Use of vasoactive/vasodilating drugs for systemic sclerosis (SSc) related digital ulcers (DU) 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 trial.

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%). 32.6% of patients with DU and 12.8% patients without DU received two drugs ($p<0.001$), while 11.5% patients with DU and 1.9% without DU were treated with 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.

Keywords: systemic sclerosis, digital ulcer, management

Introduction

Systemic sclerosis (SSc) is characterised by a complex pathogenesis where tissue and vascular fibrosis cause tissue ischemia through vessel narrowing and loss of capillaries [**1,2**]. Consequently, one of the major complications affecting the extremities are digital ulcers (DU) 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 either local and systemic treatment. In practice, a wide choice of vasoactive and vasodilating drugs, as calcium channel blockers (CCBs), sildenafil, iloprost and bosentan, are at disposal of the physician [**7**] but no head-to-head comparative studies are still available.

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*). The OT1 trial 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 trial.

Materials and methods

The DeSScipher project was based on use of the EUSTAR (European Scleroderma Trials and Research group) long-term databank MEDS online (Minimal Essential Data Set) accessible online at www.eustar-online.org. The structure of the EUSTAR database has been described previously [**8**]. For the purpose of the DeSScipher observational trials, the MEDS online data base 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 **Figure 1**.

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

DU were categorised as follows [**3**]:

- Episodic DU (rarely recurrent DU) defined as DU detected only at 1 follow-up visit and absence of DU at the remaining follow-up visits
- Recurrent DU (frequently recurrent DU) defined as DU detected at 2 or more follow-up visits and absence of DU on at least 1 follow-up visit
- Chronic DU defined as one or more DU and/or new DU detected at every follow-up visit.

All patients fulfilled ACR/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: oesophageal symptoms (dysphagia, reflux) and/or stomach symptoms (early satiety, vomiting). Intestinal symptoms were defined as diarrhoea, bloating, 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, dialysis required at present.

Ethical approval had been obtained from all participating centres' local ethics committees. 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 the OT1 and data regarding DU were analysed. The inclusion criteria of the OT1 were current treatment with vasoactive/vasodilating agents (Bosentan and Sildenafil, intravenous Iloprost, phosphodiesterase-5 (PDE5) inhibitors, endothelin receptor antagonists (ERAs), 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 data base.

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. P value<0.05 was considered statistically significant.

Results

In the OT1, clinical data of 1823 enrolled patients were available: 277 (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. Demographic and clinical characteristics of the study population (**Table 1**) show that several clinical features were significantly different between patients with DU (current or previous) and patients with no history of DU (items highlighted in bold red characters).

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 highlighted in bold green characters) are shown in **Table 1**.

Information on recurrent DU were 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 2**. Features that were significantly different between two groups are highlighted in red bold characters.

Pharmacological treatment at the enrolment visit of the OT1 is presented in **Table 3**.

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 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.

904/1823 patients (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 to 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 to 159/351 (45.3%) patients with single DU episode ($p<0.001$).

Thirty-six out of 1823 (1.9%) patients were treated with 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 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: 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 3**).

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 to patients with previous (healed) DU are highlighted in bold purple characters in **Table 3**.

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 to patients with previous DU. There were significantly more patients on Bosentan, and on Bosentan and Sildenafil combination therapy in group with current DU than in group with previous (healed) DU (40.8% vs 27.2%, $p=0.005$ and 13% vs 7.8%, $p=0.014$, respectively). Of note that the proportion of

patients with recurrent DU was higher among patients with current DU compared to those with previous DU (79.4% of vs 44.1%, p<0.000).

Patient 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 3.**

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) and 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 then 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 that 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.

There were no significant differences in the use of steroids and/or immunosuppressants in patients with and without DU. At least 1 out of 2 patients was treated with immunosuppressants and more than 40% of patients were on corticosteroids, regardless of the presence of DU. However, patients with diffuse cutaneous subset received more frequently with immunosuppressive therapy compared to patients with limited 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%)).

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 DU history [**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.

Patients with DU (current or previous) were more frequently anti-topoisomerase positive, had more frequently diffuse cutaneous subset and higher modified Rodnan skin score (mRSS), gastro-esophageal symptoms and lung fibrosis on lung Rx or HRCT compared to patients without DU. Diffuse disease subset [**8, 12-16**], anti-topoisomerase antibodies [**15,17-20**] and high mRSS [**13-16,19**] have been already identified as strong risk factors for DU in SSc in large cohort studies. Association of oesophageal involvement and DU have been shown in the analysis of the registry of the German Network for Systemic Sclerosis [**17**], and interstitial lung disease was among the most important predictive factors for DU occurrence in a Canadian Scleroderma Research Group registry [**15**].

Patients with DU had longer RP and disease duration, and had more frequently late scleroderma capillaroscopic pattern and telangiectasias than patients without DU. Potential role of telangiectasias [**21**] and late pattern [**16,22-24**] as risk factors for DU has been suggested previously.

In addition, joint contractures, tendon friction rubs and subcutaneous hand calcinosis were more frequently observed in patients with DU and with recurrent DU, suggesting the potential role of mechanical

factors /trauma in DU pathogenesis and recurrence. Of note that this study analysed only DU distal to interphalangeal proximal joints, therefore considered of ischemic origin [**25**, **26**].

Interestingly, there were no significant differences in the prevalence of PH in patients with DU compared to 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 by a previous systematic review [**16**] and a recent EUSTAR based prospective study [**27**].

In out 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 [**28**]. 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 [**29**].

Patients without history of DU were treated more frequently with CCBs alone and less frequently with intravenous Iloprost and PDE-5 inhibitors, compared to 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 was 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, Sildanafil, 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 received PDE-5 inhibitors, compared to 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 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 to patients with single 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 relatively low proportion of patients was 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 [**30**], 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 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, as pentoxyfilin, nitrates etc 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.

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

References:

1. **Varga J**, Trojanowska M, Kuwana M (2017) Pathogenesis of systemic sclerosis: recent insights of molecular and cellular mechanisms and therapeutic opportunities. J scleroderma relat disord 2: 137 - 152
2. **van Laar JM**, Varga J (2015) The immunopathology of systemic sclerosis. Semin Immunopathol 37:439-41.
3. **Matucci-Cerinic M**, Krieg T, Guillevin L, Schwierin B, Rosenberg D, Cornelisse P et al (2016) Elucidating the burden of recurrent and chronic digital ulcers in systemic sclerosis: long-term results from the DUO Registry. Ann Rheum Dis 75:1770-6
4. **Allanore Y**, Denton CP, Krieg T, Cornelisse P, Rosenberg D, Schwierin B et al; DUO Investigators (2016) 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 75:1736-40.
5. **Mihai C**, Landewé R, van der Heijde D, Walker UA, Constantin PI, Gherghe AM et al (2016) Digital ulcers predict a worse disease course in patients with systemic sclerosis Ann Rheum Dis. 75:681-6.
6. **Meunier P**, Dequidt L, Barnetche T, Lazaro E, Duffau P, Richez C et al. (2018) Increased risk of mortality in systemic sclerosis-associated digital ulcers: a systematic review and meta-analysis. J Eur Acad Dermatol Venereol. https://doi.org/10.1111/jdv.15114. [Epub ahead of print]
7. **Kowal-Bielecka O**, Fransen J, Avouac J, Becker M, Kulak A, Allanore Y et al; EUSTAR Coauthors (2017) Update of EULAR recommendations for the treatment of systemic sclerosis. Ann Rheum Dis 76(8):1327-1339.

8. **Walker UA**, Tyndall A, Czirják L, Denton C, Farge-Bancel D, Kowal-Bielecka O et al. (2017) Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database. Ann Rheum Dis 66(6): 754-63.
9. **Suliman YA**, Bruni C, Johnson SR, Praino E, Alemam M, Borazan N et al. Defining Skin Ulcers in Systemic Sclerosis: Systematic Literature Review and Proposed World Scleroderma Foundation (WSF) Definition (2017) J scleroderma relat disord 2: 115 – 120.
10. **Amanzi L**, Braschi F, Fiori G, Galluccio F, Miniati I, Guiducci S, et al. Digital ulcers in scleroderma: staging, characteristics and sub-setting through observation of 1614 digital lesions (2010) Rheumatology (Oxford) 49: 1374-82.
11. **van den Hoogen F**, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A et al (2013) Classification Criteria for Systemic Sclerosis: An ACR-EULAR Collaborative Initiative. Arthritis Rheum. 65: 2737–2747.
12. **Ferri C**, Valentini G, Cozzi F, Sebastiani M, Michelassi C, La Montagna G, et al. Systemic sclerosis: demographic, clinical, and serologic features and survival in 1,012 Italian patients. Medicine 2002;81(2):139–53.
13. **Hachulla E**, Clerson P, Launay D, Lambert M, Morell-Dubois S, Queyrel V, et al. Natural history of ischemic digital ulcers in systemic sclerosis: single-center retrospective longitudinal study. J Rheumatol 2007;34(12):2423–30.
14. **Tiev KP**, Diot E, Clerson P, Dupuis-Simeon F, Hachulla E, Hatron PY, et al. Clinical features of scleroderma patients with or without prior or current ischemic digital ulcers: post-hoc analysis of a nationwide multicenter cohort (ItinerAIR-Sclerodermie). J Rheumatol 2009;36(7):1470–6.
15. **Khimdas S**, Harding S, Bonner A, Zummer B, Baron M, Pope J. Associations with digital ulcers in a large cohort of systemic sclerosis: results from the Canadian Scleroderma Research Group registry. Arthritis Care Res 2011;63(1):142–9.

16. **Silva I,** Teixeira A, Oliveira J, Almeida I, Almeida R, Águas A, Vasconcelos C. Endothelial Dysfunction and Nailfold Videocapillaroscopy Pattern as Predictors of Digital Ulcers in Systemic Sclerosis: a Cohort Study and Review of the Literature.Clin Rev Allergy Immunol. 2015;49(2):240-52
17. **Sunderkotter C**, Herrgott I, Bruckner C, Moinzadeh P, Pfeiffer C, Gerss J, et al. Comparison of patients with and without digital ulcers in systemic sclerosis: detection of possible risk factors. Br J Dermatol 2009;160(4):835–43.
18. **Simeon-Aznar CP**, Fonollosa-Pla V, Tolosa-Vilella C, Espinosa-Garriga G, Ramos-Casals M, Campillo-Grau M, et al. Registry of the Spanish network for systemic sclerosis: clinical pattern according to cutaneous subsets and immunological status. Semin Arthritis Rheum 2012;41(6):789–800.
19. **Xu D**, Li MT, Hou Y,Wang Q, Hu CJ, Song N, et al. Clinical characteristics of systemic sclerosis patients with digital ulcers in China. Clin Exp Rheumatol 2013;31(2 Suppl. 76):46–9.
20. **Wirz EG**, Jaeger VK, Allanore Y, Riemekasten G, Hachulla E, Distler O, Airò P, Carreira PE, Tikly M, Vettori S, Balbir Gurman A, Damjanov N, Müller-Ladner U, Distler J, Li M, Häusermann P, Walker UA; EUSTAR coauthors. Incidence and predictors of cutaneous manifestations during the early course of systemic sclerosis: a 10-year longitudinal study from the EUSTAR database. Ann Rheum Dis. 2016;75(7):1285-92
21. **Zhang SZ**, Xu D, Li MT, Hou Y, Wang Q, Tian Z, Liu YT, Guo XX, Lai JZ, Zhao JL, Hu CJ, Song N, Sun QN, Zhang FC, Zhao Y, Zeng XF. Telangiectasia as a potential clinical marker of microvascular lesions in systemic sclerosis patients from EUSTAR data in China. Clin Exp Rheumatol. 2015;33(4 Suppl 91): S106-10
22. **Caramaschi P**, Canestrini S, Martinelli N, Volpe A, Pieropan S, Ferrari M, et al. Scleroderma patients nailfold videocapillaroscopic patterns are associated with disease subset and disease severity. Rheumatology (Oxford) 2007;46(10):1566–9.
23. **Caramaschi P**, Martinelli N, Volpe A, Pieropan S, Tinazzi I, Patuzzo G, et al. A score of risk factors associated with ischemic digital ulcers in patients affected by systemic sclerosis treated with iloprost. Clin Rheumatol 2009;28(7):807–13.

24. **Smith V**, Riccieri V, Pizzorni C, Decuman S, Deschepper E, Bonroy C, et al. Nailfold capillaroscopy for prediction of novel future severe organ involvement in systemic sclerosis. J Rheumatol 2013;40(12):2023–8.
25. **Galuccio F**, Matucci-Cerinic M. Two faces of the same coin: Raynaud phenomenon and digital ulcers in systemic sclerosis, Autoimmun Rev. 2011; 10(5):241-3.
26. **Bruni C**, Guiducci S, Bellando-Randone S, Lepri G, Braschi F, Fiori G, et al. Digital ulcers as a sentinel sign for early internal organ involvement in very early systemic sclerosis. Rheumatology (Oxford). 2015; 54(1): 72-6
27. **Jaeger VK**, Valentini G, Hachulla E, Cozzi F, Distler O, Airó P, Czirják L, et al. Smoking in Systemic Sclerosis: a Longitudinal European Scleroderma Trials and Research Group Study. Arthritis Rheumatol. 2018. doi: 10.1002/art.40557. [Epub ahead of print]
28. **Moinzadeh P**, Riemekasten G, Siegert E, Fierlbeck G, Henes J, Blank N, Melchers I, et al ; German Network for Systemic Scleroderma. Vasoactive Therapy in Systemic Sclerosis: Real-life Therapeutic Practice in More Than 3000 Patients; J Rheumatol. 2016;43(1):66-74.
29. **Pope J**, Harding S, Khimdas S, Bonner A, Baron M; Canadian Scleroderma Research Group. Agreement with guidelines from a large database for management of systemic sclerosis: results from the Canadian Scleroderma. J Rheumatol. 2012;39(3):524-31.
30. **Ntelis K**, Solomou EE, Sakkas L, Liossis SN, Daoussis D. The role of platelets in autoimmunity, vasculopathy, and fibrosis: Implications for systemic sclerosis. Semin Arthritis Rheum. 2017;47(3):409-417.

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

OT1 DeSScipher item

Upper limb DU items	*Lower limb ulcer items*
Pitting scars fingertips	
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 hands	Lower limbs: previous amputation

Table 1. Demographic and clinical features of the OT1 study population

	OT1 total (1823 patients)	**Patients with DU (current or previous) (905)**	**Patients without DU (never developed) (918)**	**Patients with current DU (277)**	**Patients with previous (healed) DU (628)**
Age (years)	57.3 ± 13.4	**55.8 ± 13.7**	**58.7 ± 12.9* (p<0.001)**	**53.4 ± 13.3**	**56.8 ± 13.7* (p<0.001)**
Gender (n,%) Female Male	 1511 (82.9%) 312 (17.1%)	 736 (81.3%) 169 (18.7%)	 776 (84.5%) 142 (15.5%)	 218 (78.8%) 59 (21.3%)	 518 (82.5%) 110 (17.5%)
Cutaneous subset (N,%) Limited Diffuse	 1207 (66.2%) 616 (33.8%)	 **536 (59.2%)*** **369 (40.8%)***	 **673(73.3%) *(p<0.001)** **245 (26.7%)* (p<0.001)**	 **51.6** **48.4**	 **62.6* (p=0.003)** **37.4* (p=0.003)**
RP duration (years)	14 ± 11.7	**15.1 ± 11.8**	**12.9 ± 11.5*(p<0.001)**	15.1± 11.4	15.1 ± 12
SSc duration (years)	10.1 ± 8.9	**12.2 ± 9.1**	**9.5 ± 8.6*(p<0.001)**	12.1 ± 8.9	12.2 ± 9.2
mRSS	6.9 ± 8	**8.9 ± 8.7**	**5 ± 6.7*(p<0.001)**	**11.7 ± 9.7**	**7.8±8*(p<0.001)**
SSc capillaroscopic pattern (n,%) Early	 492 (27%)	 **160 (17.7%)***		 **25**	 **37.6* (p=0.002)**

Active Late	695 (38.1%) 636 (34.9%)	**310 (34.3%)*** **434 (48%)***	**338 (36.8%)* (p<0.001)** **386 (42%) * (p<0.001)** **194 (21.1%)* (p<0.001)**	14.3 **60.7**	19 **43.4*(p=0.002)**
Autoantibody status (n,%) ANA +ve ACA +ve Scl70 +ve RNA pol III +ve Pm-Scl +ve	 1763 (96.7%) 662 (36.3%) 716 (39.3%) 133 (7.3%) 78 (4.3%)	 886 (97.9%) **302 (33.4%)*** **431 (47.6%)*** 62 (6.9%) 37 (4.1%)	 877 (95.5%) **360 (39.2%)* (p=0.016)** **286 (31.2%)* (p<0.001)** 70 (7.6%) 40 (4.4%)	 274 (98.9%) 82 (29.6%) **155 (55.9%)** 15 (5.4%) 12 (4.3%)	 612 (97.5%) 221 (35.1%) **276 (43.9%)** 47 (7.5%) 25 (4.0%)
Current cigarette smoking (n,%)	195 (10.7%)	90 (9.9%)	106 (11.5%)	**34 (12.3%)**	**56 (8.9%)* p=0.031**
Puffy fingers (n,%)	731 (40.1%)	**340 (37.6%)***	**390 (42.5%)* (p=0.001)**	114 (41.2%)	36
Teleangectasias (n,%)	1220 (66.9%)	**643 (71%)***	**578 (63%)* (p<0.001)**	**213 (76.8%)**	**420 (66.9%)* (p=0.013)**
Joint contractures (n,%)	729 (40%)	**428 (47.3%)***	**301 (32.8%)* (p<0.001)**	**158 (57%)**	**270 (43%)* (p<0.001)**
Tendon friction rubs (n,%)	109 (6%)	**69 (7.6%)***	**41 (4.5%)* (p=0.005)**	**30 (10.8%)**	**39 (6.2%)* (p=0.015)**
Subcutaneous hand calcinosis (n,%)	244 (13.4%)	**188 (20.8%)***	**58 (6.3%)* (p<0.001)**	**77 (27.8%)**	**125 (20%)* (p=0.014)**
Joint synovitis (n,%)	208 (11.4%)	**120 (13.3%)***	**88 (9.6%)* (p=0.015)**	40 (14.4%)	80 (12.7%)
Gastro-esophageal Symptoms (n,%)	1216 (66.7%)	**634 (70%)***	**582 (63.4%)* (p=0.002)**	245 (88.5%)	432 (68.8%)
Intestinal symptoms (n,%)	589 (32.3%)	287 (31.7%)	300 (32.7%)	84 (30.3%)	203 (32.3%)
Lung fibrosis (Rx or HRCT) (n,%)	1090 (59.8%)	**595 (65.7%)***	**496 (54%)* (p<0.001)**	196 (70.7%)	399 (63.6%)
Pulmonary hypertension at RHC (n,%)	71 (3.9%)	42 (4.6%)	30 (3.3%)	12 (4.3%)	30 (4.8%)
Ventricular arrhythmias (n,%)	44 (2.4%)	31 (3.4%)	16 (1.7%)	11 (3.8%)	20 (3.2%)
Renal crisis (%)	31 (1.7%)	13 (1.4%)	18 (2%)	2 (0.7%)	11 (1.8%)
Endstage organ involvement (n,%)	60 (3.3%)	34 (3.8%)	25 (2.7%)	6 (2.2%)	28 (4.5%)

N = number; RP =Raynaud's phenomenon; mRSS =modified Rodnan skin score; ANA+ve= antinuclear antibodies positive; ACA=anti-centromere antibodies positive, Scl70= 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

Table 2. Demographic and clinical features of patients with and without recurrent DU

	Patients with recurrent DU (428)	**Patients without recurrent DU (351)**

Age (years)	55.2 ± 13.9	59.6 ± 13.6
Gender (n,%) Female Male	 354 (82.7%) 74 (17.3%)	 289 (82.3%) 62 (17.7%)
Cutaneous subset (n,%) Limited Diffuse	 **223 (52.1%)** **170 (17.3%)**	 **289 (82.3%) *(p<0.00q)** **62 (17.7%) *(p<0.00q)**
RP duration (years)	15.5 ± 10.9	14.7 ± 12.5
SSc duration (years)	12.4 ± 8.4	11.9 ± 10.1
mRSS	**10.3 ± 8.9**	**6.2 ± 7.6 * p<0.001**
SSc capillaroscopic pattern (n,%) Early Active Late	 **26 (6.1%)** **53 (12.4%)** **122 (28.5%)**	 **46 (13.1%)*p<0.001** **73 (20.8%)*p<0.001** **63 (17.9%)*p<0.001**
Autoantibody status (n,%) ANA +ve ACA +ve Scl70 +ve RNA pol III +ve Pm-Scl +ve	 396 (92.5%) **118 (27.6%)** **201 (47%)** 13 (3%) 10 (2.3%)	 325 (92.6%) **120 (38.5%)*p=0.034** **127 (36.2%)*p=0.002** 15 (4.3%) 8 (2.3%)
Current cigarette smoking (n,%)	38 (8.9%)	37 (10.5%)
Puffy fingers (n,%)	163 (38.1%)	140 (39.9%)
Teleangectasia (n,%)	**310 (72.4%)**	**225 (64.1%)*p=0.003**
Joint contractures (n,%)	**245 (57.2%)**	**126 (35.9%)* p<0.001**
Tendon friction rubs (n,%)	**42 (9.8%)**	**18 (5.1%)* p =0.014**
Subcutaneous hand calcinosis (n,%)	**104 (24.3%)**	**60 (17.1%)* p =0.007**
Joint synovitis (n,%)	52 (12.1%)	38 (10.8%)
Gastro-esophageal Symptoms (n,%)	300 (70.1%)	232 (66.1%)
Intestinal symptoms (n,%)	130 (30.4%)	110 (31.5%)
Lung fibrosis (Rx or HRCT) (n,%)	**268 (62.6%)**	**166 (47.3%)*p<0.001**
Pulmonary hypertension at RHC (n,%)	19 (4.4%)	17 (4.8%)
Ventricular arrhythmias (n,%)	5 (1.2%)	3 (0.9%)
Renal crisis (n,%)	5 (1.5%)	4 (1.1%)
Endstage organ involvement (n,%)	16 (3.7%)	13 (3.7%)

RP =Raynaud's phenomenon; mRSS =modified Rodnan skin score; ANA+ve= antinuclear antibodies positive; ACA=anti-centromere antibodies positive, Scl70= 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

Table 3. 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~	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°	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<0.001)**	**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; ~ including combination with Sildenafil, ° including combination with Bosentan, *ERA (endothelin receptor antagonist) =Bosentan, Ambrisentan, Macitentan; ** PDE-5i (phosphodiesterase 5 inhibitors) =Sildenafil, Tadalafil, Vardenafil; ^= no vasodilating/vasoactive therapy

Supplementary 1.

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