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Points to consider for skin ulcers in systemic sclerosis

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Abstract

This article discusses points to consider when undertaking a clinical trial to test therapy for skin ulcers in SSc. A validated definition of skin ulcers should be used if available. Defining a uniform SSc patient population, including consideration of disease duration, history of digital ulcers and capillaroscopic patterns, is important. Excluding confounding factors such as infection, calcinosis and trauma should be strongly considered, or at least accounted for, in defining patients. Outcome measures such as time to healing, prevention of new ulcers, function, pain and objective measures such as US, laser Doppler and thermography can be considered as outcome measures, although their validation has not yet been achieved and efforts may be needed to validate them before use. Likewise, biomarkers should be considered or consideration should be given to storing serum, plasma or cells for possible future analysis. A pre-planned analysis is important and should include consideration of missing data.

Key words: clinical trials, skin ulcers, systemic sclerosis, outcome measures

Rheumatology key messages

- Randomized controlled trials are recommended for skin ulceration in SSc.
- A validated specific definition of skin ulcers should be used in trials if available.
- Outcome measures for skin ulcers in SSc such as time to healing and quality of life should be carefully considered.

REVIEW

Introduction

Digital ulcers (DUs) are a frequent complication that affects almost half of SSc patients; ~75% of the affected patients have their first DU episode within 5 years of their first non-RP symptom [1–3]. However, DUs are present in almost 25% of patients with very early SSc and there is significant correlation with gastrointestinal involvement. For this reason, some believe that DUs may be a sentinel sign for early organ involvement [4]. DUs are persistent, difficult to heal, extremely painful and can cause tissue loss, auto-amputation and impaired hand function and greatly impact quality of life [5, 6]. Moreover, DUs can become infected and, if not treated early, may lead to osteomyelitis, gangrene and septicaemia [7]. The frequent, persistent and severe nature of DUs in SSc patients has been confirmed by data from disease registries [8–11]. Data from a French study identified 44% of patients as having one or more ischaemic DUs, resulting in hospitalization in 33% of cases, with 46% requiring systemic antibiotics [1]. In a Canadian study, recurrent DUs were reported in 31.8–71.4% of SSc patients, with progression to gangrene and auto-amputation in 14–29% of cases [12]. DUs may develop on the fingers or toes and can occur over the extensor surface of the joint, on the finger creases, under the nails and on the fingertips. DUs may also develop from pre-existing calcinosis and at the site of digital pitting scars [13]. In the last decade, several randomized controlled trials (RCTs) have studied the effects of different drugs on the prevention and healing of DUs in SSc [14–32]. However, the lack of

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data uniformity makes it difficult to compare and use the results. For example, DUs were defined differently and only healing and the number of new DUs were used as outcome measures.

While DUs have been extensively studied [13], small case series have been published reporting both venous insufficiency and macrovascular obliterative arterial disease [33, 34]. Recently it has been shown that lower limb ulcers have a multifactorial pathogenesis and are therefore difficult to manage [35]. However, a recent classification may serve in the future to assess the most appropriate management of lower limb ulcers [36]. Lower limb ulcers, although not common, greatly affect SSc patients and further studies are needed to find a shared and validated classification and management [35].

Recently the importance of DUs in SSc patients has been highlighted by evidence that they predict the occurrence of DUs at follow-up and are associated with cardiovascular worsening and decreased survival [36]. We suggest points to consider when designing and conducting clinical trials of skin ulceration in SSc patients.

Trial design and duration

One should strongly consider double-blind RCTs, either placebo controlled on a background of standard local therapy or positively controlled trials versus proven therapy [14, 17]. In the first circumstance, a uniform and homogeneous protocol of background medications among the different study arms would be best to promote uniformity and avoid biases [20]. In a positively controlled trial, the validity of the positive control must be carefully considered. Due to the high rate of complications, such as amputations, the use of placebo without background therapy should be considered very carefully and fully justified.

Patients with early or very early SSc [37] may respond better and may have less irreversible damage (expert opinion). A short preliminary trial to examine the feasibility of such an approach could be considered before embarking on a large trial. The need for a valid definition of early SSc and the problem of recruiting should be acknowledged and may influence decisions on the study design.

The minimum duration of a trial evaluating efficacy in terms of prevention is most frequently at least of 24 weeks [15]. For trials on ulcer healing, a shorter period may be acceptable [19, 20].

When designing a DU trial, with placebo as a control, a single active comparator or two active comparators (drug A *vs* B) added to the standard of care can be used. Moreover, different arms of various doses (e.g. low dose *vs* high dose of a drug *vs* placebo) can be employed. Even combination therapy compared with monotherapy is an option in a trial on DUs [38].

Inclusion criteria

When considering trials in SSc, patients fulfilling the ACR/EULAR classification criteria should be used [39]. If subsets are considered, this may raise an issue with respect to the power analysis and may require increasing the number of patients for the trial [10]. To date, for DUs, the only proposed classification has been loss of tissue secondary to gangrene, calcinosis and digital pitting scars [14]. In the future, a specific definition of skin ulcers should be strongly considered and validated.

In the interest of having uniform patient populations and increasing the probability of obtaining a clear answer, strong consideration should be given to disease duration [8], to the time from onset of the first DU [9] and the capillaroscopic pattern (early, active or late) [40]. In a trial studying DUs, capillaroscopic patterns can be studied as a substudy, but a limitation in using capillaroscopy is the fact that patterns are unlikely to change over a short trial. As infections occur in patients with DUs, one should consider whether antibiotics will be allowed during the trial or if patients will be dropped if infections occur. Often, antibiotics are allowed and their use is carefully noted to be included in the analysis [14]. To obtain patients whose DUs have a more uniform origin (e.g. vasculopathy) and who have a propensity for the development of these ulcers, inclusion of a limited subset of patients, such as patients with a history of ischaemic ulcers that are not traumatic or based on calcinosis, could be considered [13]. DUs derived from calcinosis are a problem because these ulcers usually heal very slowly. Therefore we believe that calcinosis should either be carefully removed or patients should be excluded from trials devoted to DUs because they may bias the results. A separate trial may be needed to evaluate the ability of test medications to heal DUs with underlying calcinosis.

If DUs of varying aetiologies are included, consideration should be given to stratifying by aetiology and including the stratification in the analysis. In DU trials, the rate of complications may be considered an important exploratory or secondary outcome. To enhance the likelihood of recurrent ulcers, data indicate that a history of previous ulcers is useful [4, 14]. Thus one could consider including patients with a history of at least one ischemic DU or a recent history of such an ulcer. Ulcers on the distal palmar aspect of the finger and distal to the DIP may be considered. While DU location has been used to define inclusion or exclusion in trials (e.g. excluding ulcers proximal to the PIPs), it may be better to consider pathophysiology rather than location to define whether to include specific ulcers in clinical trials. The study of DUs in locations other than on the distal palmer aspect of the finger remains an unmet need. At present, based on previous trials, one could justify excluding these patients in DU trials. Whatever DU location is considered, information on all DUs should be collected even if they are not part of the outcome measures. If a trial of ulcer prevention is being considered, patients without baseline ulcers could be included, but an enrichment strategy could be considered to include patients with a history of ischaemic ulcers or who express predictive biomarkers, if validated, for development of new ulcers [41].

TABLE 1 Validity of measures used in SSc trials of skin ulcers

Measure	Truth				Discrimination		Feasibility	Ready for use in clinical trials as primary/secondary outcome?
	Face validity	Content validity	Construct validity	Criterion validity	Reliability	Sensitive to change		
Healing	Y	Y	Y	Y	Y	Y	Y	P
Prevention	Y	Y	Y	Y	Y	Y	Y	P
SHAQ-DI	Y	Y	Y	Y	Y	Y	Y	P
Reduction of dimensions	N	N	N	N	N	N	N	S
Pain scale (VAS/NRS)	Y	Y	Y	Y	Y	Y	Y	S
Time until new DU	N	N	N	N	N	N	N	S

N: no; NRS: numeric rating scale; P: primary endpoint; S, secondary endpoint; SHAQ-DI: Scleroderma HAQ Disability Index; VAS: visual analogue scale; Y: yes.

Exclusion criteria

As other diseases can confound the results, one should carefully consider whether one wishes to allow the inclusion of other CTDs or scleroderma-like diseases [16]. In most published trials and among experts, other CTDs and scleroderma-mimicking diseases have been excluded [42].

Calcinosis can delay healing [13] and involvement of the ulnar or radial arteries by the SSc can also affect healing [43]. These variables should be considered when developing inclusion and exclusion criteria, either excluding these groups, stratifying them or assuming that randomization will compensate for them. Smoking habits, concomitant diseases (e.g. diabetes or other illnesses that could delay ulcer healing) and concomitant therapies should be accounted for when designing the study protocol (i.e. smoking *vs* non-smoking) [42].

It is also recommended to record organ involvement, skin score and antibodies along with tendon friction rubs that may significantly affect hand function. In fact, DUs are associated with worse disease, including skin and lung involvement [48]. Those patients with organ involvement that may affect the test or control drug should be considered for exclusion.

Outcome measures

As reported in the literature, time to healing (expressed in days), prevention (expressed as the number of new ulcers during the treatment period) and validated measures of quality of life and/or disability indexes are often considered to be primary outcomes (Table 1) [13]. To assess function, the Scleroderma HAQ, consisting of the HAQ Disability Index (HAQ-DI) and five visual analogue scales (VASs), may be used. It may be appropriate to use only the specific VAS related to the outcome of interest. For example, ulcer and pain VASs may be useful while gastrointestinal and lung VASs may not. While the HAQ-DI has been validated, the VASs have not been fully validated and thus need to be used with caution if considering VASs for registration. It may be necessary to validate these measures before using them for a registration trial. It is often useful to consider secondary outcomes in clinical trials (Table 1).

In patients refractory to standard treatments and/or with non-healing or recurrent ulcers, a meaningful exploratory or secondary outcome, unvalidated but reasonable, might be time to healing; partial improvement or response to therapy during the treatment period, including reduction of dimension (in square millimetres, measured on sterile graph paper); reduction of ulcer-related pain (expressed by a VAS or numeric rating scale) [12] and the time until the occurrence of a new ulcer (in patients with recurrent ulcers). Functional measures such as the Cochin or Michigan hand score could be used, as can a multitude of other measures; in all cases, formal validation, including responsiveness and discrimination, should be considered before they are used.

Inclusion of capillaroscopy, thermography, arteriography, Doppler US, laser Doppler and transcutaneous tensiometry and other new but not yet validated methods of digital image analysis are warranted, as are the development of novel composite scores for the evaluation of worsening or amelioration of ulcers [43–48].

Analyses

Analysis should include as a minimum descriptive analysis and stratification of the population (if done as part of the study). Outcome statistical analysis could include analysis of variance, analysis of covariance, linear or logistic regressions, generalized estimating equations and survival analyses, among others. The primary outcome should be defined *a priori*. For proof-of-concept studies, testing for less traditional alpha values might be considered (e.g. alpha *P*-values of 0.10–0.15). A statistical power analysis should be considered before undertaking the study. A strategy to account for missing data should be considered.

Very strong consideration should be given to having a predefined plan for analysis, including considerations of

statistical power and how to handle missing data. A disposition figure, descriptive statistics and outcomes statistical analysis (parametric or non-parametric analysis) would be appropriate. If patients have or develop DU infections during the trial, their analysis as a separate subpopulation should be considered.

Conclusion

In studies investigating the treatment of DUs, double-blind RCTs should be strongly considered. A validated definition of skin ulcers should be used if available. Defining a uniform SSc patient population and excluding confounding factors such as infection, calcinosis and trauma should be strongly considered, or at least accounted for, in defining patients. Multiple exploratory/mechanistic outcome measures, including US, laser Doppler and thermography, can be considered, although they are not validated and their use must be carefully considered and justified. A pre-planned analysis is important.

Supplement

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References

1 Hachulla E, Clerson P, Launay D *et al*. Natural history of ischemic digital ulcers in systemic sclerosis: single-center retrospective longitudinal study. J Rheumatol 2007;34:2423–30.

2 Walker UA, Tyndall A, Czirják L *et al*. Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group database. Ann Rheum Dis 2007;66:754–63.

3 Steen V, Denton CP, Pope JE, Matucci-Cerinic M. Digital ulcers: overt vascular disease in systemic sclerosis. Rheumatology 2009;48(Suppl 3):iii19–24.

4 Bruni C, Guiducci S, Bellando-Randone S *et al*. Digital ulcers as a sentinel sign for early internal organ involvement in very early systemic sclerosis. Rheumatology 2015;54:72–6.

5 Mouthon L, Mestre-Stanislas C, Bérezné A *et al*. Impact of digital ulcers on disability and health-related quality of life in systemic sclerosis. Ann Rheum Dis 2010;69:214–7.

6 Nihtyanova SI, Brough GM, Black CM, Denton CP. Clinical burden of digital vasculopathy in limited and diffuse cutaneous systemic sclerosis. Ann Rheum Dis 2008;67:120–3.

7 Korn JH. Scleroderma: a treatable disease. Cleve Clin J Med 2003;70:954, 956, 958.

8 Galluccio F, Matucci-Cerinic M. Registry evaluation of digital ulcers in systemic sclerosis. Int J Rheumatol 2010;2010:363679.

9 Denton CP, Krieg T, Guillevin L *et al*. Demographic, clinical and antibody characteristics of patients with digital ulcers in systemic sclerosis: data from the DUO Registry. Ann Rheum Dis 2012;71:718–21.

10 Galluccio F, Walker UA, Nihtyanova S *et al*. Registries in systemic sclerosis: a worldwide experience. Rheumatology 2011;50:60–8.

11 Tiev KP, Diot E, Clerson P *et al*. Clinical features of scleroderma patients with or without prior or current ischemic digital ulcers: post-hoc analysis of a nationwide multicenter cohort (ItinéraAIR-Sclérodermie). J Rheumatol 2009;36:1470–6.

12 Bogoch ER, Gross DK. Surgery of the hand in patients with systemic sclerosis: outcomes and considerations. J Rheumatol 2005;32:642–8.

13 Amanzi L, Braschi F, Fiori G *et al*. Digital ulcers in scleroderma: staging, characteristics and sub-setting through observation of 1614 digital lesions. Rheumatology 2010;49:1374–82.

14 Matucci-Cerinic M, Denton CP, Furst DE *et al*. Bosentan treatment of digital ulcers related to systemic sclerosis: results from the RAPIDS-2 randomized, double-blind, placebo-controlled trial. Ann Rheum Dis 2011;70:32–8.

15 Korn JH, Mayes M, Matucci Cerinic M *et al*. Digital ulcers in systemic sclerosis: prevention by treatment with bosentan, an oral endothelin receptor antagonist. Arthritis Rheum 2004;50:3985–93.

16 Guiducci S, Cerinic MM. Lack of efficacy of quinapril on vascular damage in limited cutaneous systemic sclerosis. Nat Clin Pract Rheumatol 2008;4:288–9.

17 Shenoy PD, Kumar S, Jha LK *et al*. Efficacy of tadalafil in secondary Raynaud's phenomenon resistant to vasodilator therapy: a double-blind randomized cross-over trial. Rheumatology 2010;49:2420–8.

18 Hachulla E, Hatron PY, Carpentier P *et al*. Efficacy of sildenafil on ischaemic digital ulcer healing in systemic sclerosis: the placebo-controlled SEDUCE study. Ann Rheum Dis 2016;75:1009–15.

19 Abou-Raya A, Abou-Raya S, Helmii M. Statins: potentially useful in therapy of systemic sclerosis-related Raynaud's phenomenon and digital ulcers. J Rheumatol 2008;35:1801–8.

20 Fiori G, Galluccio F, Braschi F *et al*. Vitamin E gel reduces time of healing of digital ulcers in systemic sclerosis. Clin Exp Rheumatol 2009;27(3 Suppl 54):51–4.

21 Gliddon AE, Doré CJ, Black CM *et al*. Prevention of vascular damage in scleroderma and autoimmune Raynaud's phenomenon: a multicenter, randomized, double-blind placebo-controlled trial of the angiotensin-converting enzyme inhibitor quinapril. Arthritis Rheum 2007;56:3837–46.

22 Kawald A, Burmester GR, Huscher D, Sunderkötter C, Riemekasten G. Low versus high-dose iloprost therapy over 21 days in patients with secondary Raynaud's phenomenon and systemic sclerosis: a randomized, open, single-center study. J Rheumatol 2008;35:1830–7.

23 Rosato E, Borghese F, Pisarri S, Salsano F. The treatment with n-acetylcysteine of Raynaud's phenomenon and ischemic ulcers therapy in sclerodermic patients: a prospective observational study of 50 patients. Clin Rheumatol 2009;28:1379–84.

24 García de la Peña-Lefebvre P, Rodríguez Rubio S, Valero Expósito M *et al*. Long-term experience of bosentan for treating ulcers and healed ulcers in systemic sclerosis patients. Rheumatology 2008;47:464–6.

25 Airò P, Rossi M, Scarsi M. Disease-modifying effects of long-term cyclic iloprost therapy in systemic sclerosis. A retrospective analysis and comparison with a control group. Clin Exp Rheumatol 2007;25:722–7.

26 Sfikakis PP, Papamichael C, Stamatelopoulos KS *et al*. Improvement of vascular endothelial function using the oral endothelin receptor antagonist bosentan in patients with systemic sclerosis. Arthritis Rheum 2007;56:1985–93.

27 Ferri C, Giuggioli D, Sebastiani M, Colaci M. Treatment of severe scleroderma skin ulcers with recombinant human erythropoietin. Clin Exp Dermatol 2007;32:287–90.

28 Chung L, Fiorentino D. A pilot trial of treprostinil for the treatment and prevention of digital ulcers in patients with systemic sclerosis. J Am Acad Dermatol 2006;54:880–2.

29 Ciompi ML, Bazzichi L, Melchiorre D *et al*. A placebo-controlled study on urokinase therapy in systemic sclerosis. Biomed Pharmacother 1996;50:363–8.

30 Robertson LP, Marshall RW, Hickling P, Treatment of cutaneous calcinosis in limited systemic sclerosis with minocycline. Ann Rheum Dis 2003;62:267–9.

31 Filho JP, Sampaio-Barros PD, Parente JB *et al*. Rhythmic external compression of the limbs: a method for healing cutaneous ulcers in systemic sclerosis. J Rheumatol 1998;25:1540–3.

32 Zachariae H, Halkier-Sørensen L, Bjerring P, Heickendorff L. Treatment of ischaemic digital ulcers and prevention of gangrene with intravenous iloprost in systemic sclerosis. Acta Derm Venereol 1996;76:236–8.

33 Hafner J, Schneider E, Burg G, Cassina PC. Management of leg ulcers in patients with rheumatoid arthritis or systemic sclerosis: the importance of concomitant arterial and venous disease. J Vasc Surg 2000;32:322–9.

34 Shanmugam VK, Price P, Attinger CE, Steen VD. Lower extremity ulcers in systemic sclerosis: features and response to therapy. Int J Rheumatol 2010;2010:747946.

35 Blagojevic J, Piemonte G, Benelli L *et al*. Assessment, definition, and classification of lower limb ulcers in systemic sclerosis: a challenge for the rheumatologist. J Rheumatol 2016;43:592–8.

36 Mihai C, Landewé R, van der Heijde D *et al*. Digital ulcers predict a worse disease course in patients with systemic sclerosis. Ann Rheum Dis 2016;75:681–6.

37 Avouac J, Fransen J, Walker UA *et al*. Preliminary criteria for the very early diagnosis of systemic sclerosis: results of a Delphi Consensus Study from EULAR Scleroderma Trials and Research Group. Ann Rheum Dis 2011;70:476–81.

38 Bellando-Randone S, Lepri G, Bruni C *et al*. Combination therapy with bosentan and sildenafil improves Raynaud's phenomenon and fosters the recovery of microvascular involvement in systemic sclerosis. Clin Rheumatol 2016;35:127–32.

39 van den Hoogen F, Khanna D, Fransen J *et al*. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum 2013;65:2737–47.

40 Cutolo M, Sulli A, Secchi ME, Paolino S, Pizzorni C, Nailfold capillaroscopy is useful for the diagnosis and follow-up of autoimmune rheumatic diseases. A future tool for the analysis of microvascular heart involvement?. Rheumatology 2006;45(Suppl 4):iv43–6.

41 Avouac J, Meune C, Ruiz B *et al*. Angiogenic biomarkers predict the occurrence of digital ulcers in systemic sclerosis. Ann Rheum Dis 2012;71:394–9.

42 Khimdas S, Harding S, Bonner A *et al*. Associations with digital ulcers in a large cohort of systemic sclerosis (SSc). Arthritis Care Res 2011;63:142–9.

43 Khanna D, Furst DE, Allanore Y *et al*. Twenty-two points to consider for clinical trials in systemic sclerosis, based on EULAR standards. Rheumatology 2014;54:144–51.

44 Lizaka S, Sugama J, Nakagami G *et al*. Concurrent validation and reliability of digital image analysis of granulation tissue color for clinical pressure ulcers. Wound Repair Regen 2011;19:455–63.

45 Allanore Y, Seror R, Chevrot A *et al*. Hand vascular involvement assessed by magnetic resonance angiography in systemic sclerosis. Arthritis Rheum 2007;56:2747–54.

46 Alivernini S, De Santis M, Tolusso B *et al*. Skin ulcers in systemic sclerosis: determinants of presence and predictive factors of healing. J Am Acad Dermatol 2009;60:426–35.

47 Sebastiani M, Manfredi A, Colaci M *et al*. Capillaroscopic skin ulcer risk index: a new prognostic tool for digital skin ulcer development in systemic sclerosis patients. Arthritis Rheum 2009;61:688–94.

48 Hasegawa M, Nagai Y, Tamura A, Ishikawa O. Arteriographic evaluation of vascular changes of the extremities in patients with systemic sclerosis. Br J Dermatol 2006;155:1159–64.