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Abstract

Introduction: The cutaneous vascular manifestations of systemic sclerosis (SSc) comprise Raynaud's phenomenon, cutaneous ulceration, telangiectasia formation and critical digital ischaemia; each of which are associated with significant disease-related morbidity. Despite the availability of multiple classes of vasodilator therapy, many of which have been the subject of RCTs, a limited number of pharmacological interventions are currently approved for the management of cutaneous vascular manifestations of SSc.

Areas covered: A major challenge has been demonstrating treatment efficacy with examples of promising therapies yielding contrasting results in controlled trial settings. Differences between consensus best-practice guidelines, evidence-based recommendations and marketing approvals in different jurisdictions has resulted in geographic variation in clinical practice concerning the management of cutaneous vascular manifestations of SSc. Difficulty demonstrating treatment efficacy risks waning industry engagement for drug development programmes in this field. This article highlights the key challenges in establishing treatment efficacy and barriers that must be overcome to support successful clinical trial programmes across the spectrum of cutaneous vascular manifestations of SSc.

Expert Opinion: The paucity of approved treatments for cutaneous vascular manifestations of SSc relates as much to challenges in clinical trial design and the need for reliable clinical trial endpoints, as to lack of therapeutic options.

Abstract word count: 200 words

Key Words: Systemic sclerosis, Raynaud's phenomenon, Outcome Measures, Clinical Trials, Digital Ulceration, Critical Digital Ischaemia, Telangiectasia

1.0 Introduction

Systemic sclerosis (SSc) is a multisystem disease characterised by a complex interplay of autoimmunity, aberrant tissue remodelling and vasculopathy related to dysregulated tissue injury and repair. When considering cutaneous disease in SSc, attention typically focusses on excessive dermal collagen deposition that justifies the historical appellation “scleroderma”; despite skin thickening not being a universal feature, one that is often absent at diagnosis and not uncommonly confined to the digits where its impact can remain limited. *Cutaneous vascular manifestations*, however, are omnipresent and an important requisite to diagnosis and classification of early disease. The relevance of the cutaneous vascular manifestations are easily overlooked by clinicians and researchers pre-occupied by potentially life-threatening internal organ manifestations but their importance to patients and impact on daily living should not be under-estimated. Unsurprisingly, vasodilator treatments have formed the mainstay of therapeutic intervention but such approaches do not directly target the endothelial damage and obliterative vascular remodelling that produce the cutaneous vascular manifestations of SSc. Delivering and demonstrating treatment efficacy for cutaneous vascular manifestations of SSc has been challenging and carries a risk of waning industry engagement for clinical trials within this field.

The present review shall consider the cutaneous microangiopathy of SSc and its contribution to the four major cutaneous vascular manifestations of SSc; Raynaud’s phenomenon (RP), cutaneous ulceration (which includes but is not restricted to digital ulcers [DU]), telangiectasia formation and critical digital ischaemia (CDI). Many valuable reviews and clinical practice guidelines have considered the evidence-base for intervention for these disease manifestations and this review shall not attempt to replicate such work. Instead, I shall focus on our existing methods for assessing cutaneous manifestations of SSc, challenges surrounding clinical trial design and, where applicable, what clinical trial data might teach us of the relative merits and limitations of past endeavours. The review shall primarily focus on outcome measures included in the provisional core set of outcomes for SSc clinical trials and those currently accepted by regulatory bodies assessing labelling claims for marketing authorization [1]. The potential future role of emerging methods such as non-invasive microvascular imaging as endpoints in clinical trials of cutaneous vascular manifestations of SSc shall be discussed where applicable. This article highlights many of the key challenges in establishing treatment efficacy and the barriers that must be overcome to support successful clinical trial programmes across the spectrum of cutaneous vascular manifestations of SSc. Presently, I shall first consider the nature of cutaneous vasculopathy in SSc and its relevance to disease pathogenesis.

2.0 Body

2.1 The nature of cutaneous vasculopathy in SSc

Endothelial injury is an important initiating event in SSc and histological analysis in early disease reveals a peri-vascular cellular infiltrate in tissues long before the emergence of overt fibrosis [2]. The inter-relationship between vasculopathy and fibrosis formed the basis of the “Vascular Hypothesis” proposed by Campbell and LeRoy which remains central to current doctrine regarding SSc pathogenesis [3]. The exact temporal relationship between endothelial injury and emergence of clinical sequelae of SSc has not been fully elucidated but it is cutaneous vascular features such as RP and puffy fingers (caused in part by vascular leak) that typically herald the onset of SSc; with both clinical manifestations forming part of the clinical criteria (alongside ANA positivity) in the proposed classification of *very early* systemic sclerosis [4, 5]. The period between the onset of RP and other disease manifestations varies greatly according to disease subset (and autoantibody specificity) with a mean time of 6.5 years between RP-onset and the first non-RP symptom (a curious but commonly applied method for delineating SSc disease onset) in patients carrying the anti-centromere autoantibodies typically associated with limited cutaneous SSc (lcSSc) [6]. The episodic nature of RP (at least in the early stages of the disease) highlights the functional impact of early vascular injury but peripheral vascular compromise in SSc is compounded by a progressive structural obliterative microangiopathy; the effects of which can be directly visualised at the nailfold where morphological abnormalities can be used in the diagnosis and classification of early disease when skin thickening and other fibrotic complications of SSc may not be present [7, 8, 9] (Figure 1). The gradual evolution of nailfold capillary abnormalities (best observed over months and years) highlights the progressive nature of the cutaneous vasculopathy and is reflected in the terminology applied to the characteristic nailfold capillary changes associated with “early” (relatively few giant capillaries and microhaemorrhages with little or no capillary drop out) and “late” (more extensive capillary drop out and occasional large ramified bushy capillaries) disease [10]. Attention has relatively recently shifted from the diagnostic utility of nailfold capillaroscopy to its prognostic potential and there is growing evidence of an association between “late” nailfold capillary abnormalities and a broad range of clinical outcomes that, relevant to the scope of this review, include telangiectases [11], calcinosis [12], acro-osteolysis [13] and DU disease [14, 15, 16]. The progressive obliterative microangiopathy and capillary loss are thought to contribute to more pronounced and sustained cutaneous ischaemia. This could have important, but hitherto overlooked, implications for both current methods of assessment and potential efficacy of therapeutic intervention, as shall now be discussed.

2.2 Raynaud’s phenomenon

RP occurs in virtually all patients with SSc and is consistently the highest ranked disease-specific manifestation of SSc in terms of frequency and impact [6, 17]. Whilst not life-threatening, SSc-RP is a major cause of disease-related morbidity in SSc and self-management is typically insufficient to control symptoms [18]. The term RP describes a symptom complex and is routinely used as an umbrella term to describe a heterogeneous group of disorders associated with varying degrees of functional and structural peripheral macro- and microvascular compromise, whose individual pathophysiologies differ markedly. The seemingly innocuous shared use of the term RP has had significant undesirable effects. Firstly, it has encouraged investigators to undertake mechanistic studies and clinical trials in mixed heterogeneous populations of patients [19, 20]. Secondly, it has resulted in a large number of reviews and clinical practice guidelines reporting on matters pertaining to the pathogenesis and management of “Raynaud’s” that insufficiently segregate the different causes of RP during the subsequent discourse. Finally, it has resulted in the same outcome measures being applied within different populations of patients despite the aforementioned marked differences in aetiopathogenesis.

The 2-week Raynaud’s Condition Score (RCS) diary emerged in the mid-1990s for clinical trials of prostanoid therapy for SSc-RP [21, 22, 23]. The RCS diary allows patients to capture the frequency (weekly or daily number of attacks), duration and severity/impact of their Raynaud’s symptoms. Severity/impact of Raynaud’s is assessed using the RCS; a single-item 11-point numeric rating scale in which respondents are asked to consider up to 8 features of RP when considering their score; with the frequency and duration of attacks featuring prominently in the list. It is curious to note that the exact item wording of the RCS (and its predecessor the Raynaud’s Severity Scale) differ slightly in different studies which could have an important influence on RCS scores (Table 1). Data from the original negative clinical trial of oral iloprost was used to validate the RCS diary [22, 24] although the approach taken was restricted by the clinical trial data available. For example, reliability assessments used pooled data from participants receiving active treatment, whereas responsiveness to change analysis used pooled data obtained from patients receiving placebo therapy [22, 24]. Moreover, whilst the RCS was shown to discriminate between patients with and without DU, the RCS item wording itself encouraged patients to consider painful sores when choosing their score (Table 1) [22, 24]. Nonetheless, the RCS diary has subsequently been included in the provisional core set of outcome measures for SSc clinical trials and incorporated into the majority of SSc-RP clinical trials since its development [1]. In the UK, nifedipine (a calcium channel blocker) has been licensed by the Medicines and Healthcare Products Regulatory Agency as a treatment for RP since 1998. Since then, there have been a large number of clinical trials incorporating the RCS diary of vasodilator therapies including prostanoid therapies [22, 23], phosphodiesterase inhibitors [25, 26], nitrates [27],

endothelin receptor antagonists [28] and a non-prostanoid prostacyclin receptor agonist [29] in which treatment efficacy has been shown to be absent or modest at best. As a result, there are currently no EMA- or FDA-approved treatments for SSc-RP although treatments such as phosphodiesterase inhibitors, nitrates and prostanoid therapies have each been included in clinical guidelines on the management of SSc-RP [30, 31, 32]. Clinical trials incorporating the RCS diary (and other PRO instruments for assessing SSc-RP) have identified a high placebo response [33]. Recent work has also identified poor concordance with non-invasive vascular imaging approaches to assessing digital cutaneous perfusion [34, 35]. There is recognition within the SSc community that the RCS diary might be a barrier to drug development programs for SSc-RP [36]. Recent work has re-appraised the patient experience of SSc-RP as groundwork for a novel patient-derived patient-reported outcome (PRO) instruments for assessing SSc-RP. A large multicentre qualitative research study was undertaken that has identified a number of important patient experiences of SSc-RP that are not currently captured using existing PRO instruments or that challenge accepted doctrine on what actually constitutes SSc-RP (Figure 2) [37]. RP is usually defined as *episodic* digital vasoconstriction in response to cold exposure or emotional stress. This definition implies the absence of digital microvascular compromise in between “attacks”. This paradigm is at the heart of the diary-based approaches to assessing RP severity but may not entirely capture the experience of patients with SSc, for whom the obliterative microangiopathy results in more persistent digital ischaemia. For example, the Raynaud’s Severity Score diary (predecessor of the RCS diary) defined a Raynaud’s attack as an episode of pallor followed by cyanosis *with or without associated pain* [21]. Our recent qualitative research suggests the term RP represents a more nebulous concept for patients with SSc; whose physical symptoms comprise discrete attacks occurring on a background of more persistent pain, numbness and digital discolouration secondary to more sustained digital ischaemia [37]. Some patients report difficulty knowing when they are experiencing a RP “attack” and others report their fingers feeling constantly cold, numb, discoloured and painful (all symptoms they associate with their “Raynaud’s”) [37]. The RCS diary does not capture a number of important experiences relevant to SSc-RP including emotional distress, body image dissatisfaction, relevant physical symptoms (such as feeling cold), adaptation and functional impairment (Figure 2) [18, 37]. This could have important implications for our interpretation of previous clinical trials. For example a double-blind randomised-controlled trial of bosentan therapy did not identify any improvement in the RCS diary parameters but did identify significant improvement in the Health Assessment Questionnaire Disability Index (HAQ-DI) in patients receiving active treatment [28]. Both “difficulty using hands” and “impact on daily life” were highlighted as important experiences of SSc-RP by patients with SSc and it is possible the HAQ-DI partially captures such experiences which are not

directly evaluated by the RCS diary [37]. Moreover, the RCS diary makes no account of the considerable efforts taken by patients to avoid or ameliorate the symptoms of RP [37, 38]. Unlike other rheumatic diseases characterised by disease flares, patients with SSc exert some control over their RP symptoms through cold avoidance. In the extreme, this can result in reticence to venture outdoors for fear of the effects of cold exposure which itself can become a cause of social isolation. These efforts can considerably under-estimate the true burden of RP captured using diary-based instruments such as the RCS diary and may account for its relative poor performance in RP clinical trials (particularly those in which frequency of RP is the designated primary endpoint). Consistent with many early PRO instruments, there was no patient involvement in the development of the RCS diary but work is currently ongoing to develop novel outcome measures for SSc-RP that are grounded in the patient experience of SSc-RP and conform to regulatory standards for PRO development [39, 40]. It is hoped these efforts will deliver a PRO that fully captures the patient experience of SSc-RP and allow a more detailed appraisal of the severity and impact of SSc-RP. This could support both drug development programs but also provide much needed comparative practice-based evidence for future clinical guidelines concerning existing treatments used in the management of SSc-RP.

Non-invasive microvascular imaging techniques provide an alternative approach to assessing therapeutic intervention in SSc-RP. Imaging protocols typically incorporate assessment of functional microvascular responses to provocation tests such as the local cold challenge [34, 35] or post-occlusive reactive hyperaemia [41]. A number of clinical trials of SSc-RP have incorporated objective tests of cutaneous perfusion using thermal imaging [42] or laser-derived imaging modalities [43, 44, 45, 46]. This approach is attractive as it can facilitate short-term proof-of-concept testing of novel therapeutic agents as a prelude to more costly clinical trials. Discordance between assessment of SSc-RP using PRO instruments and non-invasive microvascular imaging [34, 35] is a concern but it is hoped efforts to refine both methods will see convergent validity improve and encourage greater use of microvascular imaging as an accepted clinical trial endpoint.

2.3 Digital ulcers

DU disease is another major source of disease-related morbidity in SSc but, in contrast to RP, does not affect all patients with SSc. Large registry analyses suggest approximately 58% of patients with SSc will experience DU at some stage during the disease course [47]. Approximately one third of all SSc patients (particularly those with limited cutaneous SSc carrying anti-centromere or anti-Scl-70 antibodies) will experience persistent or recurrent DU, of whom a third (approximately 10% of all patients with SSc) will experience complications of gangrene, require digital sympathectomy or

amputation as a result of their DU disease [47, 48]. A prospective study of a large SSc cohort estimated the incidence of new DU to be 17.4% over 18 months [49]. The incidence of finger amputation as a consequence of DUs was estimated to be 1.2 per 100 patient-years [49]. DUs are a common reason for hospitalisation in SSc and often necessitate the use of strong opioid analgesia [48, 49]. A history of SSc-DU is also a predictor of poorer outcome in SSc, including cardio-pulmonary involvement and survival [50]. SSc-DU are accompanied by reduced quality of life and impaired function, resulting in decreased work capacity and increased reliance on others for activities of daily living [51, 52, 53, 54]. Capillary loss at the nailfolds is strongly associated with DU disease [16, 55, 56, 57, 58, 59] and can help predict future occurrence of DU [14, 15] suggesting *irreversible* digital ischaemia to be an important aetiological driver of DU disease - which itself may have important implications for both assessment and management.

The management of SSc-DU concerns both healing of existing DU and prevention of new DU. The principle challenge in establishing efficacy for both objectives relates to defining what actually constitutes a DU and at what stage an existing DU can be considered healed. There is no universally agreed definition for DU and observational studies and clinical trials apply bespoke and sometimes diverse definitions of DU. For example, some studies specifically exclude calcinosis-related ulcers [54, 60, 61] whereas others do not [15, 62]. Some studies specify the site of the ulcer as being distal to the metacarpophalangeal joints [15], others distal to the proximal interphalangeal joints (PIPs) [60, 61, 62], whereas others place no restriction on the site of the cutaneous ulceration [54]. The appropriateness of allowing DUs on the volar aspect of the fingertips to be considered equal alongside DUs on the extensor aspects of the PIPs and distal interphalangeal joints, despite likely differences in aetiology, remains contentious and usually left to the discretion of investigators to define [61]. Hachulla et al. partially addressed this important issue by proposing three principal types of SSc-DU [63]. These comprise “(i) ulcers occurring at bony prominences, usually at metacarpophalangeal or interphalangeal joints of the fingers, promoted by microtraumatic events and by traction exerted on the sclerous skin when the fingers are flexed; (ii) ulcerations occurring at the level of subcutaneous calcifications where mechanical and inflammatory phenomena are also involved; and (iii) ischemic DU that occur most frequently on distal areas of fingers, involving pulp or sometimes lateral edges.”[63]. Successful clinical trial programmes for DU management (resulting in marketing authorisation) have tended to focus on ischaemic DUs. For example, the RAPIDS-1 clinical trial evaluating the efficacy of bosentan therapy in the management of SSc-DU focussed on “ulcers at or distal to the proximal interphalangeal joint”, whilst the subsequent RAPIDS-2 trial focused on DUs that were “in a location judged compatible with a vascular aetiology, specified by protocol as volar surface of the digit distal to the proximal interphalangeal digital crease”. Case reports have

suggested traditional vasodilating approaches such as endothelin receptor antagonists might be less-efficacious for non-ischaemic cutaneous ulcer management in SSc, and strongly supports sub-classification of DUs for the purposes of SSc clinical trials of SSc-DU [64, 65].

The presence of overlying dry eschars (and whether to remove to seek evidence of ongoing denudation or re-epithelialisation) presents a particular problem when defining the presence and stage of SSc-DU with various attempts made to define “active ulcer”, “inactive ulcers”, “indeterminate ulcers”, “healed ulcers” and “non-ulcers” [61, 66]. Even when consensus has been achieved as to what constitutes a DU and training in the application of agreed definitions undertaken, the inter-rater reliability remains low-moderate [61] and appears lower when photographs are used to determine ulcer grading, even when clinical contextual information is supplied [66, 67]. It should be noted that the strength of exercises to evaluate inter-rater agreement in DU classification is equally dependent on the diversity of digital ischaemic lesions chosen for grading as to the quality of the definitions applied. Even when the issue of DU ulcer definition has been addressed, the overall burden of DU can differ greatly between patients. Large registry analysis has led to the proposal of a novel categorisation approach to patients with SSc-DU disease that differentiates patients according to “no DU history” (33.2%), “episodic” (9.4%), “recurrent” (46.2%) and “chronic” (11.2%), in acknowledgment of the differing care needs of patients within these distinct sub-populations of patients [54]. Others have proposed similar classification approaches to “skin ulcers” in SSc [68]. These DU categorisation and classification approaches have important implications for clinical trial programmes for DU disease in SSc.

Primary prevention of SSc-DU disease is challenging as DU often occur early in the course of SSc; with nearly half of patients with DU disease experiencing their first DU within 1 year of the first non-RP symptom of SSc [63]. Conducting primary preventative studies would present a number of investigative challenges, which is a major frustration considering the potential “window of opportunity” and possibility of enhanced treatment efficacy at an earlier stage in the evolution of the obliterative microangiopathy of SSc. Unsurprisingly, cold exposure appears to be a risk factor for DU occurrence in SSc [69] which also has implications for clinical trial design with regards geographic location of recruiting centres and season of enrolment. The strongest predictor of future DU appears to be a prior history of DU [50]. This has resulted in clinical trials and prognostic studies examining future DU risk focussing on patients with a recent history of DU [15, 60, 62]. Several randomised controlled trials have examined secondary DU prevention and DU healing in SSc but differences between the evidence-base [70], expert consensus recommendations [30, 31], evidence-based recommendations [32] and regulatory marketing authorisation has resulted in geographic differences in management. For example, bosentan has marketing approval from the EMA for

secondary prevention of SSc-DU disease (following RAPIDS-1 and RAPIDS-2 clinical trials) but was not approved by the FDA for use in the US where bosentan use in SSc is almost exclusively limited to pulmonary vascular disease. Within the EU, the availability of bosentan for the management of DU disease may also be influenced by differing commissioning policies governing high-cost drug use within each member state. Registry data suggests significant geographic variation in practice when it comes to vasoactive therapy in SSc (encompassing SSc-RP and SSc-DU disease). For example, contemporary evaluations of intravenous iloprost use ranges from 1.3% of patients in Canada to 21.1% of patients in Germany [71, 72].

Non-pharmacological approaches to DU management have not been the focus of controlled studies and the scleroderma community remaining evenly split as to whether interventions such as local DU debridement have no effect on DU healing, actively *delay* wound healing or actively *encourage* DU healing [61].

Similar to SSc-RP, non-invasive microvascular imaging modalities such as laser Doppler and laser speckle contrast imaging are now being used to objectively assess treatment response in SSc-DU disease and could be promising outcomes in future DU clinical trials. [73, 74]

2.4 Telangiectasia

Cutaneous telangiectasia are dilated post-capillary venules (without neovascularisation) that sit in the papillary or superficial reticular dermis [75, 76, 77]. There is endothelial thickening but no vasculitis or perivascular infiltrate [76]. They are a useful diagnostic marker of SSc and included in the classification of SSc [8]. Telangiectases are commonly found in exposed areas of skin of the hands and face and have been reported to occur in approximately 80% of patients with SSc [78, 79]. They are particularly prevalent in Caucasian patients carrying anti-centromere antibodies (hence their prominence in the CREST acronym) and the number of telangiectases is higher in current/ex-smokers [78, 79, 80]. One study identified the presence of telangiectases in 76% of patients with SSc with a mean of 22.9 (SD 30.1) telangiectases per patient and with 7.3% being >1 mm in size [78]. It has been suggested that existing vasodilator therapies for SSc might contribute to worsening of facial telangiectases [81]. Whilst cutaneous telangiectases are themselves not life-threatening, their presence denotes advancement of the microangiopathy of SSc with strong associations with disease duration [80, 82], capillary drop out and neovascularisation at the nailfolds [11, 83], and pulmonary arterial hypertension [80, 82, 83, 84]. The strength of the association between telangiectases and DU remains less clear [79, 83, 85, 86]. Telangiectases can be disfiguring and a major cause of body image dissatisfaction, particularly when they occur in prominent areas such as the face (Figure 3).

Management of telangiectases includes concealment methods such as make-up camouflage and ablative treatments using injected sclerosing agents or thermocoagulation methods such as pulsed dye laser therapy. There is a high rate of recurrence following use of ablative methods, possibly relating to iatrogenic tissue injury exacerbating local tissue hypoxia. Many observational studies simply consider either the documented presence or absence of telangiectases [86] whereas others have undertaken more concerted efforts to grade the severity of telangiectasia formation through counting telangiectasia and applying a nominal scoring system across 11 body sites (the telangiectasia score) [80]. Modified versions of this method have been applied to grade telangiectases as absent, mild-to-moderate (1-10 on hands or face) or diffuse (>10 on hands or face) [83]. Others have sub-classified telangiectases according to their clinical or dermatoscopic appearance resulting in the application of terms such as “spot” [11, 87], “reticular” [11, 87], “pseudo tumoral” (>5mm in diameter) [83] and “matt” telangiectases [88]. The semi-quantifiable methods applied so far include body areas not commonly affected (or complained about) and do not allow for the significant variation in severity that could exist at a single site (where 2 telangiectases vs. 9 telangiectases attract the same score). For example, a patient could have 9 telangiectases on the face resulting in significant body image dissatisfaction and yet only score 1 using the method proposed by Shah et al, resulting in a potential “floor effect” [80].

Clinical trials of interventions for telangiectases have generally assessed treatment efficacy by comparing photographs before and after therapy using ordinal scales, ranging from much worse, worse, unchanged, improved and much improved) [89, 90], or by examining lesion size and evaluation of lesion clearance [76]. Non-invasive imaging methods have been used to support clinical assessments including laser Doppler and dermatoscopy [89, 90]. The patient-reported Adapted Satisfaction With Appearance Scale (A-SWAP) has been shown to improve following laser therapy whereas the Hospital Anxiety and Depression Scale did not improve following laser treatment [90]. There are a number of barriers that need to be overcome to improve the management of telangiectases in SSc. Work is needed to establish what patients consider treatment success (reduction in size, reduction in number or eradication). It is likely that sensitivity and reliability of PRO instruments could be improved through the development of instruments specific to SSc. Greater understanding of the aetiopathogenesis and natural history of telangiectases could one day be used to develop and promote primary preventative strategies.

2.5 Critical digital ischaemia (CDI)

CDI is a rare but serious complication of SSc. Approximately 10% of all patients with SSc, will experience complications of gangrene or require digital sympathectomy or amputation at some stage in their disease course [47, 48]. Digital amputation due to digital necrosis has been estimated

to occur in approximately 5% of patients with SSc [91]. A combination of the relatively rarity and severity of CDI presentation has resulted in the majority of published work in the subject arising from case reports or small case series. Published cases often report an aggravating factor such as concomitant anti-phospholipid syndrome (APLS) [92], overlap syndromes [93], concomitant drug use [94] or vasculitis [95]. In contrast to the aforementioned cutaneous vascular manifestations of SSc, peripheral macrovascular disease often contributes to the emergence of digital necrosis in SSc [91, 96]. The evidence-based management of CDI typically involves admission to hospital for intensive vasodilator therapy (including intravenous prostanooids), aggressive management of contributory factors, surgical debridement and, depending on the clinical picture and co-morbidities, the consideration of potentially useful adjunct therapies including digital sympathectomy, anti-platelet therapy, short-term anticoagulation, statins and antibiotics [31] (Figure 4). Non-pharmacological treatments such as vacuum-assisted closure therapy have been applied to promote wound healing and save limbs [96] (Figure 5).

There are a number of challenges in the assessment and management of CDI in SSc. Similar to SSc-DU disease, there is marked variation in classification definitions that have influenced the reported prevalence of CDI in SSc [47, 49, 54, 63, 97, 98] (Table 2). A consensus definition of CDI (perhaps including a grading structure to allow categorisation) would allow more definitive assessment of the true burden of CDI to be undertaken within disease registries. The evidence-base for managing CDI is scant and controlled clinical trials are inconceivable given the rarity and severity of presentation. Nonetheless, large multicentre collaborative studies provide an opportunity to establish risk factors and compare outcomes to provide much needed “practice-based evidence” upon which future clinical guidelines may be based. A better understanding of the risk factors of CDI could be used to devise primary preventative strategies e.g. anticoagulation in patients with APLS antibodies or prophylactic angioplasty in patients with sub-clinical peripheral vascular disease.

3.0 Conclusions

Cutaneous vascular manifestations of SSc are a major cause of disease-related morbidity and have historically received less attention than potentially life-threatening internal organ complications of SSc but there is cause for optimism. Better knowledge of the pathogenesis of cutaneous vasculopathy, a deeper understanding of the patient experience of cutaneous vascular disease, efforts to improve outcome measures and a broader repertoire of therapeutic options offer encouragement that greater attention on cutaneous vascular disease shall deliver better outcomes and improved quality of life for patients with SSc.

4.0 Expert commentary

Cutaneous vascular manifestations of SSc are a major cause of disease-related morbidity in terms of pain, loss of function, work absenteeism, reduced social participation and body image dissatisfaction. The non-life-threatening nature of these important disease manifestations can result in complacency amongst clinicians in terms of primary preventative intervention and management of existing cutaneous vascular disease. The physical and psychosocial burden of cutaneous vascular manifestations of SSc should not be underestimated. The last 15 years has witnessed considerable industry interest with well-designed large multicentre clinical trials conducted in the management of SSc-RP and SSc-DU disease. Establishing treatment efficacy has presented a challenge and risks waning industry engagement in this field. Advances in the management of internal organ disease in SSc has resulted in longer life-expectancy and greater attention is now being focussed on non-life threatening manifestations of SSc such as cutaneous vascular disease. This provides cause for optimism. Better knowledge of the pathogenesis of cutaneous vasculopathy, a deeper understanding of the patient experience of cutaneous vascular disease, efforts to improve outcome measures and a broader repertoire of therapeutic options offer encouragement that greater attention shall now focus on cutaneous vascular disease, the management of which may have far-reaching unintended favourable effects within other organ systems in SSc.

5.0 Five-year review

The next five years is likely to deliver major advances in the management of cutaneous vascular disease in SSc. A number of drivers have resulted in the SSc academic community taking greater interest in this hitherto relatively neglected area of SSc therapeutics. These include greater recognition of the considerable morbidity associated with cutaneous vascular disease, the power of patient advocacy groups directing research funding strategies, improved understanding in disease pathogenesis and a broader repertoire of therapeutic options and candidate therapeutic targets. Current collaborative initiatives are expected to deliver robust definitions and clinical trial outcomes for each of the four major cutaneous vascular manifestations of SSc over the next 5 years. The expiry of drug patents shall see a fall in the price of high-cost drugs that will support more flexible reimbursement schemes that lead to repositioning of existing treatments within accepted clinical practice guidelines. This process has already begun and there is now considerably greater use of phosphodiesterase inhibitors for cutaneous vascular manifestations of SSc than could have been imagined 5 years ago. The emergence of practice-based evidence for the management of cutaneous vascular manifestations of SSc will support an appraisal of the comparative efficacy of different classes of vasodilator therapy, potentially supporting more personalised approaches to intervention and a new focus on primary preventative strategies.

6.0 Key issues

- Cutaneous vascular manifestations of systemic sclerosis comprise Raynaud's phenomenon, digital ulceration, telangiectasia formation and critical digital ischaemia; each of which are a major cause of systemic sclerosis disease-related morbidity
- Despite a large number of promising vasodilator treatments available for use, only a limited number have been issued marketing approval by regulatory agencies for managing cutaneous vascular manifestations of systemic sclerosis.
- Demonstrating treatment efficacy for cutaneous vascular manifestations of SSc is challenging and there have been several disappointing clinical trials of promising vasoactive treatments in SSc. There is a risk of waning industry engagement in drug development programmes in this field.
- Disparity between consensus best-practice guidelines, evidence-based recommendations and marketing authorisation has resulted in geographic variation in clinical practice concerning management of cutaneous vascular manifestations of SSc.
- The development of robust and reliable clinical trial endpoints will be an important step in the delivery of successful drug development programmes for cutaneous vascular manifestations of systemic sclerosis

Declaration of Interests

J Pauling has undertaken consultancy work and received speaker's bureau and unrestricted research funding from Actelion pharmaceuticals within the last 5 years. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Figure 1. Clinical and nailfold capillaroscopy findings in a lady presenting with recent-onset systemic sclerosis.

A) In addition to recent-onset bi-phasic Raynaud's symptoms there was evidence of active ischaemic digital ulceration of left 4th digit and a solitary telangiectasia overlying the dorsal aspect of the left 3rd proximal interphalangeal joint. There was no overt skin thickening. B) Despite the short disease duration nailfold capillaroscopy revealed typical structural abnormalities of SSc with giant capillaries, microhaemorrhages, capillary drop out and disorganised neoangiogenesis. Anti-centromere autoantibodies were identified on serological investigation.

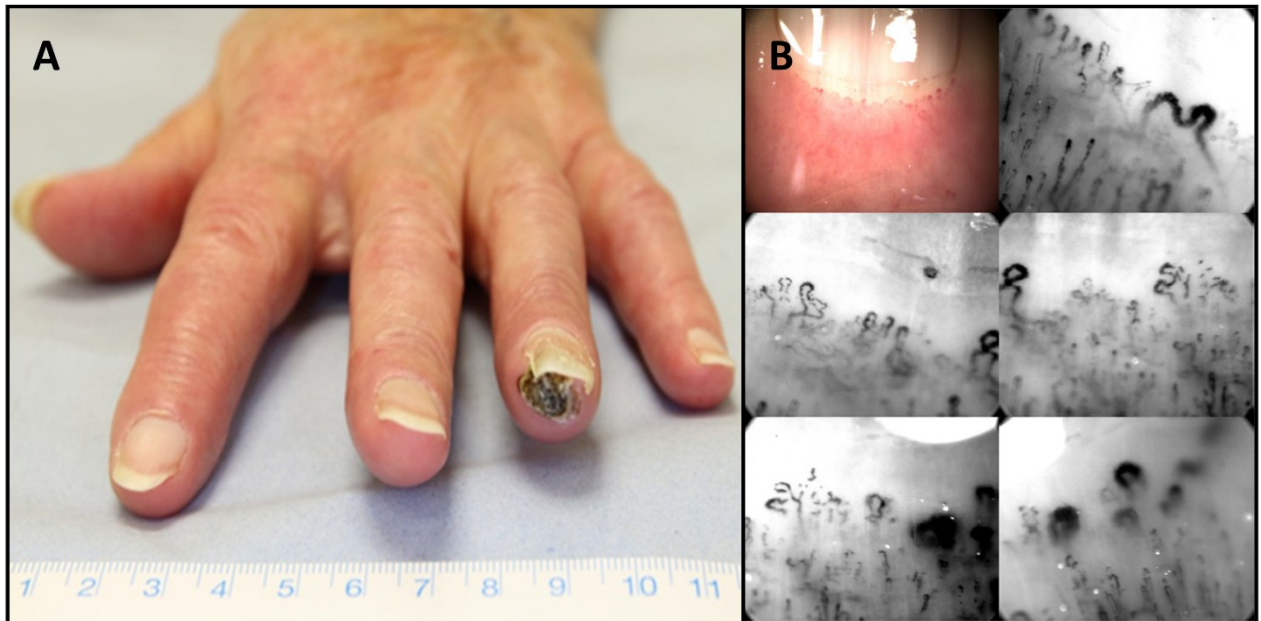
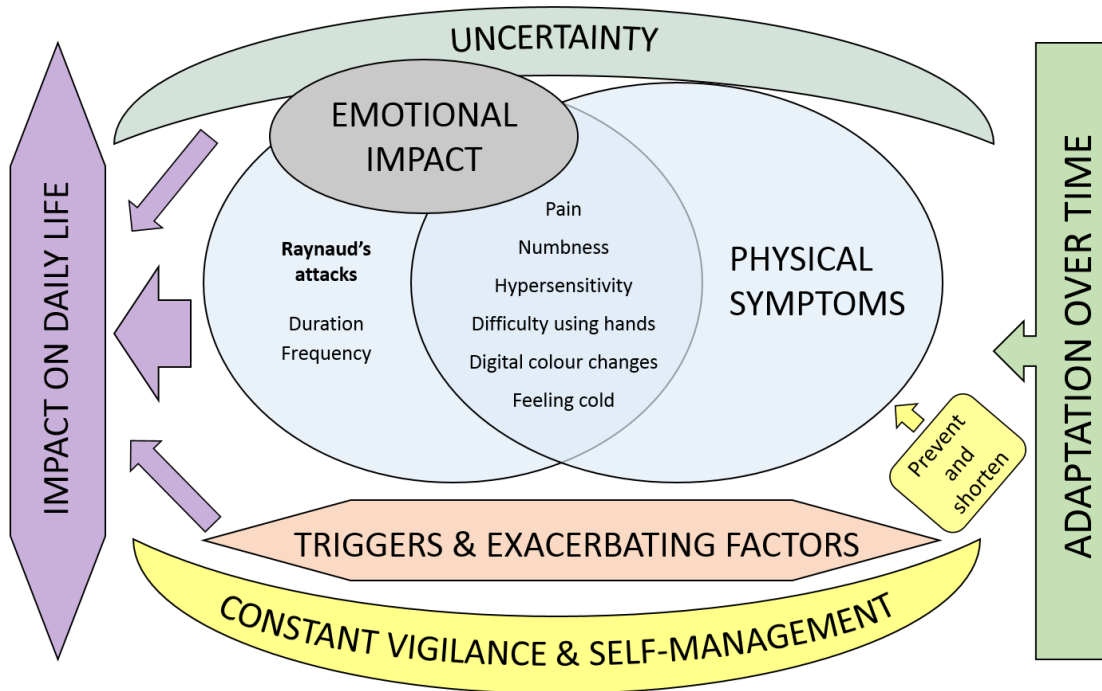


Table 1. Subtle differences in the design and item wording of SSc-RP PRO instruments (such as inclusion of painful sores) could influence outcomes when assessing SSc-RP severity

| Name | Study | Item metric | Recall Period | Score | Item Wording |
|---------------------------|-------------------------|--|---------------|-------------------------------------|--|
| Raynaud's Severity Scale | Wigley et al. 1994 [21] | 11-point numeric rating scale (0-10) | 1 day | Mean daily score over 3-week period | Patients were asked to consider in their Raynaud severity score the number and duration of attacks; symptoms, such as numbness, burning, and pain and tingling; hand disability; and influence of cold on daily activity. An attack was defined as an episode of pallor followed by cyanosis with or without associated pain. |
| Raynaud's Condition Score | Black et al. 1998 [23] | 11-point numeric rating scale (0-10); 0 None – 10 very severe | 1 day | Mean daily score over 2-week period | Please rate the difficulty you had today with your Raynaud's condition. Please consider the following when choosing your score: The number of Raynaud's attacks; the duration of the attacks; whether you had, for example, numbness, burning and tingling, and the effect cold had on your ability to use your hands and to perform other activities. |
| Raynaud's Condition Score | Wigley et al. 1998 [22] | 11-point numeric rating scale (0-10); 0 No difficulty -10 Extreme difficulty | 1 day | Mean daily score over 2-week period | The Raynaud's Condition Score is your rating of how much difficulty you had with your Raynaud's TODAY. Consider how many attacks you had and how long they lasted. Consider how much pain, numbness, or other symptoms the Raynaud's caused in your fingers (including painful sores) and how much the Raynaud's ALONE affected the use of your hands today. |

Adapted from [18]

Figure 2. A conceptual map of the inter-related themes comprising the patient experience of SSc-RP.



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Figure 3. Widespread mat telangiectasia on the face of a patient with diffuse cutaneous systemic sclerosis (anti-U3-RNP antibody positive).

The patient reported high scores for items within the social discomfort and dissatisfaction with appearance subscales of the Brief Satisfaction With Appearance (Brief-SWAP) instrument.



Table 2. Impact on reported prevalence of differing definitions applied to severe/critical digital ischaemia in SSc

DU, digital ulcer

| Author, Year | Description | Definition | Prevalence of CDI | Prevalence of Digital Necrosis /Gangrene | Amputation |
|---------------------------|-------------------------------|---|--|---|----------------------------|
| Herrick 1994 [98] | Severe Ischaemia | “amputation, surgical debridement or admission for intravenous vasodilator therapy” | 31/68 (45.6%) | | 13/68 (19%) |
| Harrison 2002 [97] | Digital ischaemia | “if 1 or more of the following were reported: hospital admission for intravenous (IV) administration of vasodilator therapy (either prostacyclin or iloprost), surgical debridement of ≥1 digits or surgical amputation of ≥1 digits” | 46/101 (46%) prostacyclin 17/101 (17%) Surgical debridement | | 15/101 (15%) |
| Haschulla 2007 [63] | Critical finger ischemia | “Cold and cyanotic finger” | 30/101 (30%) | 8/101 (8%) | 3/101 (3%) |
| | | | In patients with history of ischaemic DU: | | |
| | | | 30/44 (68%) | 8/44 (18%) | 3/44 (7%) |
| Nihtyanova 2008 [49] | Critical Digital ischaemia | “a sustained reduction in digital perfusion with impaired tissue viability” | 19/1168 (1.6) (over 18-months) | 16/1168 (1.4) (over 18/12) | 11/1168 (0.9) (over 18/12) |
| Steen 2009 [47] | “Severe” digital vasculopathy | “complicated by gangrene, or requiring digital sympathectomy or amputation” | 197/2080 (9.5%) | 11% of patients have undergone amputation or experienced gangrene (absolute figures not provided) | |
| Matucci-Cerinic 2016 [54] | Critical Digital Ischaemia | “This is not a Raynaud’s phenomenon. It is a prolonged severe persistent reduction in digital tissue perfusion without re-warming” | 379/828 (45.8) | 306/1352 (22.6) | 104/1164 (8.9) |

Figure 4. Critical digital ischaemia in systemic sclerosis.

A lady with systemic sclerosis characterised by Raynaud's phenomenon, Puffy fingers, abnormal nailfold capillaroscopy and positive anti-centromere antibodies developed critical digital ischaemia 4 years after presentation. A positive lupus anticoagulant was identified during investigation. Management consisted of approximately 1 month of near-continuous intravenous prostanoids, analgesia, low-dose steroids, calcium channel blocker, sildenafil, warfarin and bosentan. Surgical debridement of the necrotic digits was undertaken once the digital ischaemia was stabilised. A) The appearances of the digits shortly after presentation; B) The appearances of the hands post-operatively.

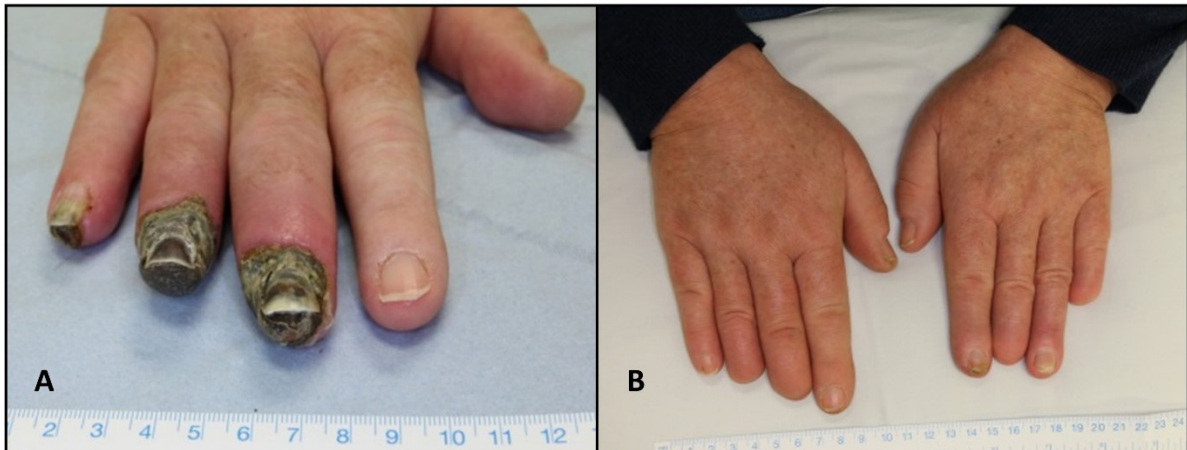
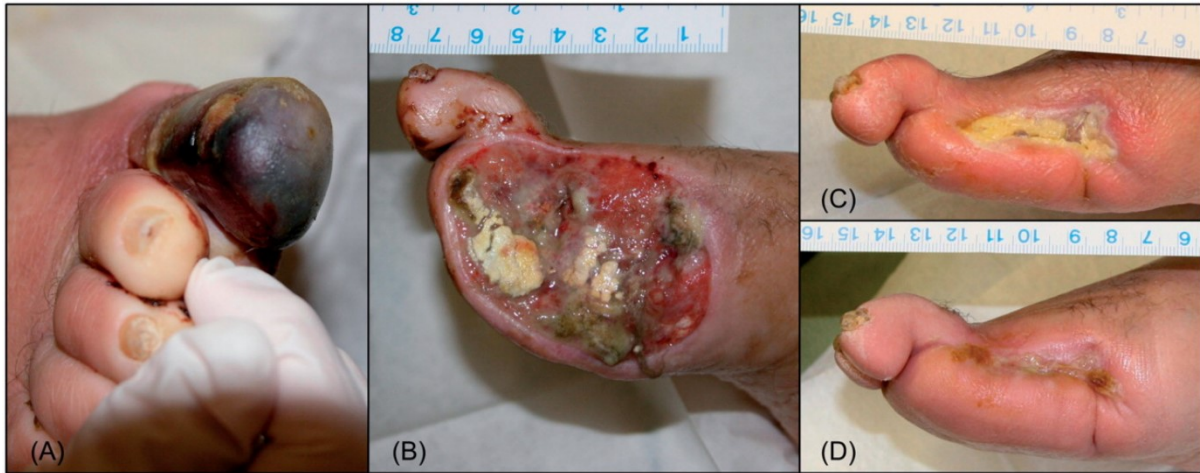


Figure 5. Vacuum-assisted closure (VAC) therapy in the management of critical digital ischaemia in SSc.

Serial photographs of the right foot of a 91 year old lady with SSc (positive anti-centromere antibodies who developed critical digital ischaemia: (A) shortly after presentation, (B) post-amputation before commencement of VAC therapy; (C) after completion of 43 days of treatment with VAC therapy; and (D) at 4 months post-VAC therapy.



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