying treatment dose/frequency adjustments or suspension were recorded (18.3% of patients): severe headache (n=5), hypotension (n=3), tachycardia (n=1), flushing (n=1) and generalised erythroderma (n=1). In all patients, the perfusion rate was reduced in the following treatment sessions with good tolerance, with the exception of the patient with the generalised erythroderma reaction, who suspended the perfusion and was later switched to bosentan. After a mean follow-up time of 6.9 (+/-) 4.0 years of treatment (range 0.06-22), 24 patients (40%) stopped the therapy, 14 (58.3%) of whom due to clinical improvement. The overall 5-, and 10-year survival rates of IV iloprost were 68.2% and 55.6%, respectively.
Conclusion: SSc patients who received this flexible IV iloprost regimen achieved clinical improvement, reflected in the high persistence rate of the drug, with a good tolerability profile. In addition, most side effects were mild and easily managed.

Keywords: Scleroderma and related disorders; Raynaud's syndrome; Iloprost

INTRODUCTION

Systemic sclerosis (SSc) is a complex connective tissue disease characterised by autoimmunity, progressive generalised obliterative vasculopathy and widespread aberrant tissue fibrosis[1,2]. Although SSc's pathophysiological mechanisms are still elusive, vascular damage is generally considered an early event in the natural history of this disease[3]. Digital vasculopathy occurs in almost every patient with SSc and can range in severity from painless Raynaud phenomenon (RP) to irreversible ischaemic tissue injury causing gangrene, potentially leading to amputation[4].

RP is the most common symptom and one of the warning signs of the disease[2,3]. Whereas in primary RP, tissue ischaemia is transient or reversible, in secondary SSc-associated RP, persistent tissue ischaemia can occur, resulting in digital ulceration or gangrene[5]. Digital ulcers (DU) are common in patients with SSc, with a point prevalence of around 10% and around half of the patients experiencing DUs during their disease course[6]. Despite the availability of effective treatments to prevent and heal DUs, one-third of patients suffers recurrent ulceration. SSc-associated DU are recognised as a poor prognostic factor, including increased risk for pro-

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gressive disease and death[6-8]. Furthermore, DU may be complicated, primarily by infections that can progress to gangrene or osteomyelitis and lead to amputation[6]. These complications, often requiring hospitalisation, increase the disease's burden on patient function and quality of life, as well as the cost of treatment[9-11]. Therefore, SSc-related vasculopathy's treatments represent priorities for clinicians dealing with SSc[12].

Currently, several drugs are available to manage RP and DU, such as calcium channel blockers (CCB), phosphodiesterase type V inhibitors (PDEVi), prostanoids, angiotensin II receptor antagonists, angiotensin-converting enzyme inhibitors, alpha-blockers, selective serotonin reuptake inhibitors, platelet aggregation inhibitors, and endothelin-1 receptor antagonists[13,14]. A systematic review of the literature reported that CCB, intravenous (IV) iloprost, bosentan, and tadalafil show the best evidence of efficacy in treating RP and DU, supporting the EUSTAR recommendations[14,15].

Iloprost is a stable analogue of natural prostacyclin (PGI2), which inhibits platelet aggregation and adhesion, dilates arterioles and venules, activates fibrinolysis, and reduces the release of oxygen-reactive species. On fibroblasts, iloprost blocks the activation of connective tissue growth factor, inhibits the expression of collagen type 1 (induced by interleukin 1, *transforming growth factor-alpha and beta* [TGF-α and β], *insulin-like growth factor 1* [IGF-1], and platelet-derived growth factor [*PDGF*][16, 17]), and inhibits the expression of vascular cell adhesion molecule-1 and intercellular adhesion molecule-1[18].

In daily practice, iloprost is used to manage critical leg ischemia, RP and ischemic ulcers secondary to connective tissue diseases[19-21]. A meta-analysis that included five randomised controlled trials (RCTs) of IV iloprost, one RCT of oral iloprost and one RCT of oral cisaprost[21-26], included a total of 332 SSc patients. Five of the seven trials were of parallel design. Five trials compared IV iloprost and one trial studied oral iloprost and another oral cisaprost. Some trials were dose finding trials so various doses of iLloprost were used, as summarized in Table I. None of the protocols included a monthly 10-hour infusion. Due to different efficacies of IV iloprost, oral iloprost and oral cisaprost, the overall efficacy of these drugs was somewhat diluted. The results showed that iloprost appears to be effective in reducing the frequency and severity of SSc-associated RP and in preventing or healing DUs. The effect seems to be prolonged even after the intravenous infusion is stopped. Oral iloprost may be less efficacious than IV iloprost. However, cisaprost had minimal or no efficacy when given orally for the treatment of RP secondary to scleroderma[27].

Currently, there is no standard protocol defined for the iloprost treatment of SSc-associated RP and DU. Over the years, several studies and RCTs evaluated different therapeutic schemes. Wigley *et al.* performed a multicentre, double-blind, placebo-controlled RCT to evaluate the efficacy and safety of six-hour IV infusions of iloprost (0.5-2.0 ng/kg/min) in five consecutive days for the treatment of RP[28]. Iloprost improved the frequency of Raynaud attacks and the patient's overall perceptions of the severity of their attacks[28]. Clinical benefits persisted for as long as nine weeks after treatment[28]. Rademaker *et al.* performed a double-blind, placebo-controlled RCT, over 12 weeks, to compare eight-hour IV infusions of iloprost (0.5–2 ng/kg/min) in three consecutive days, with a further single infusion at week 8, versus daily nifedipine (starting at 30 mg and increased to 60 mg after four weeks)[29]. There was a significant decrease in the frequency, duration, and severity of RP attacks with both treatments and a numeric reduction of digital lesions. With nifedipine, however, the side effects were more common[29]. Scorza *et al.* performed a 12-month RCT to compare the efficacy and safety of eight-hour IV infusions of iloprost (2 ng/kg/min) on five consecutive days, followed by additional single-day infusions every six weeks, versus nifedipine 40 mg/day[19]. A more recent retrospective study designed to evaluate the safety and tolerability of IV iloprost demonstrated its safety when administered weekly in patients with SSc[30].

These studies show that IV iloprost is an effective treatment for vascular complications of SSc, but there is no consensus regarding the best infusion protocol.

Our study aimed to evaluate the safety profile, tolerability and effectiveness of the IV iloprost treatment regimen used in our centre, in a real-life scenario, as the standard treatment of SSc-related vascular complications.

MATERIAL AND METHODS
We evaluated the clinical records of SSc patients, classified according to the 2013 European Alliance of Associations for Rheumatology (EULAR) criteria[31] with SSc-related DU and/or severe RP not responsive to CCB, receiving or who have received IV iloprost infusions from January 1st 2011 to March 31st 2021. There were no restrictions concerning combination treatments for SSc or comorbidities. Severe RP was defined by more than two attacks/day with intense pain, paraesthesia, loss of manual dexterity or necrosis of the digits. Mild RP was characterised by less than one daily attack with no associated pain.

IV iloprost was prepared by diluting a vial of iloprost 0.05 mg in 250 ml of 0.9% saline solution (200 ng/ml). The treatment schedule consisted of a ten-hour single-day infusion every month. This is a protocol that

has been implemented in our service for several years to date with good results. The time interval of ten-hour allows for the administration of the required dose in a time interval that reduces the likelihood of adverse effects occurring.

In more severe cases of RP or DUs, a five consecutive day regimen could be chosen as induction. Over the ten hours of perfusion, the dose was progressively increased up to the patient's maximum tolerated dose (ranging from 0.5 to 1.5 ng/kg/min). The infusion rate was started at 4 ml/h and increased according to the following scheme: 4 mL/h (first hour), 8 mL/h (second hour), 12 mL/h (third hour), and then 16 mL/h if tolerated by the patient, until the end of the infusion. The infusion rate could be reduced if there were any adverse events (AE) during the infusion and the following treatment sessions were adjusted accordingly. No pre-treatment regimen was employed (Figure 1). We considered the following AE as possible reactions to iloprost infusion: diarrhea, hypotension, painful digital swelling, flushing, headache, agitation, arrhythmia.

All patients usually receive treatment from September to July, except those with severe DUs, who may receive iloprost throughout the year. The improvement criteria for DUs were defined as resolution with assessment at the end of the first, sixth and twelve months of treatment. As for RP, its improvement was evaluated by the severity of attacks.

To evaluate the safety and tolerability of the infusion therapy with iloprost, we recorded the infusion rate (ng/kg/min) and the occurrence of any AE during the infusion or in the following hours after treatment. The number and characteristics of AE were analysed and classified according to severity and frequency. It was also recorded if the AE led to iloprost dose reduction, temporary suspension, or drug discontinuation. For AE treatment, therapeutic interventions were also recorded (e.g., paracetamol for headaches).

Regarding statistical analysis, continuous variables with normal distributions were reported as means and standard deviations. If continuous variables had skewed distributions, the medians and interquartile ranges were reported. Categorical variables were presented as absolute frequencies and percentages. Drug survival within the first five years since treatment onset was assessed using Kaplan-Meier survival analysis. Statistical analysis was performed using SPSS software (IBM, version 23, Armonk, NY, USA). All calculations made were based on the observed data.

RESULTS
Patient clinical and demographic characteristics
In the time interval assessed, 60 patients were under treatment with IV iloprost according to this treatment protocol in our centre, from January 1st 2011 to March 31st 2021. Of these 60 patients, only 49 were on treatment for more than one year. In 8.3% (n=5/60) of the patients the treatment regimen was done in inpatients, with the rest being done in day hospital. SSc patients' demographic and clinical features are presented in Table II. Most patients were females (96.7%) with a me-

Table I. Characteristics of included studies analyzing different iloprost schemes

Reference	Patient population	Treatment scheme details
McHugh 1988 (25)	29 pts with severe RP, all suffering at least 12 attacks per week	Each treatment consisted of three 6-hour infusions of iloprost or placebo on 3 consecutive days, every six weeks. Iloprost dosage was 2.0 ng/kg/min
Yardumian 1988 (26)	12 pts with severe secondary RP	3-day infusion of iloprost or placebo Day 1-1 mg/kg/min Day 2-2 mg/kg/min Day 3-3 mg/kg/min followed by a 6-week washout period and then a second treatment course
Kyle 1992 (23)	13 pts with RP severe enough to warrant admission to hospital for IV	A cycle of treatment of IV iloprost 6 h infusions on 3 consecutive days
Wigley 1992 (21)	35 pts with RP secondary to SSc	Iloprost (0.5-2.0ng/kg/min) or placebo over 6 hours IV for 5 consecutive days
Wigley 1994 (28)	131 pts with Raynaud's Phenomenon secondary to SSc	Pts randomly assigned to receive 1 of 2 parallel treatments of 5 daily sequential 6-hour IV infusions of iloprost 0.5 to 2.0 ng/kg per min or to receive a similar volume of Placebo. Duration: 11 weeks

IV – intravenous; pts – patients; RP - raynaud's phenomenon; SSc - Systemic Sclerosis

Table II. Demographic and clinical data of SSc patients

Demographic data	
Female, n (%)	58 (96.7)
Mean age, years ± SD	55.7 ± 19.3
Mean age at diagnosis, years ± SD	47.9 ± 18
Median disease duration, years (range)	13.9 (1-55)
Median disease duration at the beginning of the treatment, years (range)	2.4 (0.3-6)
Clinical subtypes	
dcSSc, n (%)	9 (15)
lcSSc, n (%)	37 (61.7)
Sine scleroderma, n (%)	1 (1.7)
VEDOSS, n (%)	1 (1.7)
Overlap syndrome, n (%)	12 (20)
Auto-antibody	
Anti-Scl 70, n (%)	8 (13.3)
ACA, n (%)	40 (66.7)
Pm/Scl, n (%)	12 (20)
Clinical manifestations	
Raynaud phenomenon, n(%)	60 (100)
Digital ulcers (active/history), n (%)	44 (73.3)
Telangiectasia, n (%)	38 (63.3)
Calcinosis, n (%)	7 (11.7)
Dysphagia, n (%)	11 (18.3)
Reflux, n (%)	29 (48.3)
ILD, n (%)	19 (31.7)
PAH, n (%)	3 (5)
Arthritis/arthralgia, n (%)	28 (46.7)
Concomitant treatment	
Nifedipine/amlodipine, n (%)	58 (96.7)
Bosentan, n (%)	14 (23.3)
Sildenafil, n (%)	4 (6.7)

ACA – anticentromere; dcSSc - Diffuse cutaneous systemic sclerosis; ILD – Interstitial lung disease; lcSSc. - limited cutaneous SSc; PAH – Pulmonary Arterial hypertension; SD - standard deviation; VEDOSS - very early diagnosis of systemic sclerosis

Table III. Adverse events leading to IV iloprost dose/frequency adjustments or suspension

Adverse event	n (%)
Headache	5 (45.4%)
Hypotension	3 (27.3%)
Tachycardia	1 (9.1%)
Generalised erythroderma	1 (9.1%)
Flushing	1 (9.1%)
Total	11 (100%)

(11.7%) patients had calcinosis at the beginning of iloprost treatment.

As for concomitant treatments, 58 (96.7%) patients were under treatment with CCB, whilst bosentan and sildenafil were being used by fourteen (23.3%) and four (6.7%) patients, respectively. Sildenafil was used as concomitant treatment in patients with severe RP, while bosentan was prescribed to prevent new ulcerations in 13 patients and for pulmonary hypertension in one.

Clinical indication and efficacy of IV iloprost

The reasons for starting iloprost were moderate–severe RP (more than two attacks/day with moderate pain) not responsive to CCB (n=16) and/or SSc related DU (n=44). The mean duration of treatment up to our analysis was 6.9 (±) 4.0 years (range 0.06-22). In total, these patients performed a total of 1634 iloprost cycles. Five patients with severe RP and DUs received the IV Iloprost 5 consecutive day regimen as induction therapy. The remaining performed the treatment schedule consisted of a ten-hour single-day infusion every month.

Thirty-one out of 44 patients with DUs (70.5%) had clinical resolution within the first month of therapy, and 38 patients (86.4%) resolved within the first 6 months. Within 12 months of therapy, 40 patients (90.9%) healed the DUs, with only 4 patients maintaining active DUs. Regarding the 16 patients with severe RP, significant improvement occurred in the first month in 9 patients (56.3%), rising to a total of 12 patients after 6 months (82%). Within 12 months of therapy, 14 patients with severe RP (87.5%) had significant clinical improvement of the problem, with only 2 patients remaining with clinical RP (one with mild and one with severe RP).

Safety and adverse events

Eleven AE implying treatment dose/frequency adjust-

dian disease duration of 13.9 (range 1–55) years. The SSc limited cutaneous subset was the most frequent (37 patients, 61.7%). The anticentromere (ACA) antibody was present in 40 (66.7%) patients. Fifty-four (90%) patients had active or a history of DU, and seven
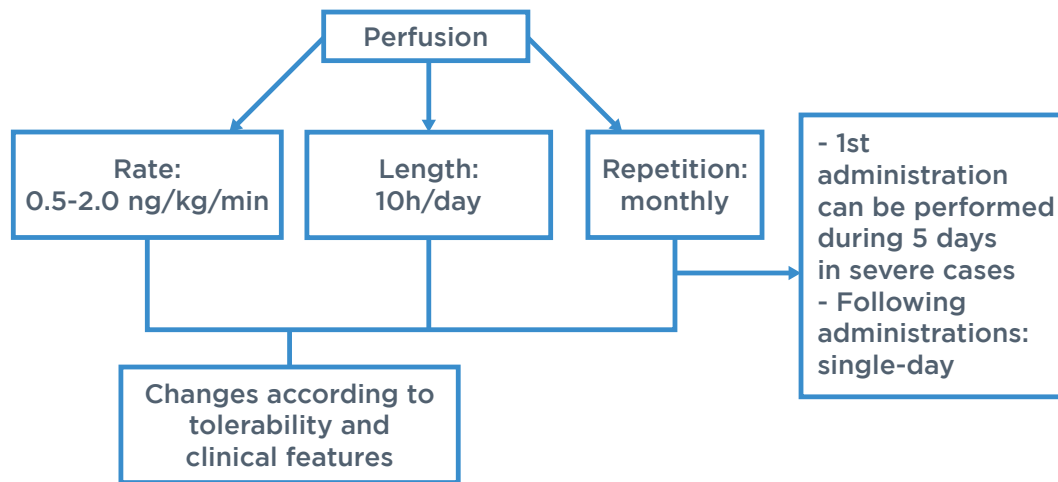
Figure 1. Scheme of the iloprost treatment strategy for digital ulcers and Raynaud phenomenon in the context of systemic sclerosis.

ments or suspension were recorded (18.3% of patients): severe headache was reported in 5 patients (45.4%), hypotension in 3 patients (27.2%), tachycardia in one patient (9.1%), flushing in one patient (9.1%) and generalised erythroderma in one patient (9.1%) (Table III).

In patients with severe headaches and hypotension, the perfusion rate was reduced in the following treatment sessions, and the symptoms resolved. The iloprost infusion was stopped in the patients with tachycardia and flushing events, and the following treatment sessions were performed at lower perfusion rates, with good tolerance. The patient with the generalised erythroderma reaction suspended the perfusion and was switched to bosentan.

Long term drug survival

After a mean follow-up time of 6.9 (±) 4.0 years of treatment (range 0.06-22), 36 patients (60%) were still on active treatment. The overall 5- and 10-year survival rates of IV iloprost were 68.2% and 55.6%, respectively (Figure 2).

The reasons for treatment discontinuation in the remaining 24 patients included clinical improvement (n=14), switch to treatment with ambulatory elastomeric pump (n=6), death (n=3) or transfer of follow-up to another hospital (N=1). The 6 patients who switched from IV perfusion to elastomeric pump, did so to allow for greater autonomy and to keep their daily activities. This resulted in improved direct costs of hospitalization, as well as in a reduction of absenteeism. On the other hand, 4 patients currently on IV iloprost were initially started on ambulatory elastomeric pump, but were later switched to IV infusions due to the occurrence of phlebitis.

DISCUSSION

Several studies showed the efficacy of iloprost in treating vascular manifestations of SSc, namely RP and DU[23-25], using different treatment regimens. Here, we present a flexible treatment protocol for IV iloprost in SSc, based on the patient's clinical symptoms and treatment tolerance (usually once a month in the day hospital with a break during the warmer summer months, provided this is medically possible according to the patient's symptoms).

In our centre, the administration of iloprost following the described protocol (Figure 1) is effective, well-tolerated and safe, as is confirmed by the high long term drug persistence. Our data suggest that the IV iloprost perfusion rate (and, hence, total dose) can be flexible, tailored by the patient's tolerability.

The data we present shows a very acceptable rate of AE, and most of them resolved after dose adjustments. With adjusted dosages, all patients but one tolerated the iloprost infusions. The most common side effects implying dose adjustments were headaches and hypotension. The most severe AE was generalised erythroderma, which caused the definitive suspension of the treatment. A similar profile of AE was noted in the study conducted by Bellando-Randone *et al.*[30].

Previous reports suggested the potential risks of ischemic cardiovascular complications (myocardial infarction or stroke) with iloprost treatment[32]. These events were more commonly reported in patients with higher baseline cardiovascular risk (14%) than in those with lower cardiovascular risk (2.4%)[32]. The myocardial infarction risk has been linked to a "stealing" vascular event in patients with extensive extramural coronary atherosclerosis[32], suggesting that iloprost may have an inciting role. Therefore, cardiovascular risk should be
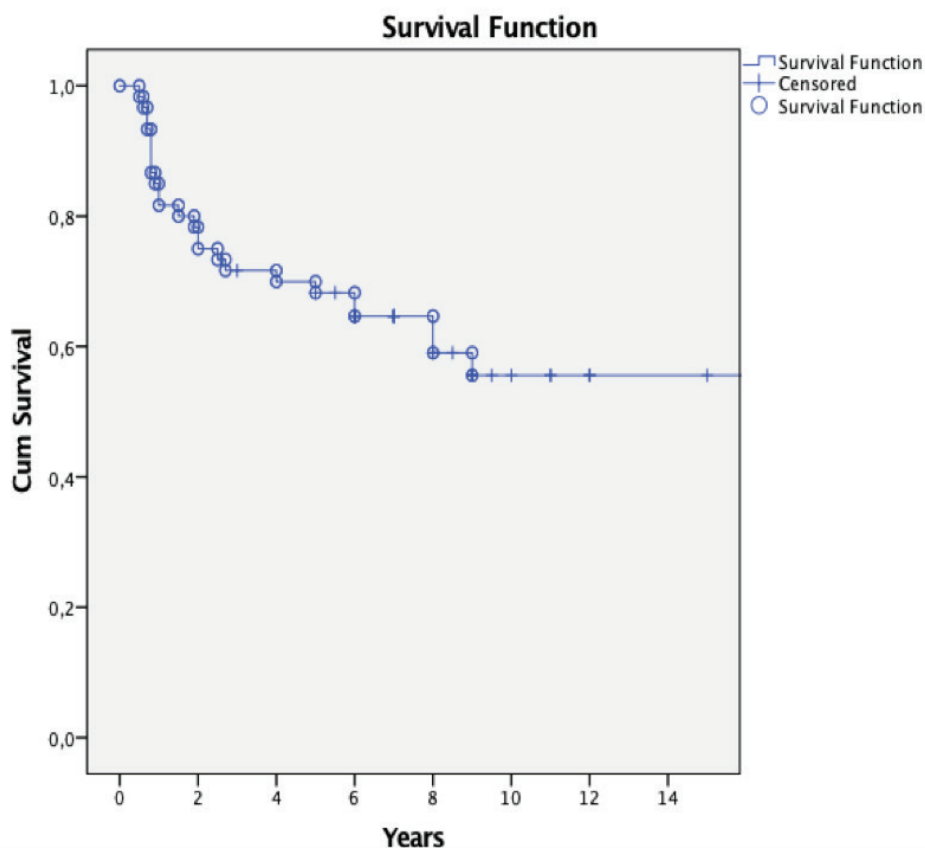
Survival Function

Figure 2. Kaplan-Meier analysis of iloprost treatment persistence.

assessed in every SSc patient before iloprost treatment onset to identify patients at higher risk for ischemic events[32]. No stroke or myocardial infarction occurred in our cohort.

Our real-world data provide helpful information on the safety and management of SSc patients using IV iloprost infusions. An important advantage of our protocol is that it avoids the need for a 5-day in-hospital admission or 5 consecutive day care visits for treatment with IV iloprost, which is the case for other commonly used treatment regimens. Of note, only a minority of the most severe cases may require an initial 5-day induction treatment regimen.

Limitations of our study include the retrospective nature of the analysis (with risk of AE notification loss), the lack of adjusting for potential confounders, the risk of under-reporting mild AE and the small sample size and the application of patient-reported outcome (PRO) to evaluate response to treatment.

CONCLUSION

SSc patients who received this flexible IV iloprost regimen achieved clinical improvement, reflected in the high persistence rate of the drug, with a good tolera-

bility profile. In addition, most side effects were managed by adapting the infusion rate. Thus, we provide evidence that monthly single iloprost infusions can be safely administered and adjusted according to the patient's clinical characteristics and drug tolerance. Further prospective, larger and multicentric studies, might help to support this treatment regimen.

REFERENCES

1. Katsumoto TR, Whitfield ML. The pathogenesis of systemic sclerosis. Annu. Rev. Pathol 2011; 6: 509–537.
2. Denton CP, Khanna DK. Systemic sclerosis. Lancet 2017;390:1685–1699.
3. Matucci-Cerinic M, Kahaleh B, Wigley FM. Review: evidence that systemic sclerosis is a vascular disease. Arthritis Rheum. 2013; 65: 1953–62.
4. Hughes M, Allanore Y, Chung L, Pauling JD, Denton CP, Matucci-Cerinic M. Raynaud phenomenon and digital ulcers in systemic sclerosis. Nat Rev Rheumatol. 2020;16(4):208-221.
5. Meier FMP. et al. Update on the profile of the EUSTAR cohort: an analysis of the EULAR Scleroderma Trials and Research group database. Ann. Rheum. Dis 2012; 71: 1355–1360.
6. Allanore Y, Denton CP, Krieg T, et al. Clinical characteristics and predictors of gangrene in patients with systemic sclerosis and digital ulcers in the Digital Ulcer Outcome Registry: a prospective, observational cohort. Ann Rheum Dis. 2016;75(9):1736–40.
7. Hughes M, Pauling JD. Exploring the patient experience of dig-

ital ulcers in systemic sclerosis. Semin Arthritis Rheum. 2019 Apr;48(5):888-894. doi: 10.1016/j.semarthrit.2018.08.001. Epub 2018 August 11th.

8. Matucci-Cerinic M, Krieg T, Guillevin L, et al. Elucidating the burden of recurrent and chronic digital ulcers in systemic sclerosis: long-term results from the DUO Registry. Ann Rheum Dis.2016;75:1770–6.

9. Mouthon L, Mestre-Stanislas C, Bérezné A, et al. Impact of digital ulcers on disability and health-related quality of life in systemic sclerosis. Ann Rheum Dis. 2010;69:214–7.

10. Mouthon L, Carpentier PH, Lok C, et al. Ischemic digital ulcers affect hand disability and pain in systemic sclerosis. J Rheumatol. 2014;41:1317–23.

11. Nihtyanova SI, Brough GM, Black CM, Denton CP. Clinical burden of digital vasculopathy in limited and diffuse cutaneous systemic sclerosis. Ann Rheum Dis. 2008;67:120–3.

12. Abraham S, Steen V. Optimal management of digital ulcers in systemic sclerosis. Ther Clin Risk Manag. 2015;11:939–47.

13. Hettema ME, Zhang D, Bootsma H, Kallenberg CG. Bosentan therapy for patients with severe Raynaud's phenomenon in systemic sclerosis. Ann Rheum Dis. 2007;66(10):1398-9.

14. Kowal-Bielecka O, Landewé R, Avouac J, Chwiesko S, Miniati I, Czirjak L, et al. (EUSTAR Co-Authors). EULAR recommendations for the treatment of systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group (EUSTAR). Ann Rheum Dis. 2009 May;68(5):620-8.

15. García de la Peña Lefebvre P, Nishishinya MB, Pereda CA, Loza E, Sifuentes Giraldo WA, Román Ivorra JA, Carreira P, Rúa-Figueroa I, Pego-Reigosa JM, Muñoz-Fernández S. Efficacy of Raynaud's phenomenon and digital ulcer pharmacological treatment in systemic sclerosis patients: a systematic literature review. Rheumatol Int. 2015 Sep;35(9):1447-59.

16. Stratton R, Rajkumar V, Ponticos M, Nichols B, Shiwen X, Black CM, Abraham DJ, Leask A. Prostacyclin derivatives prevent the fibrotic response to TGF-beta by inhibiting the Ras/MEK/ERK pathway. FASEB J. 2002 Dec;16(14):1949-51.

17. Stratton R, Shiwen X, Martini G, Holmes A, Leask A, Haberberger T, Martin GR, Black CM, Abraham D. Iloprost suppresses connective tissue growth factor production in fibroblasts and in the skin of scleroderma patients. J Clin Invest. 2001 Jul;108(2):241-50.

18. Lindemann S, Gierer C, Darius H. Prostacyclin inhibits adhesion of polymorphonuclear leukocytes to human vascular endothelial cells due to adhesion molecule independent regulatory mechanisms. Basic Res Cardiol. 2003 Feb;98(1):8-15.

19. Scorza R, Caronni M, Mascagni B, Berruti V, Bazzi S, Micallef E, Arpaia G, Sardina M, Origgi L, Vanoli M. Effects of long-term cyclic iloprost therapy in systemic sclerosis with Raynaud's phenomenon. A randomised, controlled study. Clin Exp Rheumatol. 2001 Sep-Oct;19(5):503-8.

20. Veale DJ, Muir AH, Morley KD, Belch JJ. Treatment of vasculitic leg ulcers in connective tissue disease with iloprost. Clin Rheumatol. 1995 Mar;14(2):187-90.

21. Wigley FM, Seibold JR, Wise RA, McCloskey DA, Dole WP. Intravenous iloprost treatment of Raynaud's phenomenon and ischemic ulcers secondary to systemic sclerosis. J Rheumatol. 1992 Sep;19(9):1407-14.

22. Belch JJ, Capell HA, Cooke ED, Kirby JD, Lau CS, Madhok R, Murphy E, Steinberg M. Oral iloprost as a treatment for Raynaud's syndrome: a double blind multicentre placebo controlled study. Ann Rheum Dis. 1995 Mar;54(3):197-200.

23. Kyle MV, Belcher G, Hazleman BL. Placebo controlled study showing therapeutic benefit of iloprost in the treatment of Raynaud's phenomenon. J Rheumatol. 1992 Sep;19(9):1403-6.

24. Lau CS, Belch JJ, Madhok R, Cappell H, Herrick A, Jayson M, Thompson JM. A randomised, double-blind study of cicaprost, an oral prostacyclin analogue, in the treatment of Raynaud's phenomenon secondary to systemic sclerosis. Clin Exp Rheumatol. 1993 Jan-Feb;11(1):35-40.

25. McHugh NJ, Csuka M, Watson H, Belcher G, Amadi A, Ring EF, Black CM, Maddison PJ. Infusion of iloprost, a prostacyclin analogue, for treatment of Raynaud's phenomenon in systemic sclerosis. Ann Rheum Dis. 1988 Jan;47(1):43-7.

26. Yardumian DA, Isenberg DA, Rustin M, Belcher G, Snaith ML, Dowd PM, Machin SJ. Successful treatment of Raynaud's syndrome with Iloprost, a chemically stable prostacyclin analogue. Br J Rheumatol. 1988 Jun;27(3):220-6.

27. Pope J, Fenlon D, Thompson A, Shea B, Furst D, Wells G, Silman A. Iloprost and cisaprost for Raynaud's phenomenon in progressive systemic sclerosis. Cochrane Database Syst Rev. 2000;1998(2):CD000953.

28. Wigley FM, Wise RA, Seibold JR, McCloskey DA, Kujala G, Medsger TA Jr, Steen VD, Varga J, Jimenez S, Mayes M, Clements PJ, Weiner SR, Porter J, Ellman M, Wise C, Kaufman LD, Williams J, Dole W. Intravenous iloprost infusion in patients with Raynaud phenomenon secondary to systemic sclerosis. A multicenter, placebo-controlled, double-blind study. Ann Intern Med. 1994 February 1st;120(3):199-206.

29. Rademaker M, Cooke ED, Almond NE, Beacham JA, Smith RE, Mant TG, Kirby JD. Comparison of intravenous infusions of iloprost and oral nifedipine in treatment of Raynaud's phenomenon in patients with systemic sclerosis: a double blind randomised study. BMJ. 1989 March 4th;298(6673):561-4.

30. Bellando-Randone S, Bruni C, Lepri G, Fiori G, Bartoli F, Conforti ML, Moggi-Pignone A, Guiducci S, Giuggioli D, Colaci M, Spinella A, Ferri C, Matucci-Cerinic M. The safety of iloprost in systemic sclerosis in a real-life experience. Clin Rheumatol. 2018 May;37(5):1249-1255.

31. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, Matucci-Cerinic M, et. al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/ European League against Rheumatism collaborative initiative. Arthritis Rheum. 2013 Nov;65(11):2737-47.

32. Colaci M, Sebastiani M, Giuggioli D, et al. Cardiovascular risk and prostanoids in systemic sclerosis. Clinical and Experimental Rheumatology. 2008 Mar-Apr;26(2):333-336.