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Non-surgical local treatments of digital ulcers in systemic sclerosis: a systematic literature review

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ABSTRACT

Introduction: Digital ulcers (DUs) are difficult to treat in patients with systemic sclerosis (SSc) and systemic (i.e., pharmacological) therapy is currently considered the 'standard of care'. Our aim was to examine the safety and efficacy of local, non-surgical treatment for SSc-DUs.
Methods: A systematic literature review (SLR) of original research articles up to August, 29 2022 was performed according to the PICO framework. References were independently screened by two reviewers and risk of bias was assed using validated tools. Due to study heterogeneity narrative summaries are used to present data.
Results: Among 899 retrieved references, 14 articles were included (2 randomised trials (RTs), and 12 observational (OBS) studies). The most frequently studied procedure (5 studies) was botulin A toxin (hand or single finger) injection with a reported healing rate (HR) of 71%-100%. Amniotic and hydrocolloid membranes were examined in one study each and associated with a good HR. Tadalafil 2% cream was studied in a single study

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with a reduction in the number of DUs. Vitamin E gel was associated with a reduction in ulcer healing time. Low-level light therapy, hydrodissection and corticosteroid injection, extracorporeal shock wave (ESW) and photobiomodulation were evaluated in a single study each and showed a positive trend. Dimethyl sulfoxide was associated with significant local toxicity.

Conclusions: A range of non-surgical, local treatments for SSc-DUs have been explored and showed efficacy to some extent. We have identified methodological flaws that should be avoided in the design of future studies to explore locally-acting treatments for SSc-DUs.

Introduction

Systemic sclerosis (SSc) is a complex systemic autoimmune disease characterized by vasculopathy, fibrosis of skin and internal organs, and abnormal immune system activation [1,2]. Digital vasculopathy, also encompassing attacks of Raynaud's phenomenon and digital ulcers (DUs), is one of the most common, and often early, clinical manifestations of SSc [3]. Likewise, DUs frequently occur as SSc complication and affect approximately 50% of patients being the cause of a significant burden for many SSc patients [4,5].

In general, ischaemia is believed to be the main DU driver. However, also other important aetiopathogenic drivers (e.g., recurrent microtrauma and skin sclerosis), which may be instrumental at certain sites (e.g., overlying the small joints of the hands) [6,7] have been postulated. The presence of DUs, which usually manifest already within the first 5 years of the disease, is also a negative prognostic factor as DUs have been associated with a more severe disease course including internal organ involvement [8–10].

Local wound care is a cornerstone of DU management; however, currently there are no dedicated recommendations. For example, non-surgical debridement is considered by some experts to be the standard of care in the local management of SSc-DU; however, the use of this technique internationally varies significantly [6,11–13]. Indeed, systemic (i.e., pharmacological) therapy is currently generally considered the 'standard of care' for SSc-DUs. However, there is a strong therapeutic rationale to develop local approaches to DUs as this might avoid significant side effects from systemic (pharmacological) drug therapies, and might work synergistically with systemic treatments for DUs. A multidisciplinary approach is of fundamental importance for the management of DUs which requires a careful clinical assessment and the combination of both systemic and local treatments and, in some cases, the need for surgical interventions [10,14].A DU ad-hoc committee to develop practical, evidence-based treatment recommendations for both the local and systemic pharmacological management of SSc-DU was convened.

Herein, we present the findings of a systematic literature review (SLR) on non-surgical treatments for the management of SSc-DU. These results will inform DU treatment recommendations endorsed by the World Scleroderma Foundation (WSF).

Methods

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) checklist [15]. A systematic literature search of PubMed, MEDLINE, Embase, Web of Science, Cochrane Library, Emcare (OVID) and Academic Search Premier databases was performed on August 29, 2022 to identify original research studies of adult patients with SSc DU treated with local treatments.

Based on the PICO framework, studies were eligible for inclusion if they enrolled adult (age $\geq$ 18 years) patients with definite SSc undergoing local treatment for DU and if they reported DU outcomes as either a primary or secondary endpoint (when aggregated data on SSc-DU patients could be extracted). Both prospective and retrospective studies including at least 3 patients, were included. We recorded the types of treatment and the outcomes of interest including number of DU, the DU healing rates (HR), patient-reported outcomes, safety data as well as possible prevention of new DU. Only manuscripts published in English were included in the final review. Unpublished data and abstracts were also excluded. The research questions and search strategy are detailed in Supplementary Text S1 and Figure S1.

All titles and abstracts were independently screened by two reviewers (CC, YS). The full text of all eligible citations was then independently assessed by the same reviewers and study data extracted into a standardised document. Any disagreement between reviewers was resolved by consensus.

Owing to extensive interstudy heterogeneity meta-analysis of study results was not possible so narrative summaries were used to present the data. The risk of bias (RoB) assessment was performed independently by two authors (CC, YS). For RTs the Cochrane RoB tool was used [16] whereas the ROBINS-I [17] was applied to observational (OBS) cohort studies. All disagreements were resolved by consensus.

Results

The literature search identified 899 references. After deduplication, 896 titles and abstracts were screened (Supplementary Figure 1). Local treatment of SSc-DUs was mainly performed with either surgical or non-surgical procedures. Given the different indications, timing and the overall differences across studies on surgical and non-surgical procedures, we deemed it appropriate to describe the results separately and here we describe studies of non-surgical treatment only.

Of the 14 articles included in the final review, 2 were RTs, 3 were prospective cohort studies, 1 was a retrospective cohort study and 8 were case series. Eight different non-surgical treatments were evaluated including botulin toxin A (BTA) injection (5 studies) [18–22], topical membranes (2 studies) [23,24], ointments (2 studies) [25,26], hydrodissection and steroid injection of the carpal tunnel (1 study) [27], low-level light therapy [28] (1 study), extracorporeal shock wave (ESW) (1 study) [29], and dimethyl sulfoxide (1 study) [30] and photobiomodulation (1 study) [31]. Only two studies presented a cost effectiveness analysis of therapy for DU: one using vitamin E ointment [25] and one using botulin toxin A[22] . An overview of the included study characteristics is presented in Table 1

Patients, definition of DUs and of DU healing

SSc classification criteria were specified in all but 3 studies (79%) and they were the 1980 American College of Rheumatology (ACR) criteria [32] in 4 studies [24,27,29,30], the 2013 ACR/European League Against Rheumatism (EULAR) classification criteria for SSc [33] in 6 studies [19,21,22,26,31] and the Leroy criteria [34] in 1 study [28]. A definition of DU was available only in 4 (29%) [22,29–31] studies and they were: "*loss of surface epithelialization with the exclusion of fissures and cracks*" in one study [29] and only "*loss of surface epithelialization*" in the other 3 studies [22,30,31]. The location of DUs was specified in 57% of the studies (all prospective and retrospective studies), either lesions at or distal to the proximal interphalangeal (PIP) joints. The presence of a calcinotic ulcer was a specified exclusion criteria in 3 studies [22,24,30]. Ulcer healing definition was stated in 4 (29%) studies, and it was specified as either "*complete re-epithelialisation*" in 3 studies [22,29,31] or "*stabilization or partial healing*" in 1 study [27].

Botulin toxin A

BTA was the most frequently studied non-surgical local treatment for SSc-DU as it was reported in 5 observational studies including a total of 60 SSc patients (mean age ranging from 37 to 62 years, females 70 to 100%) [18,19,21,22,35]. The RoB was moderate for the prospective cohort study [21] and severe for the retrospective cohort study [24]. The inclusion criteria for the prospective studies were chronic DU (lasting > 3 months) with stable vasodilator therapy for ≥ 1 year [21], patients with DU unable to tolerate pharmacological treatment or refractory to pharmacological treatments [19] or SSc patients with at least 1 "active" DU [22]. BTA treatment was performed as single-finger injection - proximal to the A1 pulley of affected fingers [19]; into both the medial and lateral sides of the root of every involved digit (adjacent to the neurovascular bundles, at the root of bilateral palmar proper arteries of each involved finger) [22]; whole hand injection at each finger roots [18,21], at palmar digital neurovascular bundles with additional injection performed also at the wrist level, or in proximity to the radial and ulnar artery in patients with severe vasospastic symptoms [35]. The doses injected were highly variable among the 5 studies as they ranged from 90 to 150 U per hand. In the study performed by Motegi *et al* [19] the dose was 50 U per finger, whereas in the study by Shenavandeh *et al* [22] the dose was 20 U per finger. The HR was highly satisfactory in all studies as it ranged from 71 to 100% after a median time ranging from 8 to 12 weeks. In 3 studies a concomitant reduction of pain reported on a visual analogue scale (VAS) by 20 to 100% was observed. Overall, the procedure was well-tolerated, and the most common side effect was transitory hand weakness which was reported by up to 10% of patients after the procedure. Procedure-related pain was universally reported by patients in the study by Motegi *et al* [19]; however, this resolved in all patients after 2 days. The study by Shenavandeh provided also an economic and effectiveness analysis comparing BTA with prostaglandin analog (PA) infusions. While the effectiveness analysis showed no statistically significant difference in the number of healed DUs after 1 month (95.5% BTA versus 90.5% for PA, $p > 0.05$); the cost analysis was in favor of BTA over PA (103,350 Tomans for BTA as outpatient versus 2, 291,000 Tomans for PA as inpatient with 3-5 nights in hospital, $p < 0.0001$). Among all studies, the majority of patients (20 to 100%) were also receiving concomitant systemic treatments with varying vasodilator therapies, see Table 2 and Table 1s.

Topical membranes

Topical membranes were used in 2 studies assessing the use of amniotic membranes [23] (6 patients, age range 28-50 years, females 67%) and hydrocolloid membranes [24] (7 patients, age range 37-50 years, females 100%). The RoB was moderate for the hydrocolloid membrane prospective study and severe for the amniotic membrane study. The inclusion criteria for the hydrocolloid study were the presence of a DU of at least 2 mm in diameter or 4 mm^2 in size present for ≥ 2 weeks, whereas, in the amniotic membrane study was the presence of chronic DU (≥ 12 weeks). The healing rate was extremely satisfactory in both studies (90 and 100%) after a median time ranging from 3 to 8 weeks and was statistically significant for the hydrocolloid membrane. No pain assessment was performed in either of the two studies. While no adverse events were reported for the amniontic membrane application, the use of the hydrocolloid membrane was associated with a 10% local infection rate. Even in these two studies, most patients were also on systemic treatments with different classes of vasodilators, see Table 2 and Supplementary Table 1.

Ointments

Tadalafil 2% cream was utilised in a single case series study (13 patients, mean age 54 ± 15 years, females 69%) with a severe RoB [26]. The only inclusion criterion was the absence of vascular treatment modifications in the 4 weeks prior to tadalafil 2% cream introduction. The mean number of DUs per patient numerically decreased from 1.6 ± 1.0 to 1.0 ± 1.0 after 4 weeks of treatment but without reaching statistical significance ($p = 0.088$). A weak trend in VAS pain reduction was

Table 1
Characteristics of randomized trials and cohort studies included in the SLR.

Study, Ref, Year,	Type of study	Treatment	N of patients	Comparator	Primary outcome	Follow-up	Risk of bias
Lautenbach [21] 2020	Case series	BTA median 90 U per hand	7	None	NA	NA	High
Nagarajan [20] 2020	Retrospective Cohort study	BTA high-concentration hand	7	Contralateral hand	NA	49 months	High
Uppal [18] 2013	Case series	BTA 100 U non-dominant hand	20	None	Hand function	6 months	High
Motegi [19] 2016	Case series	BTA single finger 50 U	10	None	Raynaud's	16 weeks	High
Shenavandeh [22] 2022	Prospective Cohort study	BTA 20 U per finger	16	Prostaglandin infusion	DU healing	4 weeks	Moderate
Frech [23] 2018	Case series	Amniotic membrane	3	None	NA	6 months	High
Milburn [24] 1988	Prospective Cohort study	Hydrocolloid membrane	7	Local DU care protocol	Not stated	NA	Moderate
Fernández-Codina [26] 2020	Case series	Tadalafil 2% cream	13	None	NA	4 weeks	High
Fiori [25] 2009	RT	Vitamin E gel	15	Local DU care protocol	Time to healing	24 weeks	Moderate
Hughes [28] 2018	Case series	Low-level light therapy	8	None	Safety	8 weeks	High
De Lea [27] 2011	Prospective Cohort study	Hydrodissection and corticosteroid injection	12	Rheumatoid Arthritis	Pain (VAS)	6 months	Moderate
Saito [29] 2016	Case series	Extracorporeal shock wave	9	None	Number DUs	20 weeks	High
Spinella [31] 2022	Case series	Photobiomodulation	12	Local DU care protocol	DU healing	8 weeks	High
Williams [30] 1985	RCT	Dimethyl sulfoxide	84	Placebo	Number DUs	12 weeks	Low

BTA = botulin toxin A. RT = randomized trial. C = controlled. NA = not applicable.

Table 2
Baseline characteristics and outcomes of studies with comparators included in the SLR on non-surgical local treatments

Study, year	Treatment	Groups	BaselineDU Number	Background therapy (%)			ETA	CCB	APA	PG	ARB	ACE-I	PDE-5i	IS	Follow-up (weeks)	Healing rate*	Pain Reduction(VAS/10)
De Lea [27], 2011	Hydrodissection and corticosteroid injection	SSc (I)	NR	NR	NR	0	NR	NR	NR	NR	NR	NR	NR			33%	4.4
		Rheumatoid arthritis (C)	NR	NR	NR	0	NR	NR	NR	NR	NR	NR	NR		2	NR	3.5
Fiori [25], 2009	Vitamin E gel	SSc (I)	3.5±2.3	NR	NR	NR	0	NR	NR	NR	NR	NR	0			Reduced time to heal*	NR
		Local DU care (C)	2.8±2.6	NR	NR	NR	0	NR	NR	NR	NR	NR	0		24		NR
Milburn [24], 1988	Hydrocolloid membrane	SSc (I)	10	0	28	0	0	0	28	0	0		14			90%**	NR
		Local DU care (C)	10	0	28	0	0	0	28	0	0	14	14		8	10%	NR
Nagarajan [20], 2020	BTA High-concentration	SSc (I)	NR	14	85	NR	14	NR	NR	NR	NR	NR	NR			71%	NR
	BTA Single finger 20 U	Contralateral hand (C)	NR	14	85	NR	14	NR	NR	NR	NR	NR	NR		49	NR	NR
Shenavandeh [22], 2022		SSc (I)	22	0	100	87	0	0	0	0	44	87	87		4	95%	50%
		PG infusion(C)	21	0	100	50	100	0	0	0	30	50	50			90%	53%
Spinella [31], 2022	Photobiomodulation	SSc (I)	12	67	67	NR	100	NR	NR	25	50					42%	47%
		Local DU care (C)	8	87.5	87.5	NR	87.5	NR	NR	12.5	12.5	8				25%	15%
Williams[30], 1985	Dimethyl sulfoxide (DMS)	DMS 2% (I)	45	0	NR	NR	0	0	0	0	0	0					
		DMS 70% (I)	47	0	NR	NR	0	0	0	0	0	0			12	Withdrawal due to skin toxicity	Withdrawal due to skin toxicity
		Placebo (C)	48	0	NR	NR	0	0	0	0	0	0					

*Unless otherwise stated. **Statistically significant. ARB= angiotensin receptor antagonist. ACEi= ACE inhibitors. APA= anti-platelet agents. CCB= calcium channel blockers. ETA = endothelin antagonist. IS= immunosuppression. PG= prostaglandins. PDE-5i= Phosphodiesterase type-5 inhibitors. NR = not reported. I = intervention. C = comparator.

also reported. No treatment-related side effects were reported by the authors.

Vitamin E gel was studied in a single open-label randomized prospective study (15 patients, mean age 52 ± 12 years, females 87%) with a moderate RoB [25]. The only inclusion criterion was the presence of a DU. The comparator was the use of the standard DU care protocol of the study center which was applied to both groups twice a week. A statistically significant reduction in the time to healing was observed (vit. E group: 13.2 ± 2.7 versus standard of care: 20.9 ± 3.6 weeks, $p<0.001$). However, no assessment of pain or treatment-related adverse events were reported. This was one of the two studies in which a cost analysis was performed, and showed a significant reduction in the costs of required medications (per patient) due to the reduction in time to DU healing: vitamin E: 6,919.15 € versus controls: 11,056.32 € ($p<0.0001$). In these two studies, most patients were also on systemic treatments with different classes of vasodilators, see Table 2 and Supplementary Table 1.

Other local treatments

Low-level light therapy, hydrodissection and glucocorticoid injection of the carpal tunnel, ESW, photobiomodulation and local dimethyl sulfoxide were also evaluated in a single study each.

Low-level light therapy was studied in a single case series (8 patients, mean age 48 ± 15 years, females 87%) whose primary outcome was safety and with a severe RoB [28]. Low-level light treatment combines infrared, red, and violet wavelengths which were specifically selected due to known promotion of wound healing (e.g., 'biostimulation'), anti-bacterial properties, and to induce vasodilation (via nitric oxide release) [36]. The light treatment (10 J/cm^2) was administered twice weekly for 3 weeks (with follow-up at weeks 4 and 8). All the ulcers healed at 8 weeks. Both patients' and physicians' global DU assessment (GA) were significantly lower at 8 weeks (patients GA 6.4 ± 1.6 versus 1.07 ± 2.27; physicians GA 5.38 ± 1.48 versus 1.13 ± 2.53; $p>0.01$ for both comparisons). No treatment-related adverse event was reported, and the treatment was well-tolerated and a mean VAS pain of 1.6 ± 5.2 was reported by patients during the procedure. A limitation of the study was the drop-out rate of the included participants (20%) which was due to medical concern for DU in one case and patients' personal/unrelated reasons in the other 2 cases.

Hydrodissection and glucocorticoid injection was studied in a single prospective cohort study (12 patients, mean age 43 ± 8 years, females 83%) with a moderate RoB [27]. The study investigated the effect of hydrodissection of the carpal tunnel (an ultrasound-guided syringe is inserted to anesthetize, aspirate, and then hydrodissect and dilate the carpal tunnel space) followed by glucocorticoid injection for painful scleroderma hands. The primary endpoint was pain, while number of DUs was a secondary endpoint. The control group included patients with rheumatoid arthritis (RA). The inclusion criteria were the presence of persistent hand pain with a VAS pain >5 and failure of oral medications and local measures. The major exclusion criterion was the presence of DU infection. DU HR was 33% after 2 weeks. An overall trend for VAS pain reduction for both RA and SSc patients was also observed. No treatment-related complications were observed, and the procedure was well-tolerated (mean VAS pain during the treatment was 2.0 ± 1.8).

ESW was studied in a single prospective phase 2 single arm pilot study with a moderate RoB [29]. ESW consists of a sequence of sonic pulses characterized by high peak pressure, fast pressure increase, and short lifecycle, which have been shown to have antalgic, anti-inflammatory and tissue regenerative effects [37]. Exclusion criteria were the presence of severe cardiovascular/respiratory disorders and/or DU infection. DU HR was 41% after 4 weeks. The number of DUs 4 weeks after treatment was lower compared to baseline (49 versus 20; $p<0.05$), and this outcome was paralleled by a reduction in DUs dimensions (10.9 ± 0.7 versus 2.5 ± 0.8 mm; $p<0.001$) at week 20. A trend in VAS pain reduction was also observed at 20 weeks. No

treatment-related complication was observed. In these studies, most patients were also on systemic treatments with different classes of vasodilators (Table 2 and Supplementary Table 1).

Photobiomodulation was studied in a single case series (12 patients, mean age 62.7 ± 8.3 years, females 67%) with a severe RoB [31]. Photobiomodulation consists of the emission of blue LED lights that stimulates endogenous chromophores in the blood and skin which in turn enhance wound healing [38]. The treatment was used in patients already treated with the standard local DU and an historical cohort of 8 SSc-DU patients treated only with standard local DU protocol was used as control. In this study the blue LED light was applied through a medical device called "EmoLEDÒ" which emits blue light at 400–430 nm. The device was applied for 60 seconds at a distance of 4 cm from the DU on every 50-mm-diameter circular sub-area. A complete DU healing rate of 42% was observed after 8 weeks in EmoLEDÒ-treated patients compared to 25% of controls ($p = 0.392$). This was also paralleled by a reduction of VAS pain which was higher, although not statistically significant, in the EmoLEDÒ-treated group compared to controls (2.4 versus 0.7, $p = 0.130$). No treatment-related complication was observed. Most of patients were also on systemic treatments with different classes of vasodilators (Table 2).

Dimethyl sulfoxide was investigated in a RCT [30] which was interrupted early due to absence of significant changes and high withdrawal rate from significant skin toxicity (including cracking, blistering, sloughing, and burning) with the 70% topic formulation.

Discussion

Local treatment for DUs currently often represents the preferred option in patients who are intolerant of or refractory to systemic treatment. Our SLR has highlighted the potential use of different local non-surgical treatments to manage SSc-DUs, however no study provided evidence of efficacy of any of the investigated approaches without background systemic therapy.

Although some studies are promising, the evidence base is overall weak. The retrospective nature of several studies, low number of included patients, the heterogeneity (or even lack) of DU definition (including ulcer healing) [39–42], the frequent lack of a control group and the objective difficulty in assessing the impact of local measures *combined* with systemic treatments prevents from drawing any definitive conclusions. Moreover, the study heterogeneity prevented any quantitative analysis.

Topical membranes, which are commonly used and advocated by many clinicians in SSc-DU clinics [43] were found to be effective in DU healing, with the best evidence from the study examining hydrocolloid membranes. However, safety concerns were highlighted from the study concerning the use on infected DUs as a possible cause of infection in up to 10% of DUs.

BTA seems well-tolerated, and also associated with a high efficacy rate consistently among the 5 included studies. However, several questions remain unanswered about BTA treatment for DUs including the optimal dose, site of injection, and the need and timing of retreatments. Of note, BTA was the only local non-surgical treatment which was investigated against a systemic treatment (prostaglandin analogue infusion) and which was found to be as effective as the systemic treatment with significantly lower costs.

Other treatments which may have a satisfactory efficacy and safety profile were vitamin E gel and ESW. Both these treatments were associated with a high ulcer HR in the absence of significant adverse events. Moreover, the study performed with vitamin E gel included an economic evaluation demonstrating benefit with an estimated saving of 4'000 euros per patient. ESW was examined in a prospective study which demonstrated a high healing rate and efficacy with a reduction in DU pain. No clear conclusion can be drawn about low-level light therapy as the number of patients included was small and a high drop-out rate was observed in the study. Nonetheless, this treatment might offer a possible option in specific patients if the preliminary results will be further confirmed. In addition, photobiomodulation, which relies on a similar principle was also found to be effective in a small cohort of SSc-DU patients thus further suggesting that the use of localized light therapies on top on standard of care procedures might be beneficial for SSc-DU patients. Of note, the only treatment which was found to be toxic and therefore should not be used for SSc-DUs is dimethyl sulfoxide.

Different DU clinics have developed local approaches for the local treatment of DUs on the basis of some shared principles (e.g. debridement of necrotic material and wound cleansing with 0.9% NaCl) [10]. However, the specific treatment protocols performed by healthcare professionals might significantly differ as none is currently endorsed by international medical societies due to the lack of a robust evidence base [11,13]. Future research is required to define the optimal (local) wound bed management strategy for SSc-DU, including tissue/wound bed management (especially debridement), where there is currently significant international variation in practice [13].

Due to the above-mentioned limitations of the included studies, these findings need to be interpreted with caution and therefore likely cannot be generalized for the treatment of all SSc-DUs. In particular, infected ulcers warrant further investigation including the possibility that local treatments could potentially worsen the course of DUs, such as hydrocolloid membranes, including due to damage to the perilesional skin [11]. Specific recommendations for the local management of infected DUs are lacking and most of the studies included in our SLR excluded the presence of infected DU.

Evidence to guide the local management to *prevent* DUs is also lacking. Specifically, all the included treatments examined the healing rate of existing DUs, and no local treatments were applied in areas of intact skin (i.e., without DU), apart from studies examining the local injection of corticosteroids into the carpal tunnel and possibly the use of BTA (which was used also for the management of refractory RP).

The results of our SLR highlight that there is an urgent need to further investigate the role of local non-surgical treatments for SSc-DU patients in well-designed future clinical trials. A first step should be made towards a better standardization of DU definitions used in trials and on how the use of local and systemic treatments should be reported (i.e., what kind of local procedures were used, the standardization of systemic treatments before patients' recruitment, etc.). Furthermore, the contemporary healing of DUs should be benchmarked, including consideration of 'chronic' DU [44,45]. Local treatments can indeed represent a valuable option for patients who are either refractory to or intolerant of systemic treatments or can be considered as add-on treatments in patients already on systemic treatments. These two different aims should be kept in mind when designing future trials as the characteristics and the healing rates of different local treatments can be extremely diverse between the two populations. In addition, as previously stated, the specific treatment protocols used for the management of DUs should be standardized in order to provide the lowest risk of bias when evaluating the potential role of any additional local treatment.

Conclusions

In conclusion, across five treatment approaches our SLR has demonstrated that BTA, vitamin E, ESW, photobiomodulation and hydrocolloid membranes might be suitable options for the local non-surgical management of SSc-DUs and deserve further well-designed controlled trials. However, we have identified key areas of unmet need for further research to confirm the safety and efficacy of such treatments, including as add-on therapy to systemic (pharmacological) therapies.

Declaration of Competing Interest

CC: No conflict of interest to declare
YAS: No conflict of interest to declare

MH: Speaking fees from Actelion Pharmaceuticals, Eli Lilly, and Pfizer, outside of the submitted work. Member of a Data and Safety Monitoring Board for Certa Therapeutics.

JWS: No conflict of interest to declare

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MB: No conflict of interest to declare

LC: Has served as an Advisor and Steering Committee member for Eicos Sciences. Has received consulting fees from Mitsubishi Tanabe, Genentech, Kyverna, and Jasper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2023.152267.

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