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 Loïc Guillevin,3 Barbara Schwierin,4 Daniel Rosenberg,4 Peter Cornelisse,4 Christopher P Denton5

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, leading to increased deposition of extracellular matrix and fibrosis. Raynaud’s phenomenon and hardening of the skin (sclerodema) are hallmarks of the disease. The clinical presentation of SSc varies, with symptoms presenting in the skin, cardiovascular, gastrointestinal (GI), musculoskeletal and pulmonary systems. Digital ulcers (DUs) are a frequent external manifestation of vasculopathy in sclerodema and occur in up to half of patients with SSc. 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. 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, an increased frequency of hospitalisation and cardiovascular worsening and decreased survival.

Previous studies have proposed various categorisations for DUs; 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. 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. 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® V9.2 (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.

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>
<thead>
<tr>
<th>Demographic and clinical characteristics of the four recurrence categories</th>
<th>No-DU (n=484)</th>
<th>Episodic (n=137)</th>
<th>Recurrent (n=674)</th>
<th>Chronic (n=164)</th>
<th>Total (N=1459)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n</td>
<td>484</td>
<td>137</td>
<td>674</td>
<td>164</td>
<td>1459</td>
</tr>
<tr>
<td>Female, %</td>
<td>80.6</td>
<td>81.8</td>
<td>83.7</td>
<td>88.4</td>
<td>83.0</td>
</tr>
<tr>
<td>Age at enrolment, n</td>
<td>484</td>
<td>137</td>
<td>674</td>
<td>164</td>
<td>1459</td>
</tr>
<tr>
<td>Mean (SD), years</td>
<td>55.9 (13.2)</td>
<td>54.7 (13.7)</td>
<td>53.2 (14.5)</td>
<td>50.9 (12.4)</td>
<td>54.0 (13.8)</td>
</tr>
<tr>
<td>Age at first RP, n</td>
<td>418</td>
<td>121</td>
<td>607</td>
<td>148</td>
<td>1294</td>
</tr>
<tr>
<td>Mean (SD), years</td>
<td>43.0 (15.3)</td>
<td>42.9 (15.1)</td>
<td>39.5 (15.6)</td>
<td>35.2 (13.6)</td>
<td>40.4 (15.4)</td>
</tr>
<tr>
<td>Age at first DU, n</td>
<td>345</td>
<td>111</td>
<td>555</td>
<td>135</td>
<td>1146</td>
</tr>
<tr>
<td>Mean (SD), years</td>
<td>49.5 (14.9)</td>
<td>48.7 (14.5)</td>
<td>46.1 (15.2)</td>
<td>41.7 (14.0)</td>
<td>46.8 (15.1)</td>
</tr>
<tr>
<td>SSc classification, n</td>
<td>482</td>
<td>136</td>
<td>667</td>
<td>163</td>
<td>1448</td>
</tr>
<tr>
<td>Diffuse SSc, %</td>
<td>29.7</td>
<td>30.1</td>
<td>39.3</td>
<td>46.6</td>
<td>36.0</td>
</tr>
<tr>
<td>Limited SSc, %</td>
<td>56.2</td>
<td>58.8</td>
<td>51.3</td>
<td>42.4</td>
<td>52.8</td>
</tr>
<tr>
<td>Overlap/mixed CTD, %</td>
<td>8.9</td>
<td>5.1</td>
<td>6.3</td>
<td>7.4</td>
<td>7.2</td>
</tr>
<tr>
<td>Other, %</td>
<td>5.2</td>
<td>5.8</td>
<td>3.1</td>
<td>1.8</td>
<td>3.9</td>
</tr>
<tr>
<td>Organ manifestations, n</td>
<td>484</td>
<td>137</td>
<td>674</td>
<td>164</td>
<td>1459</td>
</tr>
<tr>
<td>GI, %</td>
<td>54.8</td>
<td>52.6</td>
<td>58.2</td>
<td>63.4</td>
<td>57.1</td>
</tr>
<tr>
<td>Heart, %</td>
<td>9.7</td>
<td>7.3</td>
<td>8.6</td>
<td>9.8</td>
<td>9.0</td>
</tr>
<tr>
<td>Kidney, %</td>
<td>6.4</td>
<td>2.2</td>
<td>3.7</td>
<td>3.7</td>
<td>4.5</td>
</tr>
<tr>
<td>Lung fibrosis, %</td>
<td>34.9</td>
<td>38.7</td>
<td>39.8</td>
<td>52.4</td>
<td>39.5</td>
</tr>
<tr>
<td>Antibodies, n1/n2 (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACA</td>
<td>165/339 (48.7)</td>
<td>41/98 (41.8)</td>
<td>213/528 (40.3)</td>
<td>34/123 (27.6)</td>
<td>453/1088 (41.6)</td>
</tr>
<tr>
<td>ANA</td>
<td>411/438 (93.8)</td>
<td>115/124 (92.7)</td>
<td>592/623 (95.0)</td>
<td>154/158 (97.5)</td>
<td>1272/1343 (94.7)</td>
</tr>
<tr>
<td>Anti-Scl 70</td>
<td>126/350 (36.0)</td>
<td>53/101 (52.5)</td>
<td>263/567 (46.4)</td>
<td>90/149 (60.4)</td>
<td>532/1167 (45.6)</td>
</tr>
<tr>
<td>Anti-U1 RNP</td>
<td>31/239 (13.0)</td>
<td>5/65 (4.6)</td>
<td>32/395 (8.1)</td>
<td>12/99 (12.1)</td>
<td>78/798 (9.8)</td>
</tr>
<tr>
<td>Anti-U3 RNP</td>
<td>8/150 (5.3)</td>
<td>0/44 (0.0)</td>
<td>8/254 (3.1)</td>
<td>9/68 (13.2)</td>
<td>25/516 (4.8)</td>
</tr>
<tr>
<td>RNA polym III</td>
<td>29/178 (16.3)</td>
<td>3/44 (6.8)</td>
<td>27/276 (9.8)</td>
<td>6/64 (9.4)</td>
<td>65/562 (11.6)</td>
</tr>
<tr>
<td>History of previous DU-associated complications/interventions, n1/n2 (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Critical digital ischaemia</td>
<td>128/261 (49.0)</td>
<td>36/91 (39.6)</td>
<td>167/380 (43.9)</td>
<td>48/96 (50.0)</td>
<td>379/828 (45.8)</td>
</tr>
<tr>
<td>Gangrene</td>
<td>88/444 (19.8)</td>
<td>16/126 (12.7)</td>
<td>157/627 (25.0)</td>
<td>45/155 (29.0)</td>
<td>306/1352 (22.6)</td>
</tr>
<tr>
<td>Autoamputation</td>
<td>15/448 (3.3)</td>
<td>7/127 (5.5)</td>
<td>21/629 (8.1)</td>
<td>18/156 (11.5)</td>
<td>51/343 (14.9)</td>
</tr>
<tr>
<td>Soft tissue infection requiring systemic antibiotics</td>
<td>78/420 (18.6)</td>
<td>3/44 (6.8)</td>
<td>27/276 (9.8)</td>
<td>6/64 (9.4)</td>
<td>65/562 (11.6)</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>15/438 (3.4)</td>
<td>3/124 (2.4)</td>
<td>22/268 (8.3)</td>
<td>12/153 (7.8)</td>
<td>52/343 (15.2)</td>
</tr>
<tr>
<td>Hospitalisation for DUs</td>
<td>164/444 (36.9)</td>
<td>54/124 (42.2)</td>
<td>298/633 (47.1)</td>
<td>93/155 (60.0)</td>
<td>609/1360 (44.8)</td>
</tr>
<tr>
<td>Upper limb sympathectomy</td>
<td>17/442 (3.8)</td>
<td>6/125 (4.8)</td>
<td>21/621 (3.4)</td>
<td>14/150 (9.3)</td>
<td>58/338 (17.3)</td>
</tr>
<tr>
<td>Digital sympathectomy</td>
<td>8/441 (1.8)</td>
<td>0/125 (0.0)</td>
<td>16/619 (2.6)</td>
<td>6/148 (4.1)</td>
<td>28/333 (8.4)</td>
</tr>
<tr>
<td>Arterial reconstruction</td>
<td>5/442 (1.1)</td>
<td>1/125 (0.8)</td>
<td>3/617 (0.5)</td>
<td>2/149 (1.3)</td>
<td>11/333 (3.3)</td>
</tr>
<tr>
<td>Arthrodesis</td>
<td>5/388 (1.3)</td>
<td>3/106 (2.8)</td>
<td>12/629 (1.9)</td>
<td>6/153 (4.0)</td>
<td>20/136 (14.7)</td>
</tr>
<tr>
<td>Debridement</td>
<td>22/390 (5.7)</td>
<td>6/106 (5.7)</td>
<td>68/543 (12.7)</td>
<td>27/125 (21.6)</td>
<td>123/1152 (10.7)</td>
</tr>
<tr>
<td>Surgical amputation</td>
<td>23/390 (5.9)</td>
<td>7/106 (6.6)</td>
<td>54/542 (10.0)</td>
<td>20/126 (15.9)</td>
<td>104/1164 (9.0)</td>
</tr>
<tr>
<td>Use of parenteral prostanoids</td>
<td>223/439 (50.8)</td>
<td>70/127 (55.1)</td>
<td>394/608 (64.8)</td>
<td>113/150 (75.3)</td>
<td>800/1324 (60.4)</td>
</tr>
<tr>
<td>Number of DUs at enrolment, n</td>
<td>481</td>
<td>135</td>
<td>668</td>
<td>161</td>
<td>1459</td>
</tr>
<tr>
<td>0*, %</td>
<td>66.1</td>
<td>48.9</td>
<td>31.7</td>
<td>10.6</td>
<td>42.4</td>
</tr>
<tr>
<td>1–2, %</td>
<td>24.9</td>
<td>37.0</td>
<td>45.2</td>
<td>36.0</td>
<td>36.7</td>
</tr>
<tr>
<td>3+, %</td>
<td>8.9</td>
<td>14.1</td>
<td>23.1</td>
<td>53.4</td>
<td>20.9</td>
</tr>
<tr>
<td>Ongoing medication at enrolment, n</td>
<td>484</td>
<td>137</td>
<td>674</td>
<td>164</td>
<td>1459</td>
</tr>
<tr>
<td>Analgesics and anti-inflammatories, %</td>
<td>52.7</td>
<td>60.6</td>
<td>58.9</td>
<td>67.7</td>
<td>58.0</td>
</tr>
<tr>
<td>Immunosuppressants, %</td>
<td>37.0</td>
<td>34.3</td>
<td>31.8</td>
<td>34.8</td>
<td>34.1</td>
</tr>
<tr>
<td>Systemic antibiotics, %</td>
<td>6.0</td>
<td>13.9</td>
<td>18.8</td>
<td>27.4</td>
<td>15.1</td>
</tr>
<tr>
<td>ERA, any combination, %</td>
<td>41.5</td>
<td>38.7</td>
<td>49.6</td>
<td>46.3</td>
<td>45.5</td>
</tr>
<tr>
<td>Prostacyclins, %</td>
<td>27.1</td>
<td>28.5</td>
<td>42.1</td>
<td>43.3</td>
<td>36.0</td>
</tr>
<tr>
<td>CCB, %</td>
<td>43.6</td>
<td>41.6</td>
<td>47.5</td>
<td>53.7</td>
<td>46.3</td>
</tr>
<tr>
<td>PDE5i, %</td>
<td>4.8</td>
<td>4.4</td>
<td>6.1</td>
<td>4.9</td>
<td>5.3</td>
</tr>
<tr>
<td>PDE5i+prostacyclin, %</td>
<td>0.6</td>
<td>0.0</td>
<td>2.5</td>
<td>2.4</td>
<td>1.6</td>
</tr>
<tr>
<td>ERA+PDE5i, %</td>
<td>2.1</td>
<td>2.2</td>
<td>1.5</td>
<td>1.2</td>
<td>1.7</td>
</tr>
<tr>
<td>ERA+prostacyclin, %</td>
<td>10.3</td>
<td>10.9</td>
<td>17.7</td>
<td>19.5</td>
<td>14.8</td>
</tr>
</tbody>
</table>

Continued
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 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.
**Clinical and epidemiological research**

**Table 3 Functional assessment (N=670)**

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

*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 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). 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, while increased frequency of pulmonary fibrosis has been previously observed in patients with DUs. 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, GI tract and lung. Fewer patients in the chronic category were positive for anticientromere antibodies compared with the other categories in contrast to a previous study that found that patients who were positive for anticientromere 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, 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. 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. 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.

**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.

**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). 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’ bureaux for Actelion, Pfizer, GSK, BMS and AbbV. 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 lectures 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.

**Open Access** This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**REFERENCES**


APPENDIX

List of DUO Investigators:

AT – AUSTRIA
A WILLFORT-EHRINGER
B MONSHI
B RAFFIER
F HAFNER
F KARLHOFER
F TRAUTINGER
H BROLL
H HINTNER
H JUST
H KOLLE
J POPP-HABELER
J SAUTNER
K SEMMELWEIS
M AUSSERWINKLER
M HIRSCHL
M HUNDSTORFER
M KUEN-SPIEGL
M STETTER
M TAKACS
N TOMI
P MESARIC
R FELDMANN
R KNOBLER
R STROHAL
R THONHOFER
S METZ

CH - SWITZERLAND
B MAURER
D VERNER
O DISTLER
R SCHMIDT-BOSSHARD
S JORDAN
T CHOKCHAMPA

CZ – THE CZECH REPUBLIC
A SMRZOVA
D SUCHY
I ZEMANOVA
J BOHMOVA
J VITOVA
L BORTLIK
L PROCHAZKOVA
P NEMEC
R BECVAR
R ZAHORA
T SOUKUP
Z FOJTIK
DE – GERMANY
A BARATAY
A BOECKER
A BRAND
A DE DONNO
A DELFS
A FUNKERT
A GAUSE
A GAWLIK
A GERBER
A HALLECKER
A HAZENBILLER
A HIMSEL
A HOFFMANN
A KACZMACZYK
A KATZEMICH
A KETTENBACH
A KRAUSE
A KREUTER
A LUNGWITZ
A MITCHELL
A NIEDEMEIER
A SCHWARTING
A UNHOLZER
A VON ELLING
B ALSHEIMER
B BELLONI
B HELLMICH
B HILDEBRANDT
B HUETTIG
B KROG
B LAUTERWEIN
B MERK
B NÜTZEL
B RABE
B VOSS
B WILLIG
C BAUMANN
C BEYER
C ERFRUT-BERGE
C GUENTHER
C HALLERMANN
C HILLEBRECHT
C KELLNER
C KNEITZ
C Loeffler
C LUCKGENS
C MENSING
C METZLER
C MUEGLICH
C NIELEN
C PFEIFFER
C PFÖHLEH
C RASCHE
C RUMBAUR
IC MONTES
J BARBADO
J CRUZ
J DEL PINO
J FERNANDEZ
J MONTES
J MUNOZ
J PEGO
J SANCHEZ
J USON
J ZUBIETA
JA CARRASCO
JA MOSQUERA
JA TODOLI
JAM FILLOY
JAMIE CALVO
JAP TASENDE
JAVIER CALVO
JB DIAZ LOPEZ
JC MEJIA
JCF LOPEZ
JG GIL
JJ ALEGRE SANCHO
JJ ALONSO
JJ DIAZ
JJ PEREZ
JJR BLANCO
JL CALLEJAS
JLG VAZQUEZ
JM MASCARO
JM SABIO
JR CALABUIG
JR IVORRA
JR LARRANAGA
JR MANEIRO
JS BLANCO
JV COLEMAN
L GONZALEZ HOMBRADO
L LOSADA
L SAEZ
M ALPERI LOPEZ
M ANGELES AQUIRRE
M CORTEGUERA
M CRESPO
M DEL CARMEN FREIRE
M DEL CARMEN ORTEGA DE LA O
M DEL CARMEN TORRES MARTIN
M DEL MAR RIOPO MACIAS
M FREIRE GONZALEZ
M MONTO RO ÁLVAREZ
M RAMOS
M RUBIO
M VICTORIA EGURBIDE
M YEBRA
MA ABAD HERNANDEZ
G VEGOUDAKI
I GKOUGKOURELAS
I KRITIKOS
M MICHAILEDJOU
N GALANOPoulos
N PAPADOPoulos
N TSIFETAKI
P ATHANASSIOU
P VLACHOYANNOPOULOS
S ASLANIDIS
S KAMALI
T DIMITROULAS
V GALANOPOULOU

IE - IRELAND
A GRIER
D VEALE
M O'ROURKE

IT – ITALY
A AMOROSO
A BENENATI
A BORTOLUZZI
A CORRADO
A DELLA ROSSA
A GABRIELLI
A GIARDINA
A MATHIEU
A MAZZONE
A MUSSI
A NIGRO
A SEVERINO
A VACCA
B CAPUANO
B MARASINI
C BOSELLO
C FERRI
C LUNARDI
C SALVARANI
C SELMI
CM MONTECUCCO
D GIUGGIOLI
E BATTAGLIA
E FUSARO
E ROSATO
F BELLISAI
F CANTATORE
F COZZI
F DALL'ARA
F GALLUCCIO
F PUPPO
F SALSANO
F TROTTO
G BAJOCCHI
G CUOMO
S MAZZUCA
S NEGRINI
S PALLOTTA
S PARISI
S STISI
S TRINCON
S ZENI
S ZINGARELLI
V CARRARO
V CODULLO
V RICCIERI
W GRASSI
W MAGLIONE

NL – THE NETHERLANDS
A SPOORENBERG
AA SCHOUFFOER
AE HAK
AE VAN DEN BIJL
AE VOSKUYL
AH GERARDS
AHM HEURKENS
AJ PEETERS
AJ SMIT
AJG SWAAK
AJL DE JONG
AJM SCHUERWEGH
B NAAFS
C BIJKERK
C VAN DURME
C VAN GULDENER
CEI LEBRUN
CW DEN HENGST
D SIEWERTSZ VAN REESEMA
D VAN ZEBEN
DG KUIPER-GEERTSMA
DJ MULDER
DR SIEWERTSZ VAN REESEMA
E KNIJFF-DUTMER
E TON
ESG STROES
F BONTE-MINEUR
F EGGELMEIJER
F UBELS
FHJ VAN DEN HOOGEN
FJMA VAN NEER
G BRUIJN
GAW BRUYN
GJM VAN VEEN
H BOOTSMA
H HOUBEN
H HULSMANS
H RONDAY
H VAN PAASSEN
H VISSE
VEA GERDES  
W HISSINK MULLER  
W VERCOUTERE  
WM DE BEUS  
ZN JAHANGIER DE VEEN  

NO - NORWAY  
A BENDVOLD  
A-M HOFFMANN-VOLD  
B GRANDAUNET  
B-Y NORDVAG  
CG GJESDAL  
EK STRAND  
G BAKLAND  
G KORNELUK-THOR  
H BITTER  
HK ASLAKSEN  
J SKOMSVOLL  
M SEIP  
O MIDTVEDT  
RS THOMSEN  
S KALSTAD  
T PEDERSEN  
TM MADLAND  
V BAKKEHEIM  
W KOLDINGSNES  

PT – PORTUGAL  
A CORDEIRO  
A GRILO  
AC RODRIGUES  
C PONTE  
C RESENDE  
C SANTOS  
F SILVA  
I ALMEIDA  
I CAMARA  
I SILVA  
J ALVES  
J COSTA  
M OLIVEIRA  
N RISO  
P COELHO  
PA FERREIRA  
S OLIVEIRA  

SE - SWEDEN  
A HOLMSTRAND  
A MOHAMMAD  
A NORDIN  
A OSTENSON  
B MOLLER  
C STAHL HALLENGREN  
C THORSSON  
E HERMANSSON
Supplementary Table S1  Sensitivity analysis

<table>
<thead>
<tr>
<th></th>
<th>Cohort A (n=1459)</th>
<th>Cohort B (n=1586)</th>
<th>Cohort C (n=923)</th>
<th>Cohort D (n=566)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n, %</td>
<td>1459</td>
<td>1586</td>
<td>908</td>
<td>566</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>83.0 81.0</td>
<td>81.8</td>
<td>82.0</td>
</tr>
<tr>
<td>Age at enrolment, n, years</td>
<td>1459</td>
<td>1586</td>
<td>906</td>
<td>566</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>54.0 (13.8)</td>
<td>55.2 (14.6)</td>
<td>55.5 (14.4)</td>
</tr>
<tr>
<td>Age at first RP, n, years</td>
<td>1294</td>
<td>1394</td>
<td>784</td>
<td>506</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>40.4 (15.4)</td>
<td>42.1 (15.6)</td>
<td>41.7 (15.6)</td>
</tr>
<tr>
<td>Age at first DU, n, years</td>
<td>1146</td>
<td>1235</td>
<td>690</td>
<td>441</td>
</tr>
<tr>
<td></td>
<td>Mean (SD)</td>
<td>46.8 (15.1)</td>
<td>48.6 (15.4)</td>
<td>48.1 (15.2)</td>
</tr>
<tr>
<td>SSc classification, n, %</td>
<td>1448</td>
<td>1578</td>
<td>893</td>
<td>561</td>
</tr>
<tr>
<td></td>
<td>Diffuse SSc</td>
<td>36.0 35.7</td>
<td>37.0</td>
<td>37.6</td>
</tr>
<tr>
<td></td>
<td>Limited SSc</td>
<td>52.8 55.4</td>
<td>54.1</td>
<td>52.4</td>
</tr>
<tr>
<td></td>
<td>Overlap/mCTD</td>
<td>7.2 5.5 6.5</td>
<td></td>
<td>6.1</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>3.9 3.4 2.4</td>
<td></td>
<td>4.0</td>
</tr>
<tr>
<td>Organ manifestations, n, %</td>
<td>1459</td>
<td>1586</td>
<td>923</td>
<td>566</td>
</tr>
<tr>
<td></td>
<td>GI</td>
<td>57.1 53.5</td>
<td>53.5</td>
<td>52.7</td>
</tr>
<tr>
<td></td>
<td>Heart</td>
<td>9.0 11.2</td>
<td>10.5</td>
<td>9.7</td>
</tr>
<tr>
<td></td>
<td>Kidney</td>
<td>4.5 4.0 5.4</td>
<td></td>
<td>4.8</td>
</tr>
<tr>
<td></td>
<td>Lung fibrosis</td>
<td>39.5 39.6</td>
<td>41.4</td>
<td>41.5</td>
</tr>
<tr>
<td></td>
<td>PAH</td>
<td>13.8 13.7</td>
<td>12.7</td>
<td>13.6</td>
</tr>
<tr>
<td>Antibodies, n^1/n^2, %</td>
<td></td>
<td>453/1088 (41.6)</td>
<td>496/1202 (41.3)</td>
<td>278/669 (41.6)</td>
</tr>
<tr>
<td></td>
<td>ACA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibody Type</td>
<td>n1 (n2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------</td>
<td>-----------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANA</td>
<td>1272/1343 (94.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-Scl 70</td>
<td>532/1167 (45.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-U1 RNP</td>
<td>78/798 (9.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-U3 RNP</td>
<td>25/516 (4.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RNA polym III</td>
<td>65/562 (11.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of DUs at enrolment, n, %</th>
<th>1445</th>
<th>1572</th>
<th>881</th>
<th>561</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>42.4</td>
<td>41.0</td>
<td>40.2</td>
<td>45.1</td>
</tr>
<tr>
<td>1–2</td>
<td>36.7</td>
<td>40.2</td>
<td>41.4</td>
<td>32.6</td>
</tr>
<tr>
<td>3+</td>
<td>20.9</td>
<td>18.8</td>
<td>18.4</td>
<td>22.3</td>
</tr>
</tbody>
</table>

ACA, anti-centromere antibodies; ANA, anti-nuclear antibodies; DU, digital ulcers; GI, gastrointestinal; mCTD, mixed connective tissue disease; n, n1, number of patients; n2, total number of patients for which information was available, PAH, pulmonary arterial hypertension; RP, Raynaud’s phenomenon; SSc, systemic sclerosis.

### Supplementary Table S2 Univariable logistic regression odds ratios with p<0.15

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI manifestation</td>
<td>3.96 (1.28–12.21)</td>
</tr>
<tr>
<td>Previous soft tissue infection requiring antibiotics</td>
<td>5.85 (1.56–21.97)</td>
</tr>
<tr>
<td>Ongoing soft tissue infection requiring antibiotics</td>
<td>4.30 (0.55–33.85)</td>
</tr>
<tr>
<td>Anti-U1-RNP</td>
<td>0.18 (0.03–1.20)</td>
</tr>
</tbody>
</table>

CI, confidence interval; GI, gastrointestinal.
### Supplementary Table S3 Multivariable logistic regression model for the chronic category

<table>
<thead>
<tr>
<th>Parameters</th>
<th>N</th>
<th>Wald chi square</th>
<th>p-value</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI manifestation</td>
<td>149</td>
<td>4.73</td>
<td>0.03</td>
<td>3.73</td>
<td>1.14–12.20</td>
</tr>
<tr>
<td>Previous soft tissue infection</td>
<td>6.66</td>
<td>0.01</td>
<td>5.86</td>
<td>1.53–22.41</td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; GI, gastrointestinal.