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RECENT ADVANCES IN THE PATHOGENESIS AND MANAGEMENT OF RAYNAUD'S PHENOMENON AND DIGITAL ULCERS

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ABSTRACT

Purpose of review: Systemic sclerosis (SSc)-related digital vasculopathy can progress from severe Raynaud's phenomenon (RP) to digital ulceration, is a major cause of pain and disability, and impacts negatively on quality of life. Current treatments are often ineffective and poorly tolerated. This review summarises some of the progress which has been made in the last 12 to 18 months in terms of our understanding of disease process, measurement and treatment.

Recent findings: The most important findings include that we can now better predict which patients with SSc are most likely to develop digital ulcers. In terms of treatment, a multicentre trial showed that the phosphodiesterase inhibitor sildenafil confers some benefit in SSc-related digital ulceration. Topical therapies are being explored: iontophoresis of vasodilators increases local blood flow, and in an avian model, VEGF₁₂₁ fibrin applied in a gel matrix improved wound healing.

Summary: Progress is being made. Advances in our understanding of SSc-related vasculopathy continue to lead to exploration of new treatment approaches. Clinical trials and observational studies are challenging, but are being facilitated by developments in outcome measures and improved infrastructures and networking, allowing trials in much larger numbers of patients than have previously been possible.

KEY WORDS: Systemic sclerosis, Raynaud's phenomenon, digital ulcers, treatment

INTRODUCTION

Raynaud's phenomenon (RP) occurs in almost all patients with systemic sclerosis (SSc) [1] and can be very severe, often progressing to digital ulceration (in around 50% of patients) (Figure 1) and occasionally to gangrene [2,3**]. This severity relates to the fact that in SSc, structural as well as functional vascular abnormalities occur, in contrast to primary (idiopathic) RP when the vascular abnormality is thought to be purely functional and entirely reversible, never progressing to irreversible tissue injury. Recent studies have highlighted the burden of associated disability of both RP [4*] and digital ulceration [3**,5], and the lack of effective treatments (only 16% of 443 patients with RP responding to a survey reported that current medication was effective [4*]).

A number of challenges confront clinicians and scientists with an interest in SSc-related digital vasculopathy, specific questions being:

1. What mechanisms drive the digital vasculopathy and lead to structural as well as functional change?
2. Can we predict which patients progress to digital ulceration?
3. Can we measure disease process reliably (in terms of both RP and digital ulcers), to provide outcome measures to facilitate clinical trials?
4. Are we making progress in developing safe and effective treatments, for both severe RP and SSc-related digital ulceration?

In this review I shall outline developments over the last 12-18 months in answering these four questions, under the headings of pathophysiology, predictors of digital ulceration, measurement of disease process, and management. Under each heading I shall consider firstly RP and secondly digital ulceration, although this is a false distinction because both are part of the spectrum of SSc-digital vasculopathy.

PATHOPHYSIOLOGY

Raynaud's phenomenon

The pathophysiology of RP is complex and most likely involves an interplay between vascular factors, neural control mechanisms and intravascular factors [6]. Flavahan, in a recent review [7**], describes thermoregulatory mechanisms as central to an understanding of RP, highlighting the role of arteriovenous anastomoses, and how local cooling leads to increased activity of α_2 -adrenoceptors, resulting in reduced blood flow. In patients with SSc, structural microvascular changes mean that upstream vasoconstriction can irretrievably compromise nutritional blood flow and lead to tissue injury [7**,8]. The review also gives a framework for targeted therapeutic interventions [7**].

Digital ulceration

A commonly held view is that fingertip ulceration is ischaemic, whereas ulceration over the extensor surfaces of fingers is 'traumatic'. To date there has been very little direct evidence to support this theory. However, a study by Ruaro et al [9*] of 20 patients with SSc and fingertip ulcers demonstrated that blood flow is reduced at the site of fingertip ulcers (and improves with healing).

Saigusa et al performed a series of experiments investigating the role of CCN1 (a secreted cysteine-rich heparin-binding protein) in SSc, and reported reduced circulating levels in patients with current or previous digital ulcers [10*]: they postulated that the reduced levels were at least in part caused by Fli1 deficiency. The same investigators [11*] suggested that Fli1 deficiency might result also in downregulation of endothelial protein C receptor (EPCR), serum levels of which were reduced in patients with digital ulcers compared to those without: reduced levels of EPCR could lead to a prothrombotic state which might contribute to ulceration by further compromising microcirculatory

flow. Therefore work is ongoing examining the cellular and molecular mechanisms underpinning the vascular abnormalities which drive digital vasculopathy.

A review article by Chora et al [12*] summarised reported correlations between a large number of 'vascular biomarkers' and digital ulcers, and also with nailfold capillaroscopic change. Although associations do not prove causation, nonetheless it is tempting to speculate that some of the associates of digital ulceration might in the future be targets for therapy.

PREDICTORS OF DIGITAL ULCERATION

Accurate prediction of which patients with SSc are most likely to develop digital ulcers would allow risk stratification, relevant not only to clinical practice but also in the design of future clinical trials aimed at ulcer prevention.

Several studies in the last 18 months have described predictors of digital ulceration [13*,14*,15*,16,17*], and Manfredi et al described a prediction risk chart [18]. A large prospective study 623 patients with SSc from 59 centres reported that of the 468 patients with a history of previous digital ulceration, the capillary density in the middle finger of the dominant hand, the number of digital ulcers, and the presence of critical ischaemia, at baseline, were the strongest risk factors for development of new digital ulcers over the following six months [15*], therefore lending further support to previous studies suggesting that abnormal capillaroscopy (including reduced capillary density) is associated with future development of digital ulcers [13*,19,20]. Other predictors from recent studies included anti-topoisomerase antibodies [16,17*], the presence of autoantibodies against endothelin 1 (ET-1) Type A receptor [14*] and increased circulating levels of ET-1 [13*] and (reflecting functional vascular change), impaired thermal hyperaemia [21], endothelial dysfunction as assessed by flow-mediated dilatation [13*] and the severity of change on thermography [22*].

A recent systematic review [23*] summarised risk factors and concluded that the diffuse cutaneous disease subtype, early onset RP/disease, anti-topoisomerase antibodies, capillaroscopy pattern, raised ET-1 levels, and low vascular endothelial growth factor (VEGF) levels were all risk factors for digital ulcers.

How can the clinician synthesise all these findings? In everyday clinical practice, those patients most likely to ulcerate are those with a history of severe RP/previous ulcers, antibodies to topoisomerase, and severe change on capillaroscopy (this last makes sense: the more severe the microvascular disease, the higher the likelihood of ischaemic ulcers). Other markers may be useful in the research setting but require further validation. It is worth highlighting that digital ulceration in patients with SSc has recently been shown to be a predictor of internal involvement and reduced survival [24*, 25**].

MEASUREMENT OF DISEASE PROCESS

Raynaud's phenomenon

The only validated measure of RP is the Raynaud's Condition Score [26]. Clinical trials tend to rely on this and other patient reported outcomes, namely frequency, duration and severity of attacks. However, patient reported outcome measures are subjective, and a vision is to develop objective, non-invasive measures of digital blood flow: although these are unlikely to be used in large multicentre studies they have potential in proof-of-concept, early phase studies. Methods currently being used include thermography (an indirect measure of blood flow) and laser Doppler techniques [27,28,29*,30*]. However, full validation and standardisation of protocols is required before these can be used more widely.

Digital ulceration

Digital ulcers are often a primary endpoint in randomised controlled trials (RCTs), and yet there is poor agreement as to their definition [31,32]. A recent study [33*] showed that adding contextual information (e.g presence of pain, discharge) to the visible appearance of the ulcers did not improve reliability. International efforts to standardise definition are ongoing.

TREATMENT

The purpose of this article is not to provide a state-of-the-art review of management but rather to highlight key recent advances. The UK Scleroderma Study Group consensus best practice pathways [34*] provides flow-charts of current management of RP, digital ulceration and critical ischaemia, but with the proviso (as discussed below) that these pathways are already slightly outdated because phosphodiesterase type 5 (PDE5) inhibitors should now be 'moved up' the pathways. Clinical practice will vary between countries depending on accessibility to the different treatments. Other than bosentan, the drugs discussed are not licenced for SSc-related digital vasculopathy.

Raynaud's phenomenon (which has not progressed to digital ulceration or critical ischaemia)

A recent systematic review highlighted the lack of evidence base for treatment of SSc-related RP [35]. However, progress is being made. The major point to highlight in the last 18 months for the practising clinician has been the increased use of PDE5 inhibitors, and many clinicians are now very likely to use a PDE5 inhibitor as a second choice after a calcium channel blocker in patients with SSc-related RP. This is because (a) PDE5 inhibitors have now been shown to confer benefit in a number of randomised controlled trials [36,37,38,39], and in a recent meta-analysis [40] (although the trials were all short-term, with a treatment period of 6 weeks or less) and (b) reduced costs of PDE5 inhibition from previously. Figure 2 is a modification of the UK best practice pathway, with a repositioning of PDE5 inhibitors alongside other oral vasoactive therapies. A recent study from the German Network for Systemic Sclerosis registry showed PDE5 inhibitors were prescribed in only 1.5% of patients with SSc-related RP (but without digital ulcers) first registered after 2009, and in

5.5% of those with digital ulcers [41*]. Likewise numbers of patients prescribed PDE5 inhibitors in the recent Digital Ulcer Outcomes Registry (DUO) study were very low [3**]. It will be interesting to see how the situation changes over the next two to three years.

As Figure 2 outlines, intravenous prostanoids are used in some cases of severe 'uncomplicated' RP (RP which has not progressed to digital ulceration or critical ischaemia), but require hospitalisation. Selexipag, an oral IP prostacyclin receptor agonist which has been shown to be effective in pulmonary arterial hypertension, held promise also for RP. Disappointingly a recent clinical trial, so far published only in abstract form [42], showed no benefit from selexipag in SSc-related RP.

It seems likely that in SSc-related digital vasculopathy as in pulmonary arterial hypertension, combination therapy may be helpful given that different classes of drugs have very differing (and potentially synergistic) modes of action. Bellando-Randone et al [43] reported a retrospective study of 123 patients with SSc and suggested that combination treatment with bosentan and sildenafil conferred benefit on RP. Prospective studies are required.

Randomised controlled trials of RP are, however, challenging, given the heterogeneity of RP, the requirement to run studies over the winter months, and the subjectivity of patient reported outcome measures. Early phase proof-of-concept studies allow early assessment of promising therapies. Bose et al [44*] reported a 12 week double-blind, parallel-group, controlled trial comparing the endothelin Type A receptor antagonist ambrisentan (15 patients) with placebo (5 patients). Although no improvement in finger blood flow was demonstrated with ambrisentan (as assessed by laser Doppler perfusion imaging), as the authors concluded, there are a number of different mechanisms through which ET-1 blockade could exert benefit in SSc-related digital vasculopathy and ET-1 receptor antagonists warrant further research.

Digital ulcers

Several recent reviews give detailed descriptions of management [45*,46*,47*], with Figure 3 providing a summary flow-chart of current practice. Recent studies have highlighted the importance of adequate analgesia[48,49]: this is welcome as this key aspect of care is sometimes overlooked.

Randomised controlled trials. Three large scale randomised placebo-controlled trials of SSc-related digital ulceration have been published in the last year. The SEDUCE study of 83 evaluable patients (with 192 digital ulcers), compared 12 weeks' treatment with sildenafil 20mg three times daily to placebo (1:1 randomisation)[50**]. Although the primary end-point (time to healing) was not reached, sildenafil conferred some benefit with a greater healing rate in the sildenafil group compared to placebo at week 8 ($p=0.01$) and week 12 ($p=0.03$). The DUAL-1 and DUAL-2 studies[51**], randomising 289 and 265 patients respectively, both compared (over 16 weeks) macitentan 3mg daily, macitentan 10mg daily and placebo (1:1:1 randomisation). Macitentan, similarly to bosentan (which is licenced for the prevention of SSc-related digital ulcers) is a dual ET-receptor antagonist but has sustained receptor binding and increased tissue penetration. It reduces morbidity and mortality in pulmonary arterial hypertension [52] and was therefore a promising treatment for SSc-related digital ulcers. However, the cumulative number of new ulcers (the primary endpoint for each of DUAL-1 and DUAL-2) was no different between macitentan and placebo treatment: DUAL-2 was halted prematurely on the recommendation of the independent data monitoring committee. Irrespective of their outcomes, the SEDUCE and DUAL studies are testimony to the ability of the international community to mount large scale multicentre studies of SSc-digital ulcers. This represents a major step forward, and will facilitate addressing the need (highlighted by a meta-analysis in 2013 [53]) for larger studies with standardised outcome measures.

Observational studies of vasoactive therapies. The RAPIDS-1 and RAPIDS-2 randomised controlled trials studies demonstrated the efficacy of bosentan in the prevention of SSc-related digital ulceration [54,55]. Agard et al [56*] conducted a retrospective study in 10 French centres to examine characteristics of 89 patients treated with bosentan in a 'real-world' setting: patients

treated with bosentan (median treatment duration until data collection was 17.5 months) had severe disease (61% with at least 2 previous digital ulcer episodes, and 63% had had previous intravenous iloprost infusions). As with 'uncomplicated' RP, there is increasing interest in combination therapy: a retrospective analysis of 34 patients suggested that adding bosentan to monthly iloprost infusions was associated with ulcer healing in around 50% of patients [57]. While ideally controlled trials of combination therapy are needed, study design will prove highly challenging.

Procedural treatments. In SSc, these tend to be confined to patients who have progressed to digital ulceration or critical ischaemia. The increasing interest in botulinum toxin injections continues [58], with a prospective study of 20 patients with SSc reporting improvement in hand function after 8 weeks [59]. Randomised controlled trials are required and are underway.

Digital sympathectomy [60,61] also continues to attract interest and is probably being performed increasingly in specialist centres. A recent retrospective study of 17 patients with SSc (26 hands operated on) reported symptomatic improvement in pain in 92.3% of hands and ulcer healing in all patients [62*], with the authors suggesting that the procedure should be considered earlier on in the disease rather than as a 'last resort'.

Fat grafting has been proposed as another possible therapy for severe secondary RP [63].

Extracorporeal shock wave therapy was reported to confirm some benefit in a study of 9 patients with SSc and 49 ulcers [64].

Therefore more 'aggressive' approaches to digital ulceration are being investigated and gaining ground. Although a systematic review concluded that the evidence base for surgical procedures for RP is lacking [65*], this is perhaps unsurprising given the relatively small numbers of patients coming to surgery and the difficulties in mounting clinical trials. Observational studies with standardised outcome measures should be encouraged.

Topical therapies. Many patients with RP, with or without digital ulcers, do not tolerate oral or intravenous treatment because of systemic vasodilatory side effects. Effective topical therapies which act locally on the digits, and which are free from systemic side effects, are badly needed. It is encouraging that both preclinical and human studies are exploring topical delivery systems, including with iontophoresis, to improve blood flow [66,67,68]. An exciting potential development is the prospect of being able to apply local therapies to ulcers to induce angiogenesis and promote healing: a study in UCD-206 chickens showed that application of VEGF₁₂₁-fibrin in a gel matrix improved ischaemic comb and neck lesions, with increased microvascular density compared to in fibrin treated and untreated lesions [69**].

CONCLUSION

Advances in the understanding and treatment of SSc-related digital vasculopathy have been published in the last 12-18 months. Patients at high risk of progressing to digital ulcers can now be better identified, paving the way for studies of early intervention. Large multicentre studies can and are being mounted, and also smaller proof of concept studies of novel treatment modalities (facilitated by standardisation of outcome measures). The next five years should see further translation of research findings into patient benefit.

WORD COUNT: 2528

KEY POINTS

1. Digital vasculopathy is one of the major contributors to pain and disability in patients with SSc.
2. Pathophysiology remains elusive, but more is now known about the mechanisms of thermoregulatory imbalance and of structural vasculopathy.
3. Research is ongoing into outcome measures, including into definition of digital ulcers.
4. Randomised controlled trials, both early phase and larger multicentre, are feasible and providing an evidence base to treatment (e.g. for PDE5 inhibitors).
5. Other treatment approaches (e.g. botulinum toxin injections) are being advocated, but controlled clinical trials and/or carefully designed observational studies are required.

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This paper is potentially very exciting: results from a series of experiments indicated that VEGF₁₂₁-fibrin, applied in a gel matrix, induced angiogenesis. This finding should pave the way for studies in humans, the key question being whether this form of treatment could be used to treat SSc-related digital ulcers.

CONFLICTS OF INTEREST

ALH has done consultancy work for Actelion, served on a Data Safety Monitoring Board for Apricus, received research funding and speaker's fees from Actelion, and speaker's fees from GSK. She is or has recently been a principal investigator on studies sponsored by Actelion and Bayer.

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LEGENDS TO FIGURES

Figure 1. (a) Fingertip ulcer (ring finger) in a patient with SSc and previous amputations of the index and middle fingers. Multiple telangiectases can also be seen. (b) An attack of RP (pallor phase).

Figure 2. Modification of the UK Scleroderma Study Group Best Practice Recommendations on the management of Raynaud's phenomenon[34*]. Phosphodiesterase inhibition has been 'moved up' the original pathway to be positioned along with other oral vasodilator therapies. Note that clinicians outside the UK might modify their approach depending on their access to therapies. ACE:

angiotensin-converting enzyme; ARB: angiotensin receptor blocker; CCB: calcium channel blockers; PDE5: phosphodiesterase type 5; SSRI: selective serotonin reuptake inhibitor.

Figure 3. Modification of the UK Scleroderma Study Group Best Practice Recommendations on the management of SSc-related digital ulceration [34*]. ERA: endothelin-1 receptor antagonist; PDE5: phosphodiesterase type 5.

Management of Raynaud's Phenomenon

1.

Establish diagnosis and identify any underlying cause amenable to treatment

No underlying cause amenable to treatment

Treat underlying cause e.g. cryoglobulinaemia

2.

General/lifestyle measures:
Patient education
- Avoid cold, keep warm
- Stop smoking
(Complementary therapies)

Ineffective

3.

Drug therapy: first line
CCB, PDE5 inhibitor, ARB, SSRI, alpha blocker, ACE inhibitor, topical nitrate

4.

Antiplatelet and /or statin therapy

±

Effective

Ineffective oral therapies/refractory disease

5.

Drug therapy: refractory
IV prostanoid

Effective

Ineffective

6.

Progression to digital ulceration and/or critical ischaemia flowchart