ORIGINAL ARTICLE

Use of vasoactive/vasodilating drugs for systemic sclerosis (SSc) -related digital ulcers (DUs) in expert tertiary centres: results from the analysis of the observational real-life DeSScipher study

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Abstract

Introduction DeSScipher is the first European multicentre study on management of systemic sclerosis (SSc), and its observational trial 1 (OT1) evaluated the efficacy of different drugs for digital ulcer (DU) prevention and healing. The aim of this study was to assess current use of vasoactive/vasodilating agents for SSc-related DU in the expert centres by analysing the baseline data of the DeSScipher OT1.

Method Baseline characteristics of patients enrolled in the OT1 and data regarding DU were analysed.

Results The most commonly used drugs, in both patients with and without DU, were calcium channel blockers (CCBs) (71.6%), followed by intravenous iloprost (20.8%), endothelin receptor antagonists (ERAs) (20.4%) and phosphodiesterase 5 (PDE-5) inhibitors (16.5%). Of patients, 32.6% with DU and 12.8% without DU received two drugs ($p < 0.001$), while 11.5% with DU and 1.9% without DU were treated with a combination of three or more agents ($p < 0.001$). Sixty-five percent of the patients with recurrent DU were treated with bosentan and/or sildenafil. However, 64 out of 277 patients with current DU (23.1%) and 101 (23.6%) patients with recurrent DU were on CCBs alone.

Conclusions Our study shows that CCBs are still the most commonly used agents for DU management in SSc. The proportion of patients on combination therapy was low, even in patients with recurrent DU: almost one out of four patients with current and recurrent DU was on CCBs alone. Prospective analysis is planned to investigate the efficacy of different drugs/drug combinations on DU healing and prevention.

Key Points
- *The analysis of DeSScipher, the first European multicentre study on management of SSc, has shown that the most commonly used vasoactive/vasodilating drugs for DU were CCBs, followed by intravenous Iloprost, ERAs and PDE-5 inhibitors.*
- *More than half of the patients with recurrent DU received bosentan and/or sildenafil.*
- *However, the proportion of patients on combination therapy of more than one vasoactive/vasodilating drug was low and almost one out of four patients with current and recurrent DU was on CCBs alone.*

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Introduction

Systemic sclerosis (SSc) is characterised by a complex pathogenesis with tissue fibrosis and vascular remodelling which cause vascular narrowing and loss of capillaries resulting in tissue ischemia [1,2]. Consequently, one of the major complications affecting the extremities are digital ulcers (DUs) that may lead in the most severe cases to gangrene and amputation [3, 4]. In SSc patients, the presence of DU is a predictor of a

worse disease course and of a poor survival [5, 6]. For this reason, the management of DU is a clinical challenge which includes local as well as systemic treatment. In practice, a wide choice of vasoactive and vasodilating drugs, such as calcium channel blockers (CCBs), sildenafil, iloprost and bosentan, are at disposal of the physician [7] but head-to-head comparative studies are not available yet.

DeSScipher is the largest European multicentre observational study with the aim to decipher the optimal management of SSc. It contains five observational trials (OTs) focusing on DU, hand arthritis, interstitial lung disease, pulmonary hypertension and heart disease (https://www.unigiessen.de/faculties/f11/facilities/desscipher-en?set_language=en). Observational trial no. 1 (OT1) evaluated the effectiveness of different vasoactive/vasodilating drugs for DU prevention and healing.

The aim of this study was to assess the current use of vasoactive/vasodilating therapies employed in expert centres for the treatment of SSc-related DU, by analysing the baseline data of the DeSScipher OT1.

Materials and methods

OT1 is one of the five trials of the DeSScipher project (ClinicalTrials.gov; OT1 Identifier: NCT01836263). The DeSScipher project was based on use of the EUSTAR (European Scleroderma Trials and Research group) long-term database MEDS (Minimal Essential Data Set) online accessible online at www.eustar-online.org. The structure of the EUSTAR database has been described previously [8].

The names of the EUSTAR co-workers are reported in the Supplementary material 1.

For the purpose of the DeSScipher observational trials, the MEDS online database was extended and adapted according to the needs of the individual projects. The OT1 specific DeSScipher dataset included more than 30 supplementary clinical items in addition to three items on upper limb lesions contained in the original MEDS online database (digital ulcers, pitting scars on fingertips and gangrene). In particular, the DU section was characterised by the items displayed in Table 1.

The chosen definition of ulcers was the one proposed by the World Sleroderma Foundation (WSF) [9]. DUs were classified according to their main features into DU associated with digital pitting scars (DPS), with calcinosis and with gangrene and DU due to loss of tissue not associated with DPS or calcinosis (Pure DU) [10].

DUs were divided in not recurrent (only one episode) and recurrent DU.

All patients fulfilled American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) 2013 classification criteria for SSc [11]. Lung involvement was defined when signs of interstitial lung disease were detected at chest X-ray or high-resolution computed tomography (HRCT). Gastro-oesophageal symptoms were defined in MEDSONLINE as follows: esophageal symptoms (dysphagia, reflux) and/or stomach symptoms (early satiety, vomiting). Intestinal symptoms were defined as diarrhoea, bloating and constipation. End-stage organ involvement was defined as at least one of the following features: hyperalimentation required at present, oxygen required at present, left ventricle ejection fraction > 30% measured at the latest echocardiography and dialysis required at present.

Ethical approval had been obtained from all participating centres' local ethics committees according to Helsinki and its later amendments. Each patient signed a written informed consent form. Moreover, there was an external data monitoring as a part of study quality control.

OT1 data were collected prospectively from March 2013 to November 2016. For the purpose of this study, baseline demographic and clinical characteristics of patients enrolled in OT1 and data regarding DU were analysed. The inclusion criteria of OT1 were current treatment with vasoactive/vasodilating agents (intravenous iloprost, phosphodiesterase-5 (PDE-5) inhibitors such as sildenafil, endothelin receptor antagonists (ERAs) such as bosentan and/or CCBs) and/or ACE inhibitors.

At the time of the analysis (November 2017), clinical data of 1823 patients enrolled into OT1 were stored in the database.

The statistical analysis was performed by SPSS software, version 25. The results were expressed as mean ± standard deviation (SD), unless otherwise indicated. For group comparisons of continuous variables, the Mann–Whitney U test was used and, for categorical variables, chi-square test was used. A p value < 0.05 was considered statistically significant.

Results

In OT1, clinical data of 1823 enrolled patients were available. Two hundred and seventy-seven (15.2%) patients presented DU at the enrolment visit, 628 (34.4%) patients had previous DU while 918 (50.4%) patients had never experienced DU. Since it has been reported that first DU occurs around 3 years and a half after the onset of SSc [12] and that up to 70% of patients develop DU in the first 10 years [13], our study population was divided according to disease duration into the following: short disease duration (< 3 years) 318 (17.5%), intermediate disease duration (≥ 3 and < 5 years) 249 (13.7%), long disease duration (5–10 years) 455 (24.9%) and very long disease duration (> 10 years) 801 (43.9%) patients.

Table 2 shows that several demographic and clinical characteristics were significantly different between patients with and without DU and homogeneous disease duration. The features that were significantly different across all groups were

Table 1 Items of the DeSScipher project items on upper and lower limb DU

OT1 DeSScipher item	
Upper limb DU items Pitting scars fingertips	Lower limb ulcer items
Digital ulcers	Lower limbs: total number of DU
DU distal to the PIP	Lower limbs: history of DU
DU distal to the PIP: i.v. Iloprost last 3 months or present	Lower limbs: presence infection of DU
DU distal to the PIP: recurrent	Lower limbs: gangrene
Upper limbs: total number of DU distal to the PIP	Lower limbs: previous amputation
Upper limbs: history of DU distal to the PIP	Lower limbs/localisation of DU: patella
Upper limbs: presence of infection of DU distal to the PIP	Lower limbs/localisation of DU: malleoli
Upper limbs: gangrene	Lower limbs/localisation of DU: calcaneus
Upper limbs: previous amputation	Lower limbs/localisation of DU: toes
Upper limbs/localisation of DU PIP: fingertip	Lower limbs/localisation of DU: any other part of leg
Upper limbs/localisation of DU PIP: on bony prominence	Lower limbs/localisation of DU: unknown
Upper limbs/localisation of DU PIP: unknown	Lower limbs: number of new DU
Upper limbs: number of DU defined as loss of tissue	Lower limbs: number of DU healed
Upper limbs: number of DU due to calcinosis	Lower limbs: peripheral arterial disease
Upper limbs: number of DU due to digital pitting scars	Lower limbs: total number of DU
Upper limbs: number DU with unknown origin	Lower limbs: history of DU
Upper limbs: number of new DU	Lower limbs: presence infection of DU
Upper limbs: number of DU healed	Lower limbs: gangrene
Subcutaneous calcinosis of the hands	Lower limbs: previous amputation

age, disease subset and modified Rodnan skin score (mRSS) (Table 2).

Among 277 patients with current DU at the enrolment visit, 220 (79.4%) had previous DU, 143 (51.5%) had DU in the last 6 months, while for 57 (20.6%) patients it was the first DU. Demographic and clinical features and differences between patients with current and previous (healed) DU (items are in italic characters) are shown in Table 3.

Information on recurrent DU was available for 779 (86.1%) patients with DU; 428 (54%) patients with DU had recurrent DU. Clinical and demographic characteristics of patients with and without recurrent DU are shown in Table 3. Features that were significantly different between two groups are in bold characters.

Pharmacological treatment at the enrolment visit of OT1 is presented in Table 4.

Two hundred-ninety-five (32.6%) patients with DU and 116 (12.8%) patients without DU received two vasoactive/vasodilating drugs ($p < 0.001$), while 104 (11.5%) patients with DU and 18 (1.9%) without DU were treated with a combination of three or four different vasodilating/vasoactive agents ($p < 0.000$). The most commonly used drugs, in both patients with and without DU, were CCBs (71.6%), followed by intravenous iloprost (20.8%), ERAs (20.4%) and PDE-5 inhibitors (16.5%). Bosentan represented 91.4% of ERAs and sildenafil 92% of PDE-5 inhibitors prescribed.

Patients (904/1823) (49.6%) received CCBs alone: 598/908 (65.6%) patients without history of DU and 306/905 (33.8%) patients with DU (current/previous) ($p < 0.001$). Sixty-four out of 277 patients with current DU (23.1%) were on CCBs alone compared with 242/628 (38.5%) patients with previous (healed) DU ($p < 0.001$). Among 428 patients with recurrent DU, 101 (23.6%) were treated only with CCBs, compared with 159/351 (45.3%) patients with a single DU episode ($p < 0.001$).

Thirty-six out of 1823 (1.9%) patients were treated with a combination of prostanoids, PDE-5 inhibitors and ERAs, of which 24/36 (66.7%) were patients with recurrent DU. Only 13 out of 1823 patients (0.7%) were treated with a combination of CCBs, prostanoids, PDE-5 inhibitors and ERAs and 8 of them (61.5%) had recurrent DU. Ten percent of patients with DU received bosentan and sildenafil combination treatment, raising to 13% in patients with recurrent DU.

Drugs that were used significantly more frequently in patients with DU (current or previous) in comparison to those with no history of DU were the following: iloprost (33.8% vs 8.1%, $p < 0.001$), ERAs (32.7% vs 8.2%, $p < 0.001$), bosentan (31.4% vs 6.1%, $p < 0.001$), PDE-5 inhibitors (23.9% vs 9.2%, $p < 0.001$), sildenafil (22.7% vs 7.8%, $p < 0.000$) and combination of bosentan and sildenafil (9.4% vs 1.6%, $p < 0.001$) (for more details see items highlighted in bold green characters in Table 4).

Table 2 Demographic and clinical features of patients with and without DU and homogeneous disease duration

	SSc duration < 3 years (318 pts)		SSc duration 3–5 years (249 pts)		SSc duration 5–10 years (455 pts)		SSc duration > 10 years (801 pts)	
	Pts with DU (110/34.6%)	Pts without DU (208/65.4%)	Pts with DU (102/41%)	Pts without DU (147/59%)	Pts with DU (224/49.2%)	Pts without DU (231/50.8%)	Pts with DU (471/58.8%)	Pts without DU (330/41.2%)
Age (years)	50.7 ± 14.6	54.8 ± 14.1* p = 0.020	50.1 ± 13.5	55.8 ± 13.7* p = 0.002	54.1 ± 14.3	58 ± 12.6* P = 0.003	58.9 ± 12.3	62.7 ± 10.9* p < 0.001
Gender (n, %)								
Female	78 (70.9%)	157 (75.5%)	69 (67.6%)	117 (79.6%)	179 (79.9%)	195 (84.4%)	414 (87.9%)	303 (91.8%)
Male	32 (29.1%)	51 (24.5%)	33 (32.4%)	30 (20.4%)	45 (20.1%)	36 (15.6%)	57 (12.1%)	27 (8.2%)
Cutaneous subset (n, %)								
Limited	47 (42.7%)	134 (64.4%)* p < 0.001	45 (44.1%)	96 (65.3%)* p = 0.002	126 (56.3%)	159 (68.8%)* p = 0.010	319 (67.7%)	277 (83.9%)* p < 0.001
Diffuse	63 (57.3%)	74 (35.6%)* p < 0.001	57 (55.9%)	51 (34.7%)* p = 0.002	98 (43.8%)	72 (31.2%)* p = 0.010	152 (32.3%)	53 (16.1%)* p < 0.001
mRSS	11.5 ± 9.9	8.18 ± 9.8* p = 0.07	11.7 ± 10.3	5.7 ± 6.3* p < 0.001	9.4 ± 9.3	4.6 ± 5.4 p < 0.001	7.6 ± 7.3	3.2 ± 4.1* p < 0.001
SSc capillaroscopic pattern (n, %)								
Early	25 (22.7%)	89 (42.8%)	17 (16.7%)	55 (37.4%)	47 (21%)	79 (34.2%)* p = 0.005	73 (15.5%)	116 (35.2%)* p < 0.001
Active	49 (44.5%)	89 (42.8%)	51 (50%)	70 (47.6%)	75 (33.5%)	97 (42%)* p = 0.005	127 (27%)	131 (39.7%)* p < 0.001
Late	36 (32.7%)	30 (14.4%)	31 (30.4%)	22 (15%)	102 (45.5%)	55 (23.8%)* p = 0.005	271 (57.5%)	83 (25.2%)* p < 0.001
Autoantibody status (n, %)								
ANA +ve	109 (99.1%)	198 (95.2%)	98 (96.1%)	140 (95.2%)	220 (98.2%)	222 (96.1%)	461 (97.9%)	31 (96%)
ACA +ve	27 (24.5%)	71 (34.1%)	23 (22.5%)	56 (38.1%) p = 0.025	84 (37.5%)	86 (37.2%)	164 (34.8%)	140 (42.4%)
Scl70 +ve	55 (50%)	76 (36.5%)* p = 0.039	53 (52%)	61 (41.5%)	96 (42.9%)	80 (34.6%)	228 (48.4%)	69 (20.9%)
RNA pol III +ve	5 (4.5%)	28 (13.5%)	7 (6.9%)	12 (8.2%)	22 (9.8%)	14 (6.1%)	26 (5.5%)	18 (5.5%)
Pm-Scl +ve	6 (5.5%)	8 (3.8%)	5 (4.9%)	11 (7.5%)	8 (3.6%)	12 (5.2%)	15 (3.2%)	10 (3%)
Current cigarette smoking (n, %)	21 (19.1%)	29 (13.9%)	13 (12.7%)	17 (11.6%)	21 (9.4%)	29 (12.6%)	35 (7.4%)	31 (9.4%)
Puffy fingers (n, %)	59 (53.6%)	107 (51.4%)	52 (51%)	68 (46.3%)	107 (47.8%)	97 (42%)	174 (36.9%)	150 (45.5%)
Telangiectasias (n, %)	67 (60.9%)	112 (53.8%)	65 (63.7%)	81 (55.1%)	148 (66.1%)	155 (67.1%)	361 (76.6%)	227 (68.8%)
Joint contractures (n, %)	39 (35.5%)	59 (28.4%)	53 (52%)	57 (38.8%)	93 (41.5%)	75 (32.5%)	244 (51.8%)	120 (36.4%)
Tendon friction rubs (n, %)	14 (12.7%)	18 (8.7%)	9 (8.8%)	3 (2%)	13 (5.8%)	11 (4.8%)	30 (6.4%)	9 (2.7%)
Subcutaneous hand calcinosis (n, %)	10 (9.1%)	3 (1.4%)* p = 0.007	9 (8.8%)	4 (2.7%)	42 (18.8%)	15 (6.5%)* p < 0.001	142 (30.1%)	36 (10.9%)
Joint synovitis (n, %)	25 (22.7%)	24 (11.5%)* p = 0.012	17 (16.7%)	12 (8.2%)	23 (10.3%)	21 (9.1%)	53 (11.3%)	26 (7.9%)

Table 2 (continued)

	SSc duration < 3 years (318 pts)		SSc duration 3–5 years (249 pts)		SSc duration 5–10 years (455 pts)		SSc duration > 10 years (801 pts)	
	Pts with DU (110/34.6%)	Pts without DU (208/65.4%)	Pts with DU (102/41%)	Pts without DU (147/59%)	Pts with DU (224/49.2%)	Pts without DU (231/50.8%)	Pts with DU (471/58.8%)	Pts without DU (330/41.2%)
Gastro-esophageal symptoms (n, %)	64 (58.2%)	116 (55.8%)	72 (70.6%)	79 (53.7%)* p = 0.014	153 (68.3%)	155 (67.1%)	330 (70.1%)	215 (65.2%)
Intestinal symptoms (n, %)	24 (21.8%)	50 (24%)	33 (32.4%)	45 (30.6%)	50 (22.3%)	80 (34.6%)* p = 0.006	177 (37.6%)	128 (38.8%)
Lung fibrosis (Rx or HRCT) (n, %)	61 (55.5%)	100 (48.1%)	67 (65.7%)	74 (50.3%)* p = 0.032	141 (62.9%)	142 (61.5%)	330 (70.1%)	180 (54.5%)
Pulmonary hypertension at RHC (n, %)	5 (4.5%)	8 (3.8%)	7 (6.9%)	5 (3.4%)	14 (6.3%)	9 (3.9%)	39 (8.3%)	27 (8.2%)
Ventricular arrhythmias (n, %)	0 (0%)	2 (1%)	4 (3.9%)	6 (4.1%)	3 (1.3%)	0 (0%)	27 (5.7%)	8 (2.4%)
Renal crisis (n, %)	3 (2.7%)	4 (1.9%)	1 (1%)	5 (3.4%)	1 (.4%)	3 (1.3%)	6 (1.3%)	5 (1.5%)
End-stage organ involvement (n, %)	3 (2.7%)	7 (3.4%)	7 (6.9%)	5 (3.4%)	11 (4.9%)	4 (1.7%)	13 (2.8%)	5 (1.5%)

Pts patients, *n* number, *RP* Raynaud's phenomenon, *mRSS* modified Rodnan skin score, *ANA +ve* antinuclear antibodies positive, *ACA +ve* anti-centromere antibodies positive, *Scl70 +ve* anti-Scl70 (anti-topoisomerase) antibodies positive, *RNA pol III +ve* anti-RNA polymerase III antibodies positive, *Pm-Scl +ve* anti-Pml-Scl antibodies positive, *Rx* X-ray, *HRCT* high-resolution chest tomography, *RHC* right heart catheterisation. The values that were significantly different across all groups are highlighted in italic characters.

Sixty-five percent of patients with current DU at the enrolment visit were treated with CCBs, 50.2% with intravenous iloprost in and 40.8% with bosentan. Twenty-seven percent of SSc patients with current DU were on sildenafil and 13% on sildenafil and bosentan combination treatment. There was a total of 188/277 (67.5%) patients treated with bosentan, sildenafil or combination therapy in this group.

Drugs that were used significantly more frequently in patients with current DU compared with patients with previous (healed) DU are highlighted in bold purple characters in Table 4.

Patients with current DU were more frequently on iloprost (50.2% vs 26.6%, $p < 0.001$), ERAs (40.8% vs 29.1%, $p < 0.001$), PDE-5 inhibitors (28.2 vs 22%, $p = 0.046$) and sildenafil (20.7% vs 27.2%, $p = 0.036$) compared with patients with previous DU. There were significantly more patients on bosentan and on bosentan and sildenafil combination therapy in the group with current DU than in the group with previous (healed) DU (40.8% vs 27.2%, $p = 0.005$ and 13% vs 7.8%, $p = 0.014$, respectively). Of note, the proportion of patients with recurrent DU was higher among patients with current DU compared with those with previous DU (79.4% of vs 44.1%, $p < 0.000$).

Patients with recurrent DU were treated most frequently with CCBs (60.3%), followed by intravenous iloprost (47.7%), bosentan (38.1%), sildenafil (27.2%) and bosentan and sildenafil combination therapy (13.6%). There was a total of 279/428 (65.2%) patients on sildenafil, bosentan or combination therapy in this group.

Drugs that were used significantly more frequently in patients with recurrent DU in comparison to those with a single DU episode are highlighted in bold blue characters in Table 4.

Patients with recurrent DU received iloprost (47.7% vs 20.2%, $p < 0.000$), ERAs (39% vs 27.4%, $p < 0.001$) and bosentan (38.1% vs 25.4%, $p < 0.000$), PDE-5 inhibitors (28.7% vs 18.8%, $p < 0.001$), sildenafil (27.2% vs 18.2%, $p = 0.003$) and combination of sildenafil and bosentan (13.6% vs 5.4%, $p < 0.001$), more frequently than patients with single DU episode.

When patients with bosentan and sildenafil combination therapy were excluded from bosentan and sildenafil treatment groups respectively, there were no differences among patient with and without recurrent DU treated with sildenafil or bosentan alone (24.5% vs 19.9% and 13.6% vs 12.8%, respectively).

Of note, 25% of patients without recurrent DU were on bosentan treatment, alone or in combination with sildenafil. Only 4.8% of patients in this group had pulmonary hypertension (PH); therefore, this vasoactive therapy was most likely prescribed for peripheral vasculopathy.

Forty-six percent of patients were on anti-platelet treatment, regardless the history of DU, reaching 53% in patients with current DU.

Table 3 Demographic and clinical features of patients with and without current and recurrent DU

	Pts with current DU (277)	Pts with previous (healed) DU (628)	Pts with recurrent DU (428)	Pts without recurrent DU (351)
Age (years)	*53.4 ± 13.3*	*56.8 ± 13.7* (p < 0.001)*	55.2 ± 13.9	59.6 ± 13.6
Gender (*n, %*)				
Female	218 (78.8%)	518 (82.5%)	354 (82.7%)	289 (82.3%)
Male	59 (21.3%)	110 (17.5%)	74 (17.3%)	62 (17.7%)
Cutaneous subset (*n, %*)				
Limited	*143 (51.6%)*	*393 (62.6%)* (p = 0.003)*	**223 (52.1%)**	**289 (82.3%)* (p < 0.001)**
Diffuse	*134 (48.4%)*	*235 (37.4%)* (p = 0.003)*	**170 (17.3%)**	**62 (17.7%)* (p < 0.001)**
RP duration (years)	15.1 ± 11.4	15.1 ± 12	15.5 ± 10.9	14.7 ± 12.5
SSc duration (years)	12.1 ± 8.9	12.2 ± 9.2	12.4 ± 8.4	11.9 ± 10.1
mRSS	*11.7 ± 9.7*	*7.8 ± 8* (p < 0.001)*	**10.3 ± 8.9**	**6.2 ± 7.6 * p < 0.001**
SSc capillaroscopic pattern (*n, %*)				
Early	*69 (24.9%)*	*236 (37.6%)* (p = 0.002)*	**26 (6.1%)**	**46 (13.1%)*p < 0.001**
Active	*39 (14.1%)*	119 (18.9%)	**53 (12.4%)**	**73 (20.8%)*p < 0.001**
Late	*169 (61%)*	*273 (43.5%)* (p = 0.002)*	**122 (28.5%)**	**63 (17.9%)*p < 0.001**
Autoantibody status (*n, %*)				
ANA +ve	274 (98.9%)	612 (97.5%)	396 (92.5%)	325 (92.6%)
ACA +ve	82 (29.6%)	221 (35.1%)	**118 (27.6%)**	**120 (38.5%)*p = 0.034**
Scl70 +ve	*155 (55.9%)*	*276 (43.9%)*	**201 (47%)**	**127 (36.2%)*p = 0.002**
RNA pol III +ve	15 (5.4%)	47 (7.5%)	13 (3%)	15 (4.3%)
Pm-Scl +ve	12 (4.3%)	25 (4.0%)	10 (2.3%)	8 (2.3%)
Current cigarette smoking (*n, %*)	*34 (12.3%)*	*56 (8.9%)* p = 0.031*	38 (8.9%)	37 (10.5%)
Puffy fingers (*n, %*)	114 (41.2%)	226 (36%)	163 (38.1%)	140 (39.9%)
Telangiectasia (*n, %*)	*213 (76.8%)*	*420 (66.9%)* (p = 0.013)*	**310 (72.4%)**	**225 (64.1%)*p = 0.003**
Joint contractures (*n, %*)	*158 (57%)*	*270 (43%)* (p < 0.001)*	**245 (57.2%)**	**126 (35.9%)* p < 0.001**
Tendon friction rubs (*n, %*)	*30 (10.8%)*	*39 (6.2%)* (p = 0.015)*	**42 (9.8%)**	**18 (5.1%)* p = 0.014**
Subcutaneous hand calcinosis (*n, %*)	*77 (27.8%)*	*125 (20%)* (p = 0.014)*	**104 (24.3%)**	**60 (17.1%)* p = 0.007**
Joint synovitis (*n, %*)	40 (14.4%)	80 (12.7%)	52 (12.1%)	38 (10.8%)
Gastro-esophageal symptoms (*n, %*)	245 (88.5%)	432 (68.8%)	300 (70.1%)	232 (66.1%)
Intestinal symptoms (*n, %*)	84 (30.3%)	203 (32.3%)	130 (30.4%)	110 (31.5%)
Lung fibrosis (Rx or HRCT) (*n, %*)	196 (70.7%)	399 (63.6%)	**268 (62.6%)**	**166 (47.3%)*p < 0.001**
Pulmonary hypertension at RHC (*n, %*)	12 (4.3%)	30 (4.8%)	19 (4.4%)	17 (4.8%)
Ventricular arrhythmias (*n, %*)	11 (3.8%)	20 (3.2%)	5 (1.2%)	3 (0.9%)
Renal crisis (*n, %*)	2 (0.7%)	11 (1.8%)	5 (1.5%)	4 (1.1%)
End-stage organ involvement (*n, %*)	6 (2.2%)	28 (4.5%)	16 (3.7%)	13 (3.7%)

Pts patients, *RP* Raynaud's phenomenon, *mRSS* modified Rodnan skin score, *ANA +ve* antinuclear antibodies positive, *ACA +ve* anti-centromere antibodies positive, *Scl70 +ve* anti-Scl70 (anti-topoisomerase) antibodies positive, *RNA pol III +ve* anti-RNA polymerase III antibodies positive, *Pm-Scl +ve* anti-Pml-Scl antibodies positive, *Rx* X-ray, *HRCT* high-resolution chest tomography, *RHC* right heart catheterisation. The values that were significantly different between patients with current and previous DU are highlighted in italic characters. The values that were significantly different between patients with recurrent and not recurrent DU are highlighted in bold characters

There were no significant differences in the use of steroids and/or immunosuppressants in patients with and without DU. At least one out of two patients was treated with immunosuppressants and more than 40% of patients were on corticosteroids, regardless of the presence of DU. However, patients with the diffuse cutaneous subset received immunosuppressive therapy more frequently than patients with limited cutaneous SSc (69.4% vs 41.5%, p < 0.000). The most frequently used immunosuppressants were mycophenolate/mycophenolic acid (279 (33.1%)) and methotrexate (273 (32.4%)), followed by azathioprine (162 (19.2%)).

Table 4 Treatment at the enrolment visit

	Total OT1 (1823)	Patients with DU (current or previous) (905)	Patients without DU (never) (918)	Current DU (277)	Previous (healed) DU (628)	Recurrent DU (428)	Not recurrent DU (351)
CCBs	1305 (71.6%)	**601 (66.4%)**	**704 (76.8%)* (p < 0.000)**	180 (65%)	421 (67%)	**258 (60.3%)**	**254 (72.4%) (p < 0.001)***
Bosentan[1]	340 (18.7%)	**284 (31.4%)**	**56 (6.1)* (p < 0.001)**	113 (40.8%)	**171 (27.2%)* p < 0.001**	**163 (38.1%)**	**89 (25.4%)* p < 0.000**
Sildenafil[2]	277 (15.2%)	**205 (22.7%)**	**72 (7.8%)* (p < 0.001)**	75 (27.1%)	**130 (20.7%)* p = 0.036**	**116 (27.2%)**	**64 (18.2%)* p = 0.003**
Bosentan + Sildenafil	100 (5.5%)	**85 (9.4%)**	**15 (1.6%)* (p < 0.001)**	36 (13%)	**49 (7.8%)* p = 0.014**	**58 (13.6%)**	**19 (5.4%)* (p < 0.001)**
Iloprost iv in the last 3 months	381 (20.8%)	**306 (33.8%)**	**74 (8.1%)* (p < 0.001)**	139 (50.2%)	**167 (26.6%) * (p < 0.000)**	**200 (47.7%)**	**71 (20.2%)* (p < 0.000)**
ERA″	372 (20.4%)	**296 (32.7%)**	**75 (8.2%)* (p < 0.001)**	113 (40.8%)	**183 (29.1%)* (p < 0.001)**	**167 (39%)**	**96 (27.4%)* (p < 0.001)**
PDE-5i°	301 (16.5%)	**216 (23.9%)**	**84 (9.2%)* (p < 0.001)**	78 (28.2%)	**138 (22%)* (p = 0.046)**	**123 (28.7%)**	**66 (18.8%)* (p < 0.001)**
Two vasodilating/vasoactive agents	411 (22.5%)	**295 (32.6%)**	**116 (12.8%)* (p < 0.001)**	110 (39.7%)	**185 (29.5%)* (p = 0.002)**	151 (35.3%)	106 (30.2%)
Three or more vasodilating/vasoactive agents	123 (6.7%)	**104 (11.5%)**	**18 (1.9%)* (p < 0.001)**	51 (18.4%)	**53 (8.4%)* (p < 0.001)**	**74 (17.3%)**	**21 (5.9%)* (p < 0.001)**
No vasodilating/vasoactive therapy^	145 (7.9%)	**48 (5.3%)**	**97 (10.6%)* (p < 0.001)**	10 (3.6%)	**38 (6.1%)* (p < 0.001)**	27 (6.3%)	14 (3.9%)
Anti-platelet agents	846 (46.4%)	417 (46.1%)	429 (46.8%)	147 (53.1%)	**270 (43%)* (p = 0.005)**	214 (50%)	152 (43.3%)
Corticosteroids	769 (42.2%)	386 (42.7%)	383 (41.8%)	121 (43.7%)	265 (42.2%)	193 (45.1%)	139 (36.9%)
Immunosuppressants	928 (50.9%)	475 (52.5%)	453 (49.3%)	154 (55.6%)	321 (51.1%)	228 (53.3%)	174 (49.6%)

CCBs calcium channel blockers [1] Including combination with sildenafil [2] Including combination with bosentan ″ERA (endothelin receptor antagonist) = bosentan, ambrisentan, macitentan °PDE-5i (phosphodiesterase 5 inhibitors) = sildenafil, tadalafil, vardenafil ^No vasodilating/vasoactive therapy. The values that were significantly different across groups (patients with DU vs patients without DU; patients with current DU vs patients with previous DU; patients with recurrent DU vs patients with no recurrent DU) are highlighted in bold characters

Discussion

This is the first study that describes the current use of vasoactive/vasodilating agents for SSc-related DU in expert centres, including more than 1800 patients with DU, enrolled in a large multicentre cohort. The observational design of the DeSScipher project with real-life data reflects current clinical practice in tertiary centres for SSc management across Europe.

The prevalence of DU in this study cohort was 49%, higher than recently reported in a large EUSTAR cohort in which 34% of SSc patients had a history of DU [5]. This is related to the fact that OT1 was designed to be focused on use of vasoactive/vasodilating drugs for DU; therefore, patients with severe peripheral vasculopathy were recruited.

The proportion of patients with DU (current or previous) increased with SSc duration as expected. After stratifying the patients for disease duration, patients with DU (current or previous) were younger, had more frequently a diffuse cutaneous subset and had higher mRSS compared with patients without DU. Diffuse disease subset [8, 14–18] and high mRSS [15–18,19] have already been identified as strong risk factors for DU in SSc in large cohort studies.

Interestingly, there were no significant differences in the prevalence of PH in patients with DU compared with those without DU history, differently from what we expected. In addition, smoking habit was associated with current DU, but not DU history, differently from what suggested is by a previous systematic review [16] and a recent EUSTAR-based prospective study [20].

In our study, 94.7% of patients with DU (current and/or previous) and 89.4% of patients without DU history were treated with CCBs, iloprost, ERAs and/or PDE-5 inhibitors. The high proportion of treated subjects was correlated to the inclusion criteria. Since the prevalence of PH in these two groups was 4.9% and 3.3% respectively, these vasoactive/vasodilating drugs were given mainly for peripheral vasculopathy.

The most commonly used drugs in our cohort, in both patients with and without DU, were CCBs, followed by intravenous iloprost, ERAs and PDE-5 inhibitors. A similar distribution was reported in a large German cohort [21]. On the contrary, in the Canadian cohort only, a very small proportion of patients was on iloprost or bosentan (< 10%), but at the time when the article was published, these drugs had not been approved for DU in Canada [22].

Patients without a history of DU were treated more frequently with CCBs alone and less frequently with intravenous iloprost and PDE-5 inhibitors, compared with patients with current and/or previous DU. This clearly reveals the intention to treat patients with second line drugs in the presence of DU. In fact, the EULAR recommendations indicate the use of CCBs, usually oral nifedipine, as a first-line treatment for SSc-related Raynaud's phenomenon (RP) [7].

Regarding patients with current DU, half of them were treated with intravenous iloprost, alone or in combination with oral drugs (CCBs, PDE-5 inhibitors, ERAs), while half of them received only oral therapy. In addition, 67% of the patients with current DU were on bosentan, sildenafil or bosentan and sildenafil combination treatment.

The EULAR recommendations suggest that PDE-5 inhibitors should be considered for the treatment of DU and advise intravenous iloprost in patients with DU not responding to oral therapy [7]. The use of bosentan is recommended in patients with multiple DUs despite treatment with other vasodilators, such as CCBs, PDE-5 inhibitors and iloprost, to prevent the development of new DUs [7].

In our cohort, 28% of patients with current DU received PDE-5 inhibitors, compared with 40% and 50% of patients treated with bosentan and iloprost respectively. This relatively lower usage of PDE-5 inhibitors is probably related to the fact that this drug class has not yet been approved for DU management in Europe.

Patients with recurrent DU were on bosentan and/or sildenafil in 65% of cases. They were treated more frequently with these two drugs compared with patients with single a DU episode, but surprisingly, when bosentan was considered alone (not in association with sildenafil), no difference was observed between patients with and without recurrent DU.

In addition, 25% of patients without recurrent DU were on bosentan prescribed for peripheral vasculopathy, alone or in combination with sildenafil, despite the lack of approved drug indication.

Our results indicate that a relatively low proportion of patients were on combination treatment of two or more vasodilating/vasoactive agents: 39% and 18% of patients with current DU and 35% and 17% of patients with recurrent DU received two and three or more drugs respectively. This may reflect the concern of prescribing physicians about the potential drug-related side effect that may be enhanced using different classes of drugs concomitantly.

On the other hand, 23% of patients with current and recurrent DU were on CCBs alone, indicating that around one out of four patients with DU are probably still undertreated, even in expert centres.

Of note that half of the patients were on anti-platelet treatment, regardless the history of DU. This probably reflects the perceived importance of platelets' role in the pathogenesis of SSc-related vasculopathy [23], although no study has addressed the use of these drugs for DU or for other SSc manifestations.

In addition, our results show that more than half of the patients were on immunosuppressive treatment and more than 40% received steroid therapy, regardless the presence of DU.

This study has a number of limitations. The main limitation is represented by the fact that the study included only patients on vasoactive/vasodilating therapies currently in use for peripheral vasculopathy and DU or patients on ACE inhibitors. Other major limitations are the cross-sectional design (the analysis of the OT1 baseline data only) and the fact that the

participants were represented by the expert tertiary centres that may lead to overestimation of specific drug use in clinical practice. No sub-analysis for different PDE-5i, ERAs and prostanoids, other than sildenafil, bosentan and iloprost, was done, due to the small number of patients treated with these agents. We did not perform sub-analysis for use of ACE inhibitors or for different types of CCBs.

Most importantly, the use of specific combinations of different vasoactive/vasodilating agents, other than sildenafil and bosentan, was not assessed, due to the large number of possible drug associations. In addition, the use of other drugs, such as pentoxifylline and nitrates, was not investigated in this study.

We did not assess the use of different agents for the treatment of different subtypes of DU with possibly diverse pathogenesis (pure DU, DU due to DPS or calcinosis). Finally, we investigated only pharmacological systemic treatment for DU, and not local therapies, which may vary even across the expert centres and impact DU outcome.

Conclusions

Our study shows that CCBs are still the most commonly used agents for DU management in SSc.

In the expert centres, the proportion of patients on combination therapy with more than one vasodilating/vasoactive drug was still low, even in patients with recurrent DU: almost one out of four patients with current and recurrent DU was on CCBs alone. Prospective analysis is planned to investigate the efficacy of different drugs/drug combinations on DU healing and prevention.

Compliance with ethical standards

Disclosures None.

Ethical approval Ethical approval had been obtained from all participating centres' local ethics committees, according to the declaration of Helsinki and its later amendments. Each patient signed a written informed consent form.

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