OPEN ACCESS

EXTENDED REPORT

Elucidating the burden of recurrent and chronic digital ulcers in systemic sclerosis: long-term results from the DUO Registry

Marco Matucci-Cerinic,[1] Thomas Krieg,[2] Loic Guillevin,[3] Barbara Schwierin,[4] Daniel Rosenberg,[4] Peter Cornelisse,[4] Christopher P Denton[5]

Handling editor Tore K Kvien

▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2015-208121).

[1]Department of Experimental and Clinical Medicine, Division of Rheumatology AOUC, University of Florence, Florence, Italy
[2]Department of Dermatology, University of Cologne, Cologne, Germany
[3]Department of Internal Medicine, Centre de Référence pour les Vascularites Nécrosantes et la Sclérodermie Systémique, Hôpital Cochin, Assistance Publique-Hôpitaux de Paris, Université Paris Descartes, Sorbonne Paris Cité, Paris, France
[4]Actelion Pharmaceuticals Ltd, Allschwil, Switzerland
[5]Centre for Rheumatology and Connective Tissue Diseases, Royal Free Hospital, London, UK

Correspondence to
Professor Marco Matucci-Cerinic, Department of Rheumatology AVC, Denothe Centre, University of Florence, Florence, Italy;
cerinic@unifit.it

Received 23 June 2015
Revised 30 September 2015
Accepted 27 October 2015
Published Online First 26 November 2015

To cite: Matucci-Cerinic M, Krieg T, Guillevin L, *et al*. *Ann Rheum Dis* 2016;**75**:1770–1776.

ABSTRACT

Objectives Digital ulcers (DUs) occur in up to half of patients with systemic sclerosis (SSc) and may lead to infection, gangrene and amputation with functional disability and reduced quality of life. This study has elucidated the burden of SSc-associated DUs through identification of four patient categories based on the pattern of DU recurrence over a 2-year observation period.

Methods Patients with SSc-associated DUs enrolled in the Digital Ulcers Outcome Registry between 1 April 2008 and 19 November 2013, and with ≥2 years of observation and ≥3 follow-up visits during the observation period were analysed. Incident DU-associated complications were recorded during follow-up. Work and daily activity impairment were measured using a functional assessment questionnaire completed by patients after the observation period. Potential factors that could predict incident complications were identified in patients with chronic DUs.

Results From 1459 patients, four DU occurrence categories were identified: 33.2% no-DU; 9.4% episodic; 46.2% recurrent; 11.2% chronic. During the observation period, patients from the chronic category had the highest rate of incident complications, highest work impairment and greatest need for help compared with the other categories. Independent factors associated with incident complications included gastrointestinal manifestations (OR 3.73, p=0.03) and previous soft tissue infection (OR 5.86, p=0.01).

Conclusions This proposed novel categorisation of patients with SSc-associated DUs based on the occurrence of DUs over time may help to identify patients in the clinic with a heavier DU burden who could benefit from more complex management to improve their functioning and quality of life.

INTRODUCTION

Systemic sclerosis (SSc) is a chronic, heterogeneous connective tissue disease that is characterised by small vessel vasculopathy, autoantibody production and fibroblast dysfunction,[1] leading to increased deposition of extracellular matrix and fibrosis.[2] Raynaud's phenomenon and hardening of the skin (scleroderma) are hallmarks of the disease.[1] The clinical presentation of SSc varies, with symptoms presenting in the skin, cardiovascular, gastrointestinal (GI), musculoskeletal and pulmonary systems.[1]

Digital ulcers (DUs) are a frequent external manifestation of vasculopathy in scleroderma[3] and occur in up to half of patients with SSc.[4] Data from the University of Pittsburgh found that, of those patients who experience a DU, more than half have persistent or recurrent DUs for at least 6 months.[5] Several studies have shown that DUs are associated with significant burden, with complications such as infection, gangrene and amputation leading to reduced quality of life (QoL) due to pain and disability,[6–8] an increased frequency of hospitalisation[3] and cardiovascular worsening and decreased survival.[9]

Previous studies have proposed various categorisations for DUs;[10 11] however, their utility in the clinic has been limited. There is still a need for a categorisation that enables the physician to determine patients who are likely to have increased disease burden and thus need more complex management.

In order to detail the impact of the burden of DUs associated with systemic sclerosis (SSc-DUs) on clinical practice, we reviewed patient data from the Digital Ulcers Outcome (DUO) Registry. Our proposed categorisation, based on the longitudinal pattern of DU recurrence during a 2-year observation of >1400 patients, may help us to identify patients with a heavier DU disease burden.

METHODS

Study design and patient population

The DUO Registry was an international, prospective, observational study that collected data from European patients with a history of SSc-DUs. It was initiated on 1 April 2008 to fulfil a postmarketing commitment to the European Medicines Agency (EMA) by Actelion Pharmaceuticals, following the approval of bosentan (Tracleer®, Actelion Pharmaceuticals, Allschwil, Switzerland) for patients with SSc-DUs.[12] Patients with SSc and a history of DUs, or DUs present at the time of enrolment, were eligible for inclusion in the registry irrespective of their treatment regimen; patients underwent clinical assessment and received treatment and follow-up care as determined by their physician. For this analysis, the cohort of eligible patients was required to have ≥2 years of observation from enrolment and ≥3 follow-up visits during this time (cohort A) up to the data cut-off of 19 November 2013.

Data collection

Data were collected from the patient's medical chart and recorded on an electronic case report

form (eCRF, data were not available for every field for all patients). The quality assurance process included automatic verification in real time such as checking for range and plausibility. Source data were verified in 10% of patients once a year.

Data collected at enrolment included patients' demographic and clinical characteristics, the presence of antibodies, history of interventions/complications related to DUs and documentation of ongoing medications. Data collected through follow-up visits included the number of finger DUs, the number of months in which a new DU occurred, the incidence of complications and interventions associated with DUs and patients' self-reported functional impairment. A DU was defined on the eCRF as a denuded area with a defined border and loss of epithelialisation, loss of epidermis, excluding fissures, paronychia, extrusion of calcium or ulcers over the metacarpophalangeal joints.

Patients' functional impairment was assessed via a questionnaire that was designed for the DUO Registry and translated into the local languages of the participating countries. The questionnaire as described by Guillevin *et al*[13] is a self-reported evaluation of the extent that finger ulcers affected the patient's ability to work and perform regular daily activities, along with their need for paid and unpaid help. The analysis reported here used the questionnaire that was completed at the end of the 2-year observation period (window of 18–27 months). The recall period was the month prior to completion of the questionnaire.

Work impairment (determined in employed patients only) and daily activity impairment were scored by patients on a scale from 0 (DU-associated problems had no effect) to 10 (DU-associated problems completely prevented the patient's ability to carry out that type of activity). Impairment percentages were calculated from the scores for work and daily impairment. Work time missed was expressed as a percentage of actual hours missed during the past month out of the expected number of hours normally worked. Overall work impairment was calculated as the sum of work time missed and lost productivity at work (work time attended multiplied by work impairment percentage). If 'work hours missed' was not reported and 'productivity impairment due to DUs' was reported, work hours missed was imputed to 0. If hours of paid or unpaid help were not reported, but the question whether the patient needed help was answered, missing hours of either paid or unpaid help were imputed to 0. The maximum possible number of monthly work hours and monthly work hours missed was fixed at 42 per week multiplied by 4.3, based on the longest legal work week in any European country within the DUO Registry's remit.

Data analysis

Data were analysed descriptively with the use of counts, proportions, mean, median and 95% CIs. Kaplan–Meier analysis was used to estimate the survival distribution for time to a new DU following enrolment. In general, missing values were not imputed, unless otherwise stated. Analyses were carried out using SAS® V.9.2 (SAS Institute Inc., Cary, North Carolina, USA).

Based on the DU recurrence pattern during the 2-year observation period following enrolment, using the number of DUs recorded at each follow-up visit and the occurrence of new DUs between visits, patients were divided into four categories: (1) no-DU, (2) episodic, (3) recurrent and (4) chronic (table 1).

In order to evaluate potential factors that could predict incident complications in the chronic category, univariable logistic regression analysis (ULR) was conducted. Incident complications were defined as the occurrence of at least one of five complications during the 2-year observation period: gangrene, amputation, soft tissue infection requiring systemic antibiotics, hospitalisation for DUs and use of pain medication. Potential predictive factors for incident complications were considered among the patient characteristics recorded at the enrolment visit. Multivariable logistic regression (MLR) analysis was conducted using those factors with a p value <0.15 from the univariable models, considering interdependency among similar factors.

Sensitivity analyses were conducted in order to confirm that the demographic and clinical characteristics of the patients included in the cohort used for this analysis (cohort A) were similar to the other cohorts within the registry: patients with <2 years follow-up (cohort B); patients with no follow-up visit, enrolment visit only (cohort C); and patients with ≥2 years follow-up and <3 follow-up visits (cohort D).

Table 1 Categories based on recurrence of DUs within a 2-year observation period

Category	Definition
No-DU	No DU at any FU visit
Episodic	Rarely recurrent: only 1 FU visit with either ≥1 DU or new DU; the remaining FU visits have no DU and no new DU
Recurrent	Frequently recurrent: ≥2 FU visits with DU and/or new DU, and ≥1 visit with no DU and no new DU
Chronic	≥1 DU and/or new DU at every FU visit

DU, digital ulcers; FU, follow-up.

RESULTS

In total, 4534 patients were enrolled in the DUO Registry from 394 centres in 18 European countries (see online supplementary appendix) up to 19 November 2013. Of these patients, 1459 were eligible for inclusion in this analysis (≥2 years of observation from enrolment and ≥3 follow-up visits in the first 2-year period; cohort A). Patients included in cohort A were enrolled from 15 of the 18 countries. The sensitivity analysis confirmed that the demographic and clinical characteristics of patients in cohort A were similar to those in other cohorts (see online supplementary table S1).

Patient demographic and clinical characteristics

Overall, 33.2% of patients were categorised as no-DU, 9.4% as episodic, 46.2% as recurrent and 11.2% as chronic. The median number of follow-up visits over the 2-year period was similar in all categories (4 (no-DU), 4 (episodic), 5 (recurrent) and 4 (chronic)). Overall, 84–88% of patients had a follow-up visit at 6-months (±3 months), 84–89% had a follow-up visit at 12-months (±3 months), 78–84% had a follow-up visit at 18 months (±3 months) and 85–90% had follow-up visit at 24 months (±3 months) across the four categories. The demographic and clinical characteristics of patients in the four categories are summarised in table 2.

Patients in all categories were predominantly female. Overall, the most common SSc manifestations were gastrointestinal (GI) manifestations and lung fibrosis. Differences were apparent between each of the categories for many clinical characteristics and the presence of antibodies. Patients from the chronic category had the highest prevalence of lung fibrosis and were youngest at enrolment, at their first Raynaud's phenomenon and at their first DU compared with the other recurrence categories. At enrolment, ≥3 DUs were present in 8.9% of patients from the no-DU category, 14.1% of patients from the episodic category, 23.1% of patients from the recurrent category and 53.4% of patients from the chronic category. The chronic

Table 2 Demographic and clinical characteristics of the four recurrence categories

	No-DU (n=484)	Episodic (n=137)	Recurrent (n=674)	Chronic (n=164)	Total (N=1459)
Gender, n	484	137	674	164	1459
Female, %	80.6	81.8	83.7	88.4	83.0
Age at enrolment, n	484	137	674	164	1459
Mean (SD), years	55.9 (13.2)	54.7 (13.7)	53.2 (14.5)	50.9 (12.4)	54.0 (13.8)
Age at first RP, n	418	121	607	148	1294
Mean (SD), years	43.0 (15.3)	42.9 (15.1)	39.5 (15.6)	35.2 (13.6)	40.4 (15.4)
Age at first DU, n	345	111	555	135	1146
Mean (SD), years	49.5 (14.9)	48.7 (14.5)	46.1 (15.2)	41.7 (14.0)	46.8 (15.1)
SSc classification, n	482	136	667	163	1448
Diffuse SSc, %	29.7	30.1	39.3	46.6	36.0
Limited SSc, %	56.2	58.8	51.3	44.2	52.8
Overlap/mixed CTD, %	8.9	5.1	6.3	7.4	7.2
Other, %	5.2	5.8	3.1	1.8	3.9
Organ manifestations, n	484	137	674	164	1459
GI, %	54.8	52.6	58.2	63.4	57.1
Heart, %	9.7	7.3	8.6	9.8	9.0
Kidney, %	6.4	2.2	3.7	3.7	4.5
Lung fibrosis, %	34.9	38.7	39.8	52.4	39.5
Antibodies, n^1/n^2 (%)					
ACA	165/339 (48.7)	41/98 (41.8)	213/528 (40.3)	34/123 (27.6)	453/1088 (41.6)
ANA	411/438 (93.8)	115/124 (92.7)	592/ 623 (95.0)	154/158 (97.5)	1272/1343 (94.7)
Anti-Scl 70	126/350 (36.0)	53/101 (52.5)	263/567 (46.4)	90/149 (60.4)	532/1167 (45.6)
Anti-U1 RNP	31/239 (13.0)	3/65 (4.6)	32/395 (8.1)	12/99 (12.1)	78/798 (9.8)
Anti-U3 RNP	8/150 (5.3)	0/44 (0.0)	8/254 (3.1)	9/68 (13.2)	25/516 (4.8)
RNA polym III	29/178 (16.3)	3/44 (6.8)	27/276 (9.8)	6/64 (9.4)	65/562 (11.6)
History of previous DU-associated complications/interventions, n^1/n^2 (%)					
Critical digital ischaemia	128/261 (49.0)	36/91 (39.6)	167/380 (43.9)	48/96 (50.0)	379/828 (45.8)
Gangrene	88/444 (19.8)	16/126 (12.7)	157/627 (25.0)	45/155 (29.0)	306/1352 (22.6)
Autoamputation	15/448 (3.3)	7/127 (5.5)	51/629 (8.1)	18/156 (11.5)	91/1360 (6.7)
Soft tissue infection requiring systemic antibiotics	78/420 (18.6)	39/122 (32.0)	209/600 (34.8)	86/149 (57.7)	412/1291 (31.9)
Osteomyelitis	15/438 (3.4)	3/124 (2.4)	22/628 (3.5)	12/153 (7.8)	52/1343 (3.9)
Hospitalisation for DUs	164/444 (36.9)	54/128 (42.2)	298/633 (47.1)	93/155 (60.0)	609/1360 (44.8)
Upper limb sympathectomy	17/442 (3.8)	6/125 (4.8)	21/621 (3.4)	14/150 (9.3)	58/1338 (4.3)
Digital sympathectomy	8/441 (1.8)	0/125 (0.0)	14/619 (2.3)	6/148 (4.1)	28/1333 (2.1)
Arterial reconstruction	5/442 (1.1)	1/125 (0.8)	3/617 (0.5)	2/149 (1.3)	11/1333 (0.8)
Arthrodesis	5/388 (1.3)	3/106 (2.8)	12/539 (2.2)	6/124 (4.8)	26/1157 (2.2)
Debridement	22/384 (5.7)	6/106 (5.7)	68/537(12.7)	27/125 (21.6)	123/1152 (10.7)
Surgical amputation	23/390 (5.9)	7/106 (6.6)	54/542 (10.0)	20/126 (15.9)	104/1164 (8.9)
Use of parenteral prostanoids	223/439 (50.8)	70/127 (55.1)	394/608 (64.8)	113/150 (75.3)	800/1324 (60.4)
Number of DUs at enrolment, n	481	135	668	161	1445
0*, %	66.1	48.9	31.7	10.6	42.4
1–2, %	24.9	37.0	45.2	36.0	36.7
3+, %	8.9	14.1	23.1	53.4	20.9
Ongoing medication at enrolment, n	484	137	674	164	1459
Analgesics and anti-inflammatories, %	52.7	60.6	58.9	67.7	58.0
Immunosuppressants, %	37.0	34.3	31.8	34.8	34.1
Systemic antibiotics, %	6.0	13.9	18.8	27.4	15.1
ERA, any combination, %	41.5	38.7	49.6	46.3	45.5
Prostacyclins, %	27.1	28.5	42.1	43.3	36.0
CCB, %	43.6	41.6	47.5	53.7	46.3
PDE5i, %	4.8	4.4	6.1	4.9	5.3
ERA+PDE5i, %	2.1	2.2	1.5	1.2	1.7
ERA+prostacyclin, %	10.3	10.9	17.7	19.5	14.8
PDE5i+prostacyclin, %	0.6	0.0	2.5	2.4	1.6

Continued

Table 2 Continued

	No-DU (n=484)	Episodic (n=137)	Recurrent (n=674)	Chronic (n=164)	Total (N=1459)
Other medications, %	74.8	73.7	71.7	63.4	72.0
Topical treatment of DUs at enrolment, n	484	137	674	164	1459
Any, %	7.6	15.3	24.8	34.8	19.3
Topical antibiotics, %	1.9	3.6	6.5	10.4	5.1
Proteolytic enzymes, %	0.8	0.0	1.2	3.0	1.2
Alginates, %	0.2	0.7	1.3	1.8	1.0
Growth factors, %	0.4	0.0	0.7	1.8	0.7
Dry dressing, %	4.1	6.6	10.8	13.4	8.5
Non-adhesive dressing, %	1.0	3.6	7.1	14.6	5.6
Hydro-colloids, %	2.3	5.1	7.4	12.8	6.1
Bioengineered skin, %	0.0	0.0	0.0	0.0	0.0

*All patients had prior DUs.
ACA, anticentromere antibodies; ANA, antinuclear antibodies; CCB, calcium channel blocker; CTD, connective tissue disease; DUs, digital ulcers; ERA, endothelin receptor antagonist; GI, gastrointestinal; n, n^1, number of patients; n^2, total number of patients for whom information was available; PDE5i, phosphodiesterase 5 inhibitor; RP, Raynaud's phenomenon; SSc, systemic sclerosis.

category contained the highest proportion of patients who tested positive for anti-Scl-70 antibodies (60.4%), while the lowest proportion was in the no-DU category (36.0%).

The highest use of analgesics/anti-inflammatories, systemic antibiotics, calcium channel blockers and topical treatment for DUs was observed in patients from the chronic category, followed by recurrent, then episodic, and finally, no-DU (table 2). At enrolment, patients from the recurrent and chronic categories had the greatest proportion of previous DU-associated interventions and complications (including hospitalisation, infections requiring systemic antibiotics and amputation) (table 2).

During the 2-year period on which the definition was built, the incidence of all analysed interventions and complications increased across the categories. The incidence was lowest in the no-DU category and highest in the chronic category (figure 1).

Patients in the chronic category experienced a first new DU earlier, followed by patients in the recurrent, episodic and no-DU categories (figure 2).

The functional assessment questionnaire was completed by 34–59% of patients depending on the category (table 3). Overall median work impairment due to DUs increased from the no-DU to the chronic category (10% (no-DU), 10% (episodic), 30% (recurrent) and 50% (chronic)). Median daily activity impairment increased from 10% in the no-DU category to 40% in the recurrent and 60% in the chronic categories. The chronic category also recorded the highest proportion of patients who needed help (66%) and the highest number of hours needed for unpaid help (64 h). In contrast, only 16% of patients in the no-DU category needed help, and, on average, they only needed 11 h of unpaid help.

Identification of predictive factors for developing complications in the chronic category

Variables meeting a cut-off of $p<0.15$ in the ULR analysis (see online supplementary table S2) were taken forward to MLR analysis. The chronic category comprised these variables: GI manifestations, presence of anti-U1-RNP antibodies, previous soft tissue infection and ongoing soft tissue infection, both requiring systemic antibiotics. The multivariable model (see online supplementary table S3) showed GI manifestation ($p=0.03$) and previous soft tissue infection ($p=0.01$) to be independent predictive factors for developing incident complications in patients from the chronic category (OR 3.73, 95% CI 1.14 to 12.20, and 5.86, 95% CI 1.53 to 22.41, respectively). The model excluded anti-U1-RNP due to the high level of missing values in this variable.

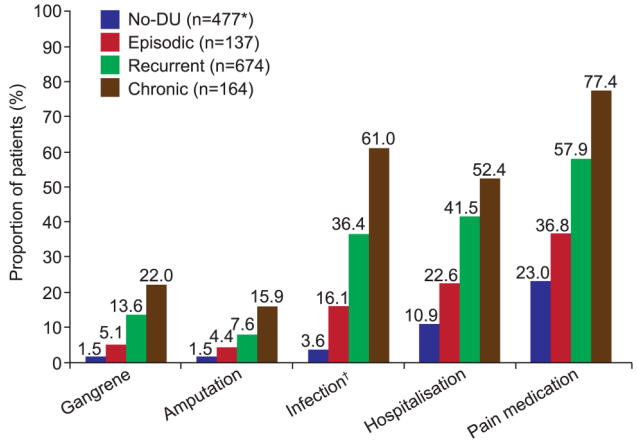

Figure 1 Proportion of patients experiencing incident complications or undergoing interventions over a 2-year observation period. *Pain medication, n=483. †Soft tissue infection requiring antibiotics or osteomyelitis. DU, digital ulcer.

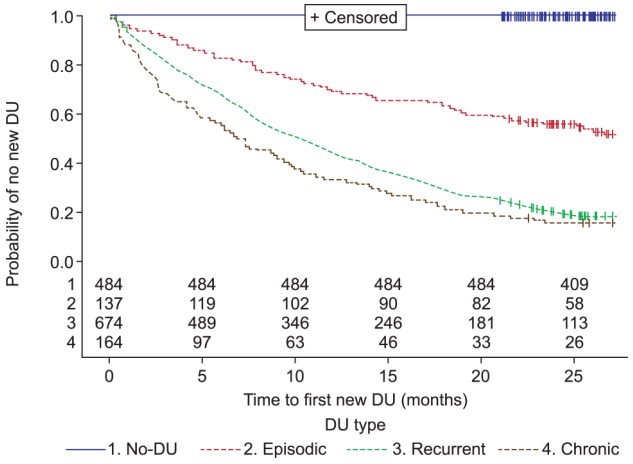

Figure 2 Time to first new digital ulcer (DU) following enrolment.

Table 3 Functional assessment (N=670)

	No-DU (n=185)	Episodic (n=47)	Recurrent (n=341)	Chronic (n=97)
Work impairment, scale 0–10,* n	51	13	122	35
Mean	17.6	12.3	33.4	48.3
Median	10.0	0.0	30.0	50.0
95% CI of median	0.0 to 10.0	0.0 to 30.0	20.0 to 40.0	40.0 to 60.0
Overall work impairment,† n	51	13	122	35
Mean	19.0	14.1	35.5	50.6
Median	10.0	10.0	30.0	50.0
95% CI of median	0.0 to 20.0	0.0 to 30.0	20.0 to 40.0	40.0 to 60.0
Daily activity impairment, scale 0–10,* n	178	45	333	96
Mean	21.2	17.8	39.6	56.8
Median	10.0	0.0	40.0	60.0
95% CI of median	0.0 to 20.0	0.0 to 30.0	30.0 to 50.0	50.0 to 70.0
Help needed, n	184	46	338	97
Yes, n (%)	30 (16.3)	7 (15.2)	148 (43.8)	64 (66.0)
Hours of paid help, n	184	46	338	97
Mean	0.3	0.0	3.1	7.1
Hours of unpaid help, n	184	46	338	97
Mean	10.9	13.8	37.4	64.3

*Scale 0 (DU-associated problems had no effect) to 10 (DU-associated problems completely affected the patient's ability to carry out that type of activity) transformed into percentage.
†Overall work impairment (expressed as percentage) calculated as the sum of work time missed and lost productivity at work (work time attended multiplied by work impairment percentage).
DUs, digital ulcers; n, number of patients.

DISCUSSION

The present data confirm that DUs are a significant burden in patients with SSc, and moreover, suggest that more severely affected subgroups can be identified in clinical practice. This analysis was performed in order to characterise and to understand better the patterns of DU occurrence and disease burden through the investigation of demographic and clinical disease characteristics. Patients with recurrent or chronic DUs showed a greater disease burden characterised by increased incidence of complications, need for interventions and impaired ability to function in their employment and daily activities.

Why develop four categories?

There is a need to categorise patients in a way that enables the physician to determine which groups of patients are likely to have increased disease burden and thus need more complex management. For example, Herrick *et al*[10] classified DUs according to their activity (active and inactive); however, the inter-rater reliability for this grouping of patients was poor. Another study categorised patients with DUs according to DU origin and main features (pure DUs, DUs derived from digital pitting scar, calcinosis or gangrene).[11] Although the categorisation worked well, it characterised patients according to type of DU rather than according to disease burden. In the present study, four patient categories were identified, based not on DU activity but rather the timing of new ulcer development. The episodic, recurrent and chronic categories were defined based on the occurrence of DU events over the 2-year follow-up. Hence, the no-DU category comprised patients with no DUs over 2 years. We believe that these four categories better reflect the level of disease burden associated with DUs and may be useful in identifying groups of patients from a prognostic perspective.

Identification of patients with chronic DUs

Patients in the chronic category had the most severe clinical characteristics and the most severe DU disease history. The patients were younger at DU disease onset, which can have implications for their working life. When younger patients develop chronic DUs, they are affected with a burdensome disease at a phase of life when they need and/or want to maintain employment. Additionally, working life is affected for a longer time period in young patients compared with older patients. Patients in the chronic category had the highest proportion of GI manifestations and pulmonary fibrosis, again demonstrating the higher disease burden for chronic patients. The pathogenesis of GI manifestations has been linked to the vasculopathy that is a hallmark of SSc,[14] while increased frequency of pulmonary fibrosis has been previously observed in patients with DUs.[15] Furthermore, the chronic category contained the highest proportion of patients on medications, the highest proportion of patients testing positive for anti-Scl-70 antibodies and with the most frequent history of DU-associated interventions/complications. Scl-70 antibodies are associated with more fibrosis—skin,[16 17] GI tract[16] and lung.[17 18] Fewer patients in the chronic category were positive for anticentromere antibodies compared with the other categories in contrast to a previous study[19] that found that patients who were positive for anticentromere antibodies were more likely to have persistent and/or severe DUs.

DU disease burden during the 2-year observation period

Patients in the recurrent and chronic categories required the most interventions (more hospitalisations, infections and pain relief medication) and had the highest impairment in productivity and daily activity. They also had the greatest need for help, reflected in the proportion who needed help and in the number of hours of unpaid help received.

The higher occurrence of complications and/or interventions in the recurrent and chronic categories may lead to a higher cost

of treatment in these patients. As survival improves,[20] the burden of disease and the potentially associated costs are imperative to consider for planning disease management. It has previously been shown that the costs of disease management are higher in patients with DUs compared with patients without DUs.[21] These costs include both the direct costs such as hospital stays, medication and payment for nurse procedures for treatment of complications, but also indirect costs, such as absence from work, lower productivity and an increased need for help from others.

A recent publication from the EUSTAR cohort analysed the characteristics, treatment patterns, healthcare resource utilisation, QoL and functional status of patients with newly diagnosed DUs from DU diagnosis to a prospective visit 3 months after end of follow-up.[22] Although this study did not categorise patients in a similar manner to our study, in general, similar rates of work and daily activity impairment were observed over the observation period of 2.6 years. Daily activity impairment was high, with half of patients with ≥1 DU at end of follow-up requiring help for completion of daily activities, similar to the recurrent and chronic categories of the current study. Of the employed patients, overall work impairment was 35%. DU-related complications were reported in 23% of patients, and 27% of patients required ≥1 DU procedure during follow-up.[22]

ULR and MLR analyses in chronic patients

In the chronic category, a logistic regression analysis was carried out to identify those factors that may help predict which patients may develop complications. Previous soft tissue infection and GI manifestations present at enrolment were both significant predictive factors associated with incident complications. Consistent with the latter observations, GI manifestations have previously been linked to increased risk of DUs in the EUSTAR cohort of patients with SSc.[23]

STRENGTHS/LIMITATIONS

The large sample size and the prospective nature of data collection through 400 international centres, including some expert centres, provided a broad sample of patients, thus allowing the data to be generalisable to a wide patient population. However, due to the nature of this registry, there may have been a selection bias towards more severe patients as mainly centres that prescribe bosentan were included as part of the EMA commitment. It may have been difficult for patients to assess and quantify accurately their functioning during the recall period (ie, the month before completing the questionnaire), and also to separate the effects of DUs from those of the underlying SSc when evaluating functioning.

CONCLUSION

This work used a unique and large prospective collection of DU data to define a group with particularly severe DU disease that have a high clinical burden of complications. Patients with recurrent and chronic DUs experienced a higher disease burden with an increased frequency of complications, more hospitalisations, greater impairment in functioning and an increased need for help compared with patients with no DUs and episodic DUs. The four categories proposed herein are complementary to other groupings based on the origin of DUs (pure, calcinosis, digital pitting scar, gangrene).[11] The four categories show striking variation in clinical impact over time and are highly relevant to clinical practice. Moreover, the categorisation may also have an impact on the design of future clinical trials.

In summary, these four novel categories may better define patients in the clinic with a high DU burden who might benefit from additional preventive therapy and consequently have improvement in functioning and QoL.

Acknowledgements The registry sponsor was involved in the registry design, and in the collection, analysis and interpretation of data. The authors wish to thank Dr Lynda McEvoy, PhD, of ApotheCom ScopeMedical, London, UK, for providing editorial writing assistance, funded by Actelion Pharmaceuticals Ltd.

Contributors All authors were involved in the drafting and reviewing of the manuscript and approved the final version. Statistical analysis: DR, BS and PC. All authors agree to be accountable for all aspects of the work.

Funding The DUO Registry was sponsored by Actelion Pharmaceuticals Ltd.

Competing interests BS and DR are employees of and own shares of Actelion Pharmaceuticals Ltd. PC is employed by SDE Services and works as a full-time contractor at Actelion Pharmaceuticals Ltd. MM-C has received grant/research support and/or attended speakers' bureaus for Actelion, Pfizer, GSK, BMS and Abbot. TK has received a grant and speaker's fees from Actelion. CPD has acted as a consultant for and received speaker's fees from Actelion, GSK, Bayer, Inventiva and Takeda, has received grant support from Actelion, and research grant support to his institution from CSL Behring and Novartis. LG has previously lectured for and attended advisory boards for Actelion, but has had no potential conflict of interest since September 2013.

Patient consent Obtained.

Ethics approval Ethical approval was obtained as required from the institutional ethics committees of the participating centres.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Hinchcliff M, Varga J. Systemic sclerosis/scleroderma: a treatable multisystem disease. *Am Fam Physician* 2008;78:961–8.
2 van den Hoogen F, Khanna D, Fransen J, *et al*. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. *Ann Rheum Dis* 2013;72:1747–55.
3 Nihtyanova NI, Brough GM, Black CM, *et al*. Clinical burden of digital vasculopathy in limited and diffuse cutaneous systemic sclerosis. *Ann Rheum Dis* 2008;67:120–3.
4 Walker UA, Tyndall A, Czirják L, *et al*. Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database. *Ann Rheum Dis* 2007;66:754–63.
5 Steen V, Denton CP, Pope JE, *et al*. Digital ulcers: overt vascular disease in systemic sclerosis. *Rheumatology (Oxford)* 2009;48(Suppl 3):iii19–24.
6 Merkel PA, Herlyn K, Martin RW, *et al*. Measuring disease activity and functional status in patients with scleroderma and Raynaud's phenomenon. *Arthritis Rheum* 2002;46:2410–20.
7 Hachulla E, Clerson P, Launay D, *et al*. Natural history of ischemic digital ulcers in systemic sclerosis: a single-center retrospective longitudinal study. *J Rheumatol* 2007;34:2423–30.
8 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;69:214–17.
9 Mihai C, Landewé R, van der Heijde D, *et al*. Digital ulcers predict a worse disease course in patients with systemic sclerosis. *Ann Rheum Dis* 2015;Published Online First 16 Feb 2014.
10 Herrick AL, Roberts C, Tracey A, *et al*. Lack of agreement between rheumatologists in defining digital ulceration in systemic sclerosis. *Arthritis Rheum* 2009;60:878–82.
11 Amanzi L, Braschi F, Fiori G, *et al*. Digital ulcers in scleroderma: staging, characteristics and sub-setting through observation of 1614 digital lesions. *Rheumatology (Oxford)* 2010;49:1374–82.
12 Actelion Pharmaceuticals Ltd. Tracleer Summary of Product Characteristics. 2013. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000401/WC500041597.pdf (accessed Dec 2014).
13 Guillevin L, Hunsche E, Denton CP, *et al*. Functional impairment of systemic scleroderma patients with digital ulcerations: results from the DUO Registry. *Clin Exp Rheumatol* 2013;31(2 Suppl 76):71–80.
14 Sjogren R. Gastrointestinal motility disorders in scleroderma. *Arthritis Rheum* 1994;37:1265–82.

15 Sunderkötter C, Herrgott I, Brückner C, *et al*. Comparison of patients with and without digital ulcers in systemic sclerosis: detection of possible risk factors. *Br J Dermatol* 2009;160:835–43.
16 Guillen-Del Castillo A, Pilar Simeón-Aznar C, *et al*. Good outcome of interstitial lung disease in patients with scleroderma associated to anti-PM/Scl antibody. *Semin Arthritis Rheum* 2014;44:331–7.
17 Steen VD, Powell DL, Medsger TA. Clinical correlations and prognosis based on serum autoantibodies in patients with systemic sclerosis. *Arthritis Rheum* 1988;31:196–203.
18 Briggs DC, Vaughan RW, Welsh KI, *et al*. Immunogenetic prediction of pulmonary fibrosis in systemic sclerosis. *Lancet* 1991;338:661–2.
19 Ingraham K, Steen V. Morbidity of digital tip ulceration in scleroderma. *Arthritis Rheum* 2006;54(Suppl 9):578.
20 Barnes J, Mayes MD. Epidemiology of systemic sclerosis: incidence, prevalence, survival, risk factors, malignancy, and environmental triggers. *Curr Opin Rheumatol* 2012;24:165–70.
21 Cozzi F, Tiso F, Lopatriello S, *et al*. The social costs of digital ulcer management in scleroderma patients: an observational Italian pilot study. *Joint Bone Spine* 2010;77:83–4.
22 Brand M, Hollaender R, Rosenberg D, *et al*. An observational cohort study of patients with newly diagnosed digital ulcer disease secondary to systemic sclerosis registered in the EUSTAR database. *Clin Exp Rheumatol* 2015;33(4 Suppl 91): S47–54.
23 Xu D, Li M-T, Hou Q, *et al*. Clinical characteristics of systemic sclerosis patients with digital ulcers in China. *Clin Exp Rheumatol* 2013;31(Suppl 76):S46–9.