Treatment of systemic sclerosis-associated digital ulcers: recommendations of the Turkish Society for Rheumatology

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Abstract

Objectives

Digital ulcers (DUs) are associated with a significant burden in systemic sclerosis (SSc) by leading to severe pain, physical disability, and reduced quality of life. This effort aimed to develop recommendations of the Turkish Society for Rheumatology (TRD) on the management of DUs associated with SSc.

Methods

In the first meeting held in December 2020 with the participation of a task force consisting of 23 rheumatologists the scope of the recommendations and research questions were determined. A systematic literature review was conducted by 5 fellows and results were presented to the task force during the second meeting. The Oxford system was used to determine the level of evidence. The preliminary recommendations were discussed, modified, and voted by the task force and then by members of TRD via e-mail invitation allowing personalised access to a web-based questionnaire [SurveyMonkey®].

Results

A total of 23 recommendations under 7 main headings were formulated covering non-pharmacological measures for the prevention of DUs and pharmacological treatments including vasodilators, anti-aggregants, antibiotics, wound care, pain control, and interventions including sympathectomy, botulinum toxin, and surgery. Risk factors, poor prognostic factors, prevention of DU and adverse effects of medical treatments were reported as 4 overarching principles.

Conclusions

These evidence-based recommendations for the management of SSc-associated DUs were developed to provide a useful guide to all physicians who are involved in the care of patients with SSc, as well as to point out unmet needs in this field.

Key words

systemic sclerosis, digital ulcer, treatment, recommendation

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Received on February 21, 2023; accepted in revised form on June 13, 2023.

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Funding. This study was supported by an unrestricted grant by Abdi Ibrahim Pharmaceuticals Company.

Competing interests: All authors have received honorarium from Abdi Ibrahim Pharm Company. A. Akdogan has also received honrarium from Roche.

Introduction

Systemic sclerosis (SSc) is a chronic autoimmune disease characterised by autoimmune dysfunction and vasculopathy leading to fibrosis of the skin and internal organs. Although SSc is a rare disease, the presence of digital ulcers (DUs) is a daily problem for physicians dealing with SSc patients. DUs are a clinical manifestation of digital ischaemia that occur in 35% to 68% of patients with systemic sclerosis (1-4). Based on the EUSTAR data, the probability of the development of DUs is 70% in 10 years of follow-up (5) and about 75% of the patients experience their first DUs within 5 years after the onset of non-Raynaud's symptoms (4).

DUs can cause tissue loss, pain and frequent infections resulting in an important decline in quality of life and functional disability (6). Moreover, progressive vasculopathy can progress to critical ischemia and gangrene which affects 1.5-9.0% of patients and can necessitate digital amputation (7-8). SSc-associated DUs tend to heal very slowly. In an observational study that included 1,614 digital lesions, the mean time to healing for pure ischaemic DUs was 76.2 days (range 7-810 days) and for calcinosis-derived DUs was 93.6 days (range 30–388 days) (9).

Although DUs are common and seriously disabling in SSc, detailed recommendations and algorithms for their management are limited (10-12). We formulated the present recommendations to provide evidence-based and up-to-date recommendations for physicians interested in the treatment of SSc-related DUs to be used in daily rheumatology practice.

Methods

Design

An evidence-based methodology as advised in EULAR's standardised operating procedures was followed (13). Guidance, as provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, was followed for the various steps of the systematic literature review (14). The relevant questions were formulated in Population, Intervention, Comparison and Outcome (PICO) format for the systematic review (15). The "Oxford system" was used to rate the quality of the available evidence and determine the strength of recommendation as advised by additional guidance on the methodology for the development/update of EULAR recommendations (16).

Task force

The task force was composed of 23 clinical experts including 1 methodologist and 5 junior researchers. The clinical experts were rheumatologists with experience in diagnosing and treating patients with SSc. Potential conflicts of interest were declared by all participants. This study is based on a systematic literature review and expert opinion, and did not include patient or public involvement.

The selection process of clinical questions

At the first meeting, to create a comprehensive list of topics of interest, the clinical experts were asked to decide on the scope of recommendations. The expert panel agreed on five topics: (1) definition and classification of DUs, (2) risk factors and prognostic markers of DUs, (3) prevention of DUs, (4) management of DUs (including non-pharmacological, pharmacological and interventional treatments) and (5) general principles for complications and special conditions to be considered when using pharmacological treatments. As a result, 22 clinical questions were created by experts for the systematic literature search (Supplementary Table S1).

Systematic literature search

PubMed was searched for publications in English including meta-analyses, systematic reviews, randomised clinical trials, cohorts, and case series consisting of at least 5 cases from the inception of the database through March 20, 2021. The systematic literature search was performed by five junior researchers (DTK, AS, OCI, AA, ME) supervised by two task force members for each topic, guided by the methodologist (GH).

For every clinical question, the relevant publications were screened for eligibility

by reading the title and abstract (Supplementary Table S2). The reference lists of meta-analyses, reviews or systematic reviews were examined to find additional studies. After the full-text screening, the selection of relevant studies for data extraction was done. Disagreements were resolved through discussion and consensus. For details regarding the selection of studies and data extraction please see Supplementary Fig. S1.

Formulation and evaluation of recommendations

Results of the systematic review were presented to the task force and draft recommendations were discussed during an online meeting. Following thorough discussions and modifications when needed, the recommendations were voted among the task force. An agreement of 75% was needed to pass each recommendation. The level of agreement for each recommendation was also determined among the task force members, on a numerical rating scale ranging from 0 (completely disagree) to 10 (completely agree). After the internal voting, recommendations were sent to all members of the Turkish Society for Rheumatology working in academic and non-academic centres for external voting electronically.

Results

Definitions for SSc-associated skin ulcers were created based on the original definitions from the recently published data and accepted with little modifications (Supplementary Table S3).

The procedure as described above resulted in 23 recommendations under 7 headings for the management of DUs (Table I). Overarching principles regarding the risk factors, poor prognostic factors, prevention of DU, possible adverse effects of medical treatments and special recommendations for patients with DUs accompanied by ILD or PH have been discussed in detail in the supplementary material (Supplementary Table S4).

Non-pharmacological measures for the prevention and treatment of DUs

Prevention of DU is the first and the most important step in the management of DUs in patients with SSc. Although for many of them there is no data supported by evidence, the expert committee felt the need to emphasize the importance of certain behaviors and habits in terms of preventing Raynaud's phenomenon (RP) and the development of DUs. These include keeping the body warm not only in the winter but also in places with air conditioning; avoiding contact with cold water; avoiding caffeine; avoiding trauma; quitting smoking and trying to control emotional distress. Critical importance of regular self-assessment of skin and providing appropriate skin moisture should also be emphasized. Although the severity and/or frequency of Raynaud's phenomenon are not associated with development of DUs, any effort for controlling RP attacks may be useful (17).

Observational studies showed that smoking was a risk factor for DU development (OR: 6.80, CI: 2.01–22.10) (18) and active smokers tended to develop DUs more frequently than non-smokers (OR 1.42, CI:1.00-2.03, p=0.0528) (19). Active smokers with DUs were more likely to receive IV treatment (OR 3.8, 95% CI 1.1–12.9) and needed ulcer debridement more than never-smokers (OR 4.5, 95% CI) (20). The risk of digital ischaemia was 2-3 times higher, surgical amputation and gangrene were more frequent than non-smokers (21).

Systemic treatment modalities for DU healing

Calcium channel blockers (CCBs)

Most of the studies with CCBs have mainly investigated the effect of nifedipine on RP. Few studies have pointed out that nifedipine may also be associated with DU healing. In two trials, primarily focusing on the number and severity of RP episodes, oral nifedipine was compared with IV iloprost, (22-23). Both drugs reduced the mean number of DUs and demonstrated comparable efficiency in DU healing. However, the results were not comparable because of the small sample size. In another study, DUs healed in the nifedipine arm while new ulcers appeared with placebo (24). Although the data about the efficacy of CCBs on DU healing is limited, CCBs have been used in clinical practice for a long time in the treatment of these patients. The committee decided to recommend continuing and if possible, escalating the dosage of CCBs in patients with DUs.

Anti-platelet agents

In an RCT, patients were randomised to a combination of acetylsalicylic acid and dipyridamole or placebo (25). Because of the small sample size and ambiguous primary outcome evaluation, it was difficult to interpret the results. However, the task force thought that the addition of low-dose of acetylsalicylic acid (ASA) to treatment may be considered in selected cases with low haemorrhage risk. Although low-dose ASA alone or in combination with other anti-platelet agents increased the risk, it was not associated with fatal bleeding (26). Due to frequent gastrointestinal involvement in patients with SSc, there may be a tendency for bleeding and ASA should be used with caution. Gastroprotective prophylaxis should be considered, particularly in elderly patients, and in patients with additional risk factors such as concomitant therapy with nonsteroidal anti-inflammatory drugs or a history of peptic ulcer complications.

Phosphodiesterase 5 inhibitors (PDE5is)

A meta-analysis of 3 RCTs had shown that PDE-5 inhibitors were effective in both improvement ([RR; 95% CI 4.29; 1.73 to 10.66], p<0.002) and healing of the DUs ([RR; 95% CI 3.28; 1.32 to 8.13], p<0.01) (27). In one RCT, patients allocated to modified-release sildenafil 100 mg/day increased up to 200 mg/day had fewer DUs compared to the placebo group (28). In another RCT, patients were randomised to sildenafil (2x50 mg) or placebo for four weeks and in 6 patients chronic DUs started to regress and in 2 patients completely disappeared. When sildenafil was discontinued DUs recurred or worsened, although there was no improvement in the placebo group (29). In the third RCT, patients with SSc or mixed connective tissue diseases

Table I. The set of recommendations for the management of systemic sclerosis associated DUs with levels of evidence, voting rates and strength of recommendation.

		Level of evidence	Level of agreement	Strength of recommendation
Non-drug methods for the prevention and treatment of DUs	Education and support should be provided to the patients about daily skin care in order to protect them from cold exposure and trauma, and to maintain the skin's moisture	V	9.49	D
	Smoking increases the risk of developing new digital ulcers and the risk of amputation due to DUs.	IIb		B
Systemic treatment recommendations for DU healing	In SSc patients with active DUs, treatment should be given by evaluating the general characteristics of the patient and the characteristics of the ulcer	V	8.98	D
	Calcium channel blockers* (CCBs) can be used in the treatment of digital ulcers. In patients using CCBs for Raynaud's phenomenon the treatment can be continued and if possible, the dose can be escalated.	IIb		B
	In selected cases, anti-platelet agents may be added to the treatment.	V		D
	PDE5is (sildenafil/tadalafil) or i.v. iloprost should be considered in any patients who are unresponsive to or who cannot tolerate CCBs.	Ia/Ib		A
	Due to its ease of oral use, PDE5is may be preferred primarily in cases where it is tolerated.	V		D
	i.v. iloprost should be considered in the treatment of the patients who cannot achieve the expected improvement with oral therapy and/or cannot tolerate PDE5is.	Ib		B
	Combination therapy may be used in patients with multiple or severe ulcers.	V		D
Systemic treatment recommendations to prevent the development of new DUs	Bosentan should be used in the treatment to prevent the development of new digital ulcers, especially in patients with multiple DUs (≥4)	Ia	8.72	A
	PDE5is may be considered in the treatment to prevent the development of new DUs.	Ib		A
	i.v. iloprost may be preferred to prevent the development of new DUs in patients who are unresponsive or intolerant to oral vasodilator treatments.	Ib		A
	Statins (atorvastatin) might be added to the treatment to prevent DU development.	Ib		C
Other therapies (Botulinum toxin, cellular therapies, digital sympathectomy and other surgical methods)	In patients with SSc-related DUs, botulinum toxin might be considered if the ulcer(s) are resistant to medical treatment.	IIb	8.66	C
	Due to methodological and technical differences, cellular treatments (regional adipose tissue transplantation, mesenchymal stem cell transplantation, etc.) might be applied in cases which do not respond to conventional systemic and local treatments, in experienced centres.	IIb		D
	Digital sympathectomy may be preferred in selected patients who cannot respond to non-invasive methods.	V		D
Antibiotics	In the presence of signs of infection on digital ulcers, empiric antibiotic therapy should be initiated, and treatment should be reviewed according to clinical response and antibiogram	V	8.41	D
Wound care	General principles of wound care should be followed in the local treatment of DUs	V	8.94	D
	Symptoms and signs that may indicate the presence of accompanying infection such as new onset pain, night pain, hyperaemia or bad odour should be questioned at each visit, and the wound healing process should be followed	V		D
	Since it may facilitate the development of infection, necrotic tissues may be debrided, either pharmacologically or surgically, when deemed necessary	IV		D
	Sterile occlusive, semi-occlusive, absorbent or moisturizing dressings may be selected and applied by making a decision on the patient basis according to the characteristics of the ulcer to provide appropriate tissue moisture.	V		D
Pain control	Appropriate doses of NSAIDs and opioids (tramadol, oxycodone, morphine) may be used in pain control	IIb	8.75	C
	Local vitamin E gel and hydrocolloid membrane may be used for pain control. Lidocaine may be used in cases where an intervention is planned	IIb		B

*The most commonly used CCB for DU treatment is nifedipine. In case of intolerance, other CCBs (felodipin, lercanidipin or amlodipine etc.), angiotensin receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors or alpha blockers may also be effective.

(MCTD) were randomised to tadalafil (20 mg every other day) or placebo for 6 weeks. Complete healing of the lesions (all 20 DUs + 4 fissures) was higher in the tadalafil arm compared to the placebo (3/13 DUs) (p<0.001) (30). Other than the RCTs included in the meta-analysis, a multicentre RCT evaluating the effect of tadalafil on DU healing (20 mg/day on alternate day for 8 weeks as an add-on therapy to previous vasodilators) showed improvement in 14/18 DUs in the tadalafil arm compared to 5/13 in the placebo (p=0.026) (31). Two open-label studies (with sildenafil 3x25 mg/day and a maximum tolerated dose of 150 mg/day) demonstrated complete healing or significant improvement with sildenafil treatment (32-33). A relatively recent study investigating the effect of sildenafil on DUs, (Sildenafil Effect on Digital Ulcer Healing in sClerodErma-SEDUCE), although did not reach the primary end

point, showed a significant reduction in the number of DUs per patient at week 8 (1.23±1.61 vs. 1.79±2.40, p=0.04) and week 12 (0.86±1.62 vs. 1.51±2.68, p=0.01, respectively). This trial also revealed a greater healing rate of sildenafil compared to placebo [at week 8 OR 1.82 (CI 1.15 to 2.88), p=0.01 and week 12 OR 1.78 (CI 1.06 to 2.97), p=0.03)] (34).

Iloprost. Recommendations related to iloprost treatment are based on a meta-analysis (26). After 10 weeks of intravenous iloprost (0.5-2 ng/kg/min for 5 consecutive days) treatment, almost complete healing of all cutaneous lesions (ulcers, fissures, and paronychia) (p=0.015) and ischemic digital tip ulcers were observed (p=0.029) (35). In the other RCT, the percentage of patients with at least a 50% reduction from baseline score in the total number of lesions (p=0.06) and the percentage of patients with digital lesions that healed completely was greater in patients receiving iloprost compared to placebo (36). The meta-analysis included two more RCTs (one with oral iloprost and one with oral treprostinil) in addition to the ones mentioned above and provided evidence that prostanoids may affect DU improvement or healing (RR 1.33; 95% CI 0.97-1.84; p=0.08) (27, 37-38).

Two RCTs comparing intravenous iloprost with oral nifedipine showed similar results both on the mean number of the DUs and the number of active DUs which completely healed (22, 39). Results of 2 large observational studies also reported the beneficial effects of prostanoids on DUs. In one of these studies, only 9 patients out of 50 had recurrent or chronic DUs, and only 1 patient developed new ulcer during10 years of follow-up (40). In the other study with 7 years follow-up, iloprost 0.5-2.0 ng/kg/min for 5 days per month, decreased DUs from 42.6% to 11.8% (p<0.001) (41).

Task force recommended PDE5is and iloprost for healing DUs. Although data from RCTs is not conclusive for either PDE5is or iloprost in DU healing, real life data supports their efficacy (42-43). Data regarding combination treatment is scarce, but may be used in selected cases with severe DUs.

Systemic treatment modalities to prevent the development of new DUs

PDE5is. There is some evidence for the efficacy of PDE5is, especially tadalafil, for the prevention of new DUs in SSc. The results of 2 small RCTs showed that PDE5is tadalafil can prevent the development of new DUs when given as adjunctive therapy to previous vasodilators. In one of these studies, at the end of 6 weeks there was only one new DU in the tadalafil arm versus 13 new lesions in the placebo arm (p=0.001). Additionally, tadalafil prevented the development of new ischemic lesions (30). In the other study, at the end of 8 weeks there was one new ulcer in the tadalafil arm and 9 new ulcers in the placebo (p=0.004) (31). An open-label study showed that during 3 months of sildenafil treatment, none of the patients developed new DUs (32). Based on these results, PDE5is may be preferred to prevent the development of new DUs.

Iloprost. Although the results of the meta-analysis including one study with oral iloprost (37), one with oral beraprost (44) in addition to the two RCTs with intravenous iloprost (35-36) did not show significant results for the prevention of new DUs (28), it showed some evidence that iv iloprost may prevent new DUs in patients with SSc (standardised mean difference (SMD); 95% CI for number of DUs: –0.77; –1.46 to –0.08, p=0.03) when the study was evaluated separately in the meta-analysis (35). In addition, in a multicentre RCT evaluating continuous IV epoprostenol in SSc patients with pulmonary hypertension, 50% less new DUs developed in the epoprostenol arm compared to placebo (44). Despite limited evidence, IV iloprost may be preferred for the prevention of new DUs in patients who are unresponsive or intolerant to previous vasodilator therapies.

Bosentan. has proven its efficacy in reducing the number of new DUs in patients with SSc in two high-quality RCTs (45-46) and a meta-analysis (27). The effect of bosentan was more pronounced in patients with multiple (≥4) DUs at baseline [effect size –0.52; (95% CI –1.01 to–0.02]) compared with fewer number of DUs (effect size –0.08; [95% CI–0.44 to 0.28]) (47). Meta-analysis revealed that bosentan was successful in DU prevention with a statistically significant reduction in the mean number of new DUs per patient (SMD-0.34 [95% CI-0.57-0.11], p=0.004) (27). Bosentan should be considered in patients with multiple DUs to reduce the number of new DUs in SSc. The effect of other ERAs on the prevention of new DUs is not known. Two trials (DUAL1 and DUAL2) did not show efficacy in the prevention of new DUs in patients with active DUs at baseline (48).

Statins. Results of one RCT evaluating the effect of statins on DUs showed that atorvastatin was effective in preventing new ulcers compared to placebo (49). There was a significant reduction in the mean number of all DUs (p=0.001) and the mean number of new DUs (p=0.003) compared to the placebo. Although the results of this study were significant, there is scarce evidence and the task force felt that further studies are required to confirm the beneficial effect. Therefore, experts suggested statins to prevent the development of new DUs in selected cases who are resistant to previous vasodilator therapy and emphasised the need for high-dose use (40 mg/day) for efficacy.

Interventional modalities (Botulinum toxin, cellular therapies, digital sympathectomy and other surgical methods)

There are RCTs and case series reporting efficacy with different doses of botulinum toxin A and B (50-55). In these studies, it was observed that botulinum toxin was generally applied in cases resistant to standard medical treatment and resulted in the accelerated healing of DUs, and a reduction in the severity of RP and DU pain. There is no evidence to suggest the superiority of different BTX derivatives to one an-

other. The treatment response is dose-related, and in general, administration of 50-100U doses of BTX-A to each hand can reduce DU-related pain and provide wound healing (51). For BTX-B, application at doses of 1000-2000 U can facilitate wound healing and help prevent the development of new DUs (55). In conclusion, botulinum toxin might be considered among the treatment alternatives in patients with SSc-related DUs that are resistant to current medical treatments.

Cellular therapies in SSc-associated DUs may be promising treatments in the future, whose safety and efficacy are currently being evaluated (56-57). Among these, regional adipose tissue transplantation has been shown as an alternative method in the treatment of DUs which do not respond to traditional systemic and local treatments. It has been shown to increase DU healing, reduce pain and increase the number of capillaries with a low side-effect profile (56, 58). Allogeneic bone marrow-derived mesenchymal stem cell transplantation is another treatment modality that has been reported to reduce pain and ulceration, and improve hand vasculopathy (59). Another interventional treatment method is local bone marrow-derived mononuclear cell injections into the muscle. These applications can be considered in selected patients who are resistant to medical treatments, as they may contribute to the healing of DU by reducing pain and improving the nail bed capillary microscopy by increasing blood flow (60).

There are case series of surgical sympathectomy in patients with SSc-related DUs. Although in these series it has been reported that sympathectomy reduced pain, increased blood flow and accelerated wound healing, wound infections emerged as a problem that could not be ignored (61-69). Therefore, sympathectomy should be considered in patients who are resistant to medical treatments and in whom other non-invasive methods cannot be applied or are ineffective. Debridement was also shown to reduce the size and depth of the DUs and pain scores (70-71).

Antibiotics

In DUs associated with SSc, infection can easily develop as a result of circulatory disorder and disruption of tissue integrity. A retrospective analysis showed that 38% of the cases developed signs of inflammation, and osteomyelitis accompanied in 4.76% (72). It has been shown that infections requiring antibiotics can develop in DUs (73-75). Therefore, in the presence of signs of inflammation (redness, oedema, increased CRP or ESR), a wound swab should be taken and, if necessary, an evaluation for osteomyelitis should be made by direct radiography or advanced radiological methods. Antibiotic therapy should be initiated in the presence of infection or necrosis (72). Antibiotic selection should be made empirically, taking into account common factors, and should be reviewed based on culture, antibiogram, or clinical response. The most common agents are staphylococcus aureus, intestinal bacteria (*Escherichia coli, Enterococcus faecalis*) and pseudomonas aeruginosa (74-75). Empirical therapy can be initiated with macrolides or amoxicillin-beta-lactamase inhibitors in combination with fluoroquinolones (74).

Wound care and local treatment

In DUs associated with SSc, local treatment procedures should follow a similar standard of care for the management of wounds of other aetiologies (76-77).

The "TIME" procedure provides a standard wound care strategy for the treatment of ulcers unrelated to aetiology (76). Tissue management (T) is the first step involving the removal of dead and necrotic tissue by physical or chemical methods. The second step is the examination for ulcer healing and the presence of infection and inflammation (I). Depending on the ulcer condition, adequate moisture (M) should be provided with wet or dry dressings. Hydrocolloid membranes, polyurethane foam or occlusive dressing can stabilise the moistening and help to reduce the number of active DUs, length of hospital stays, the need for amputation and improve quality of life (78-80). These dressings can be used as an appropriate adjunct to medical treatment. The final step in wound bed preparation includes assessment of the ulcer margin and control by excisional or selective debridement. Hyaluronic acid-based products should be avoided in patients with SSc because of the rapid inflammatory response observed in most patients, resulting in worsening of skin ulcers (77, 81).

Structured training about wound care can improve physicians' skills related to management of DUs (82).

There are no RCTs on wound care in patients with DUs associated with SSc. In our opinion, each patient with DU should be evaluated individually. In this respect, careful monitoring of wound healing is mandatory in every patient.

Pain control

Appropriate doses of NSAIDs and tramadol may be tried first as systemic therapy. In the absence of a response to these treatments, patients may benefit from the pain reduction and prolonged sleep duration effects of oxycodone 20-40 mg/day (83).

Topical application of vitamin E gel has been shown to reduce pain more rapidly and shorten recovery time (84). Hydrocolloid membrane has also been shown to reduce pain rapidly and can be considered as a local treatment option for DU-related pain control (78).

Lidocaine may be considered for pain control before an intervention such as debridement. (71). In addition, ready-to-use lidocaine + prilocaine combination preparations can be used in patients with tolerable pain. Local and, if necessary, oral morphine may be another option for patients who do not respond adequately to these treatments (83).

Discussion

The scarcity of available treatment algorithms clearly leads to variations in SSc-DUs management in daily practice. These recommendations aim to provide detailed and up-to-date definitions and recommendations based on literature review and expert opinion.

Despite the lack of data in the current literature, we emphasised patient

education in non-pharmacological recommendations, which is accepted by all task force members. Although the evidence for smoking cessation was mostly based on observational studies, it was included again with majority agreement.

The pharmacological treatment of DUs was divided into two parts, active DU recovery and prevention of DUs. The health policies of the country and the access of physicians to therapeutic agents were taken into account in ordering the treatments. At the same time, the ease of administration of drugs was also effective in the preference order of treatments.

Due to the lack of studies specific to DUs wound care, we made general wound care recommendations. With a similar approach, general principles on the use of antibiotics and advanced wound treatments were also included in the recommendations.

These recommendations are the only evidence-based recommendations specifically developed for digital ulcers, to the best of our knowledge. They were based on evidence published until 2021 and include issues that were not addressed in previous recommendations for the management of SSc including non-pharmacological measures for the prevention of DU, interventional modalities, antibiotic use, wound care, and pain control, as well as definition and classification of scleroderma skin ulcers and DU, the risk and prognostic factors for DUs, drug interactions and clinical conditions such as PH or ILD.

In conclusion, given the heterogeneity of skin lesions in SSc, we believe these recommendations will help clinicians to accurately assess DUs in SSc patients, treat DUs appropriately, prevent new ulcer development, and enable patients to receive better care. Finally, we strongly recommend that patients be followed by a multidisciplinary team, including SSc specialists, in experienced centres.

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