Digital ulcers: overt vascular disease in systemic sclerosis
V. Steen1, C. P. Denton2, J. E. Pope3 and M. Matucci-Cerinic4

RP is an almost universal manifestation of SSc, with 95% of all patients being affected, and resulting in digital ulcers (DUs) in ~30% of the patients each year. DUs are a major clinical problem, being associated with substantial morbidity (reduced quality of life, pain, disability and disfigurement) that can escalate to gangrene and amputation. Ideally, the treatment of DUs would improve tissue integrity and viability, promote ulcer healing and reduce the formation of new ulcers. Treatments that have shown potential include calcium channel blockers, prostacyclin analogues and endothelin receptor antagonists. However, until recently, management was based on empirical experience. The recent approval (in Europe) of the dual endothelin receptor antagonist, bosentan, to reduce the number of new DUs in patients with SSc and ongoing DU disease, means that there is now an approved therapy—and new hope—for the treatment of DUs in these severely afflicted patients.

KEY WORDS: RP, Endothelin receptor antagonist, Digital ulcers, Systemic sclerosis.

Introduction
RP is an almost universal manifestation of SSc [1]. It is characterized by vasospasm in response to cold or other stimuli, resulting in impaired oxygenation of the distal extremities and, in some patients, the development of digital ulcers (DUs). DUs are a manifestation of the underlying vasculopathy and fibrosis that characterizes SSc.

DUs—burden of disease
DUs are a major clinical problem in SSc, occurring in ~30% of the patients each year [1]. DUs may occur on the fingers or toes and can manifest on the tips, the finger creases, over the extensor surfaces of the joints or in association with calcinosis [1]. DUs cause local pain and functional impairment (e.g. eating and dressing), and have a major negative impact on quality of life [1]. Chronic ulcers can become infected [1], resulting in gangrene [2], osteomyelitis [3] and amputation. Of the patients with persistent ulcers, 30% develop irreversible tissue loss [2]. As a consequence of the progressive scarring and tissue loss that follow healing of ulcers, patients may exhibit permanent disability, with associated social and self-image problems [3].

The aetiology of DUs is multifactorial [3]. DUs are primary vasculopathies of the fingers and toes, in which intima of vessels can be thickened and the lumen occluded. Ischaemia due to vascular disease, repetitive microtrauma, sclerodactyly, dry skin and calcinosis have all been implicated in the pathogenesis of DUs [3]. Avascular and atrophic tissue has a reduced nutrient supply and capacity for healing, and DUs occur in poorly oxygenated tissues, compounded by the presence of infection, unhealed cuts or abrasions, epidermal thinning and tightly stretched skin with associated contractures [3].

The vasculopathy in SSc is very similar to that observed in pulmonary arterial hypertension and renal crisis [4]. Masson’s Trichrome staining of the digital arteries of patients with SSc has revealed a striking fibrotic intimal hyperplasia, adventitial fibrosis and severely compromised arterial lumen. These characteristics are universal amongst patients with SSc; they may be found in the arteries of the lung, kidney and heart, but may differ in frequency and severity depending on the SSc subtype.

The University of Pittsburgh and Royal Free Hospital London databases
Data from the University of Pittsburgh and the Royal Free Hospital in London have provided new information on the risk factors, morbidity and consequences of DUs in patients with SSc. The Pittsburgh database comprises 2080 patients with SSc, identified between 1972 and 1995, and prospectively followed up for a mean of 10 years [2]. The Royal Free Hospital database comprises 1168 patients with SSc [5].

Frequency of DU
Of the 2080 Pittsburgh patients, the majority (58%) had experienced a DU during the course of their SSc. One-third (32%, n = 666) of all patients with SSc have had persistent DUs (persistent or recurrent ulcers for at least 6 months); of these, 30% of the cases (n = 197) were severe (complicated by gangrene, or requiring digital sympathectomy or amputation) [2].

In the 1168 Royal Free Hospital patients with SSc, 203 patients (17%) had severe digital vasculopathy, defined as DUs in combination with RP, critical digital ischaemia and gangrene, or requiring digital sympathectomy [5]. Most patients had more than one ulcer (mean 2.62 ± 2 DUs per patient) [5].

Demographics of patients with DUs
The majority of Pittsburgh patients with SSc and DUs were Caucasian women (Table 1). The demographics of Royal Free Hospital patients were similar, 22% of the patients with severe digital vasculopathy DUs being male, and 53% of the patients exhibiting lcSSc [5]. Although smoking history was similar (Table 1) [2], patients with persistent DUs were more likely to be current smokers than those with no ulcers. In the Pittsburgh cohort, 25% of the patients had a single DU prior to or at the first visit. These patients with few DUs, whilst similar to those with persistent or severe DUs, had a shorter duration of follow-up. Since we do not know as much about these patients, they have been excluded from subsequent analyses.

Auto-antibodies in patients with DUs
In the Pittsburgh population, more patients with SSc and DUs had either ACAs or anti-topo I antibodies than those who had never had an ulcer (Table 2). This phenotype accounted for more
Table 1. Demographics of 2080 patients with SSc and DUs from the University of Pittsburgh database

<table>
<thead>
<tr>
<th></th>
<th>No DU (n = 880)</th>
<th>Few DU (n = 534)</th>
<th>Persistent DU</th>
<th>All (n = 666)</th>
<th>Severe (n = 197)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male), %</td>
<td>19.5</td>
<td>23.1</td>
<td>17.9</td>
<td>17.9</td>
<td>21.2</td>
</tr>
<tr>
<td>Age at onset, mean, years</td>
<td>45.3</td>
<td>39.7</td>
<td>39</td>
<td>39</td>
<td>36.7</td>
</tr>
<tr>
<td>Race (Caucasian)</td>
<td>91</td>
<td>88</td>
<td>93</td>
<td>93</td>
<td>88</td>
</tr>
<tr>
<td>icSSc, %</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>50</td>
<td>55</td>
</tr>
<tr>
<td>Duration of follow-up, mean, years</td>
<td>7.4</td>
<td>5.5</td>
<td>10.1</td>
<td>6.3</td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever, %</td>
<td>44</td>
<td>43</td>
<td>46</td>
<td>46</td>
<td>50</td>
</tr>
<tr>
<td>At first visit, %</td>
<td>18</td>
<td>20</td>
<td>26</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td>At last visit, %</td>
<td>4</td>
<td>4</td>
<td>2</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Pack-years, mean</td>
<td>13.1</td>
<td>13.5</td>
<td>11.7</td>
<td>11.7</td>
<td>11.1</td>
</tr>
<tr>
<td>Pack-years &gt;10, %</td>
<td>32</td>
<td>33</td>
<td>31</td>
<td>31</td>
<td>33</td>
</tr>
</tbody>
</table>

Table 2. Auto-antibodies in patients with SSc and DUs from the University of Pittsburgh and Royal Free London databases

<table>
<thead>
<tr>
<th>Auto-antibody</th>
<th>No DU (Pittsburgh n = 880)</th>
<th>Persistent DU (Pittsburgh n = 666)</th>
<th>All DU (Royal Free n = 203)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACA</td>
<td>17*</td>
<td>27</td>
<td>24.1</td>
</tr>
<tr>
<td>Anti-topo I</td>
<td>17*</td>
<td>27</td>
<td>34</td>
</tr>
<tr>
<td>Anti-RNA polymerase III</td>
<td>22</td>
<td>3</td>
<td>3.9</td>
</tr>
</tbody>
</table>

*Denotes significant difference from Pittsburgh patients with persistent DUs. Data adapted from [5].

Table 3. Morbidity of patients with SSc and DUs from the University of Pittsburgh database, measured using SHAQ

<table>
<thead>
<tr>
<th></th>
<th>No DU (n = 880)</th>
<th>All (n = 666)</th>
<th>Severe (n = 197)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disability index</td>
<td>1.04</td>
<td>1.44*</td>
<td>1.56</td>
</tr>
<tr>
<td>Pain scale</td>
<td>1.07</td>
<td>1.70*</td>
<td>1.78</td>
</tr>
<tr>
<td>Ulcer scale</td>
<td>0.30</td>
<td>1.71*</td>
<td>1.88**</td>
</tr>
<tr>
<td>Loss of upper extremity function</td>
<td>1.20</td>
<td>1.65*</td>
<td>1.68**</td>
</tr>
<tr>
<td>Loss of joint function</td>
<td>1.12</td>
<td>1.20</td>
<td>1.28</td>
</tr>
</tbody>
</table>

* P < 0.01 compared with no ulcers; ** P < 0.01 compared with all persistent ulcers.

than half (54%) of all patients with persistent DUs (P < 0.01), and an even greater proportion of those with severe persistent DUs (70%, data not shown) [2]. In contrast, patients with SSc but no DUs had an increased frequency of anti-RNA polymerase III (Table 2).

Of the patients in the Royal Free Hospital cohort, 58% exhibited ACAs or topo antibodies, whereas only 4% had anti-RNA polymerase III antibodies (Table 2) [5]. Ulcers, if present in these patients, were more likely to occur across the contracted joints, and less likely to occur on the digital tip.

Morbidity in patients with DUs

Disability, as measured by the Scleroderma HAQ (SHAQ), was significantly greater in Pittsburgh patients with persistent DUs (SHAQ Disability Index 1.44) compared with those who had never had an ulcer (SHAQ disability index 1.04, P = 0.001, Table 3) [2]. Patients with persistent DUs also had significantly more severe pain than those who had never had an ulcer. The loss of function was confined largely to the upper extremities, as would be expected.

Consequences of persistent DUs

Of the Royal Free Hospital patients with DUs, approximately three-quarters were receiving at least one oral vasodilator (47% of the patients with DU received one, and 28% received two or three oral vasodilators) [5]. A total of 141 patients (12% of the total cohort) required hospital admission for treatment with intravenous prostacyclin or calcitonin gene-related peptide during the 18-month window [5].

The Pittsburgh database does not document explicit reasons for hospitalization or antibiotic use, but patients with persistent and severe DUs had significantly more hospitalizations and more hospitalizations in which they were receiving antibiotics than patients without DU (16 vs 9%). This may be very meaningful since the non-DU patients were more likely to have heart and kidney (13 vs 9%) disease and more were on immunosuppressive agents (9 vs 4%).

Figure 1 shows the frequency of patients with a digital tip ulcer who have ulcers, develop gangrene or who have a hospitalization, digital tip ulcer and an antibiotic during each of the 7 years following their first visit. The frequency was determined from the number of patients evaluated during that year; however, this number varied. More than 80% of the patients were evaluated each year. The incidence of gangrenous lesions increased with the length of time since the appearance of DU, particularly after 4 years (Fig. 1).

In the Royal Free Hospital patients with DUs, 38% required hospitalization for management of their ulcers (for a mean of 6 days) [5]. A total of 18 (1.5%) patients required parenteral antibiotic treatment, 56 (4.8%) patients required oral antibiotic treatment and 20 (1.7%) patients required opioid analgesia [5]. In total, 1.4% of the patients developed digital gangrene, and 0.9% of the patients underwent auto- or required surgical amputation [5].

In the Pittsburgh database, 11% of the patients have undergone amputation or experienced gangrene: in the subset of patients with...
persistent ulcers, this rate doubles to a one in five chance of losing part of a finger. This rate is similar to that reported in the Randomized Placebo-controlled study on prevention of Ischaemic DUs in Scleroderma (RAPIDS-2) trial conducted in 188 patients with active DUs, with 11% experiencing amputation (1–2% per patient-year of follow-up) [6].

Management of DUs
Historically, the management of patients with DUs has been difficult. Cases have often been associated with poor outcomes.

Treatment of DUs
Despite the substantial impact on patients’ quality of life in terms of pain, disability and disfigurement, until recently, only iloprost was approved for severe RP in Europe. There are no guidelines for the management of DUs, and there is a need for systematic research to define new treatments for this complication of SSc. Two recent trials have, however, demonstrated that bosentan can reduce the number of new DUs in scleroderma [3, 6].

Aim of the treatment
The aim of the treatment is to reduce the burden of DUs and their impact on quality of life. This is achieved by reducing pain, restoring hand function, improving digital circulation, preventing infection, promoting healing of established ulcers, inhibiting the formation of new ulcers and/or reducing the need for hospitalization and amputation.

Current local management of ulcers
A multidisciplinary approach to the local management of DUs is required, using a combination of non-pharmacological care and antibiotics if an infection is suspected [7–9]. Good skin care is important in minimizing the occurrence of minor trauma and its consequences. Dry skin can be improved with simple topical moisturizing creams and emulsifying ointments. Vasodilatation can be reduced by avoiding precipitating factors such as cold, emotional stress and nicotine (smoking).

Non-invasive ‘debridement’ with antiseptic soaks, topical antibiotics and occlusive dressings are standard, although topical hydrocolloid and occlusive dressings can promote healing. Infection requires prompt treatment, and this generally is based on empirical judgement rather than relying on the results of cultures. Suitable antibiotics include flucloxacillin, cephalaxin, dicloxacillin (not licensed for human use in the European Union) and ciprofloxacin; prolonged and/or rotating courses and parenteral administration may be required. Often cultures are negative or consist of multiple bacteria, but if a culture demonstrates growth of a predominant bacteria, then antibiotics should be directed against that organism, choosing treatment depending upon the sensitivity. Surgical debridement may be necessary but full amputation should be avoided. Digital sympathectomy is being used in severe cases of ischaemia and pre-gangrenous lesions but there are no randomized trials in this area.

Ideally, the treatment of DUs should improve tissue integrity and viability, promote ulcer healing and reduce the formation of new ulcers.

Treatment algorithm
The approach to the management of SSc-related digital vascularopathy is to address the background RP severity (Fig. 2). Often, such patients are resistant to vasodilator therapy, probably because the digital arterial circulation is fixed and unresponsive. Potent analgesia is introduced early, and the possibility of infection and related complications must be addressed, as well as any macrovascular component (vessel occlusion). Thrombosis may require anti-platelet therapy; beneficial effects of low molecular weight heparin have been observed and merit further investigation [10]. Surgical approaches (digital sympathectomy or adventectomy) have not been prospectively studied but most observational studies have documented good pain relief and ulcer healing [11]. A digital sympathectomy by an experienced hand surgeon should be considered for patients with severe and refractory DUs.

Potential pharmacological treatments for DUs
Potential treatment options include calcium channel blockers, intravenous prostanooids and selective phosphodiesterase inhibitors, although only iloprost is approved for severe RP in Europe.

Calcium channel blockers
Calcium channel blockers, such as nifedipine, are in widespread clinical use for RP. Although there are several studies showing improvement of RP, there is little evidence of their effect on DU. A small, 16-week randomized study compared oral nifedipine with intravenous iloprost in patients with SSc and RP, who were severely affected by skin lesions (ulcers, fissures or paronychia) [12]. Although the number of patients with DUs at baseline was not clear, both drugs were associated with a reduction in the number of skin lesions [12]. This provides some support for the use of calcium channel blockers as a ‘background’ therapy in patients with DUs.

Prostacyclin analogues
Prostacyclin analogues, in particular iloprost, have become the standard of care for patients with severe SSc-related digital vasculopathy. Most experience has been gained with intravenous iloprost, which is used for patients with severe secondary RP, including those with DUs. Clinical studies have assessed efficacy in treating either RP or all digital cutaneous lesions, including DUs.

The most robust study supporting the use of iloprost was a 9-week, double-blind, placebo-controlled, multicentre trial in patients with SSc and RP [13]. A greater proportion of patients with digital cutaneous lesions experienced at least a 50% reduction in the number of lesions following iloprost treatment compared with placebo (Fig. 3). This was particularly apparent at earlier time points, but a persistent effect at 9 weeks was impressive. There was also a trend towards iloprost preventing or reducing the formation of new digital lesions (25% of the patients had new lesions after iloprost compared with 33% of the patients receiving placebo). An improvement in function of 7%, measured using the HAQ Disability Index, was observed in iloprost-treated patients, vs a 9% worsening in the placebo group (P < 0.01).
In patients with severe SSc-associated digital vasculopathy, iloprost is administered parenterally, aiming for a target dose of 2 ng/kg/min (a fairly low dose compared with the dose used in pulmonary arterial hypertension), infused for 6 h/day, for 5 days.

Epoprostenol is a prostacyclin analogue for the treatment of pulmonary arterial hypertension available for use in the USA, but it cannot be used for routine management of DU. A placebo-controlled trial for DUs is clearly needed to access the effectiveness of this therapy.

**Phosphodiesterase inhibitors**

Selective phosphodiesterase inhibitors, such as sildenafil, have been investigated for use in patients with RP and have shown significant benefit in the frequency, duration and severity of episodes of RP [14]. However, data relating to effects on DUs are very limited, and no prospective studies looking specifically at DU end points have yet been conducted.

**Endothelin receptor antagonists**

If DUs are accepted as being an external manifestation of SSc-related vasculopathy, it is plausible to think that endothelin must have a role. Endothelin is elevated in the serum of patients with SSc, especially in those with DUs, and co-segregates as a biomarker of vascular severity [15, 16], much as it does in the pulmonary hypertension population. This prompted the investigation of the dual endothelin antagonist, bosentan, for the management of DUs, in two separate studies—RAPIDS-1 and RAPIDS-2. Bosentan was subsequently approved in Europe for use in reducing the number of new DUs in SSc patients.

**RAPIDS-1.** The 16-week, randomized, double-blind, multicentre RAPIDS-1 study [3], which was conducted during cold weather, aimed to evaluate whether bosentan [62.5 mg twice daily (b.i.d.), titrated up to 125 mg b.i.d. after 1 month], was effective at preventing new DUs in patients with SSc (n = 122). Patients did not have to have an active DU at entry, but had to have a history of at least one DU during the previous year.

Bosentan was associated with a significant 48% reduction (P = 0.008) in the primary outcome measure (the number of new DUs that developed during the 16-week trial), with patients receiving bosentan (n = 78) developing a mean of 1.4 new ulcers compared with 2.7 in patients receiving placebo (n = 43). Bosentan was particularly effective in patients at risk of multiple ulcers. Patients receiving bosentan also experienced a significant and clinically meaningful improvement in hand function (Fig. 4, but there was no effect on healing of existing ulcers.

**RAPIDS-2.** The 24-week, randomized, double-blind, multicentre RAPIDS-2 study [17] was designed to confirm the positive effects of bosentan (62.5 mg b.i.d. for 4 weeks and then titrated to 125 mg b.i.d. for 20 weeks) at reducing new DUs in patients with SSc (n = 188) and at least one active DU, and to evaluate potential effects on healing. Co-primary end points were time to complete healing of a ‘cardinal’ ulcer (selected as important by the patient and investigator) and the number of new DUs, with secondary end points including the SHAQ-Disability Index. The patients receiving bosentan (n = 98) and placebo (n = 90) were well balanced in terms of demographics (Table 4), including smoking history and concomitant medications. These patients had more active ulcers at baseline than the RAPIDS-1 population.

Bosentan was associated with a significant reduction in the number of new ulcers (30% fewer). Patients who received bosentan (n = 95) developed a mean of 1.9 new ulcers compared with 3.7 in patients who received placebo (n = 89, P = 0.035), and effects were apparent as early as 12 weeks. The observed reduction was particularly marked in those patients with more than three active DUs at baseline (Fig. 5). There was no effect of bosentan on healing: at 24 weeks, 50% of the patients in each group showed complete healing of a ‘cardinal’ ulcer (selected as important by the patient and investigator) and the number of new DUs, with secondary end points including the SHAQ-Disability Index. The patients receiving bosentan (n = 98) and placebo (n = 90) were well balanced in terms of demographics (Table 4), including smoking history and concomitant medications. These patients had more active ulcers at baseline than the RAPIDS-1 population.

In contrast to what is known for RP, there was no clear influence of season on DUs, indicating that DUs may be more related to the severity of vasculopathy. There was also no effect from local (topical) treatments or changes in these concomitant medications (changes in therapy for RP), or smoking history (never smoked vs past smoker). Only current smoking appeared to have an effect on the development of new DUs, attenuating the effect of bosentan [18]. Bosentan was also associated with improved function, especially in the dressing domain (at 12 weeks, P = 0.03), and reduced pain (at 12 weeks, P = 0.034).

**Overall.** Overall, the two randomized controlled trials reported remarkably similar data. Bosentan prevented the development of new ulcers (48% reduction in RAPIDS-1 and 30% reduction in RAPIDS-2), but had no effect on the healing of existing DUs. The reduction in the number of new DUs was associated with...
improved patient function, most notably in overall hand function (RAPIDS-1) and dressing domains (RAPIDS-2).

Selecting measures to assess ulcer severity and response to therapy

Studies are required to define the most appropriate indicators of ulcer severity. When a patient presents with a DU, there is a variety of indicators guiding assessment of severity: DU size, number, location, loss of function, pain and tissue loss are all important. A very large ulcer might be associated with longer healing time, pulp loss, increased risk of infection and increased pain. The number of ulcers is an important indicator of likely course in the near future, and a patient is at more risk of persistent problems if there are multiple ulcers. Location may be important if the ulcer prevents the patient from working, and loss of function is important since it precludes normal daily activities. Pain is substantial, associated with extensive and painful ischaemia in the underlying tissue. Tissue loss is a prime consideration because the damage is cumulative with successive ulcers and causes ongoing pain even when the ulcer heals.

It is difficult to classify DUs. An active ulcer is present if it is open and draining, but a persistent ulcer may be chronic, painful, large, deep and associated with recurrent active ulcers. Activity and persistence are an important indicators of severity (for example, an ulcer that will not heal, either as a result of repetitive trauma, poor blood flow or tissue loss) as is the number of ulcers (a patient with eight ulcers has a far more severe DU pattern than someone with one or two). Recurrent ulcers, the size and depth of ulcers, and their location, should also be considered. The level of pain may or may not reflect severity or ulcer activity.

A good indicator of disease severity is quality of life (daily activities, functional loss and disability), since ‘trivial’ problems, such as inability to tie shoe laces, wash or get dressed, have a substantial impact on patient well-being. Severe DUs can result in hospitalization or intravenous or ongoing antibiotic treatment, a requirement for surgery and complications (gangrene and amputation). From a larger perspective, other indicators of severity include the cost to the patient and their family. There is no consensus on the most important indicator of disease severity, and multiple factors should be considered.

To determine disease severity and response to therapy requires measures that are reproducible. The surrogate should correlate with the outcome (e.g. does skin temperature correlate with healing?), and should be low risk, inexpensive, widely available and associated with low levels of patient discomfort. These factors probably rule out angiograms (invasive), three-dimensional MRI (expensive and not widely available) and DU biopsy (painful). Whatever surrogate is used, the scales of ulcer severity or activity should be widely available: this generally means that patient-reported and physician-reported scales are used. Previous studies have used DU counts, the reduction in the number of new DUs, speed of healing or 50% healing. Others include global assessments of severity, including patient assessment of ulcer activity [visual analogue scale (VAS)], ulcer pain VAS-HAQ, as part of the SHAQ, along with the Disability Index in that instrument and quality of life tools (SF-36) as well as physician assessment of disease measures. As with other disciplines, multiple outcomes should be measured to fully assess disease severity and response to therapy.

Conclusions

RP is an almost universal manifestation of SSc, with 95% of all patients being affected at some point, and resulting in DUs in 30% of patients each year. The substantial impact on patients’ quality of life and the availability of few approved therapies for DUs make the identification of new and efficacious management strategies a priority. Calcium channel blockers, prostacyclin analogues and PDE-5 inhibitors have the potential to improve RP and iloprost may benefit patients with DUs. Further randomized, placebo-controlled trials are urgently needed to establish the efficacy of these agents. The dual endothelin receptor antagonist bosentan has demonstrated efficacy by the prevention of new DUs and improving quality of life. Bosentan is particularly effective in more severely affected patients. Research is required to define the most appropriate indicators of disease severity, as well as identify novel agents with the capacity to improve tissue integrity and viability, promote ulcer healing and reduce the formation of new ulcers.

Rheumatology key messages

- DUs impact quality of life in patients with SSc and are a marker for disease severity.
- There are sparse trial data demonstrating healing of DUs; however, bosentan may prevent new ulcers and improve hand function.

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