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CLINICAL PRACTICE

Portuguese Recommendations for the management of Raynaud's phenomenon and digital ulcers in systemic sclerosis and other connective tissue diseases

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Objective: To develop evidence-based recommendations for the non-pharmacological and pharmacological management of Raynaud's phenomenon (RP) and digital ulcers (DUs) in patients with systemic sclerosis and other immune-mediated connective tissue diseases (CTDs).

Methods: A task force comprising 21 rheumatologists, 2 surgeons (vascular and plastic), 2 nurses, and 1 patient representative was established. Following a systematic literature review performed to inform the recommendations, statements were formulated and discussed during two meetings (one online and one in-person). Levels of evidence, grades of recommendation (GoR), and level of agreement (LoA) were determined.

Results: Five overarching principles and 13 recommendations were developed. GoR ranged from A to D. The mean ± standard difference (SD) LoA with the overarching principles and recommendations ranged from 7.8±2.1 to 9.8±0.4. Briefly, the management of RP and DUs in patients with CTDs should be coordinated by a multidisciplinary team and based on shared decisions with patients. Nifedipine should be used as first-line therapy for RP and/or DUs. Sildenafil, tadalafil, and/or iloprost IV are second-line options for severe and/or refractory patients with RP and/or DUs. Sildenafil, tadalafil and/or Iloprost IV, should be prescribed for healing and prevention (also including bosentan) of DUs.

In patients with RP and/or DUs, non-pharmacological interventions might be considered as add-ons, but there is limited quality and quantity of scientific evidence supporting their use.

Conclusions: These recommendations will inform rheumatologists, specialist nurses, other healthcare professionals, and patients about a comprehensive and personalized management of RP and DUs. A research agenda was developed to address unmet needs, particularly for non-pharmacologic interventions.

Keywords: Raynaud Phenomenon; Scleroderma and related disorders; Quality of health care; Attitude of health professionals; Patient attitude to health.

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INTRODUCTION

Raynaud's phenomenon (RP) and digital ulcers (DUs) are the most common vascular manifestations of connective tissue diseases (CTDs)[1]. RP occurs in virtually all patients with systemic sclerosis (SSc) and is often its earliest clinical manifestation[1,2]. DUs, in particular, affect approximately half of patients and are a major cause of disease-related morbidity in patients with SSc[3].A significant impact on daily life is often observed due to pain and functional impairment. Therefore, prompt recognition and management of both manifestations is required to prevent potentially irreversible damage and improve hand function and patients' quality of life[3].

The daily management of patients with RP and/or DUs in SSc and other CTDs includes both non-pharmacologic and pharmacologic interventions. Over the past decade, several scientific societies have developed recommendations for the treatment of SSc[4–7]. Some were controversial or insufficient in specific organ involvements, potentially due to a lack of evidence on efficacy or safety concerns regarding treatment options. In addition, comparative studies of different interventions essential for clinical practice are scarce, and clinicians need guidance in decision-making[8].

Therefore, the Systemic Rheumatic Diseases Study Group (GEDRESIS) of the Portuguese Society of Rheumatology set to develop recommendations on the pharmacologic and nonpharmacologic treatment of RP and DUs in patients with SSc and other CTDs.

Herein, we report on the GEDRESIS recommendations for the pharmacological and non-pharmacological management of RP and DUs in patients with SSc and other CTDs.

METHODS

Steering committee and task force

We followed the EULAR standard operating procedures for issuing recommendations (10). The steering committee included the convener (AC), co-conveners (TS, CD, VCR), and the methodologist (AS). In addition to the steering committee members, the task force comprised 12 rheumatologists, four research fellows in Rheumatology (EC, ED, DO, FS), two Rheumatology nurses (LB, RDF), one vascular surgeon (IS), one plastic surgeon (BR), and one patient with SSc (ALT). All healthcare professionals in the task force were experienced in managing patients with SSc and other CTDs. The rheumatologists included in the task force are representative of 11 out of the 18 Rheumatology Portuguese centers.

The work was developed in two steps:

Step 1: systematic review of the literature

In March 2021, the first online meeting with all members of the steering committee was performed to define the focus of the task force and the research questions for the systematic literature review (SLR). The SLR was performed by four research fellows (EC, ED, DO, FS) under the supervision of the methodologist (AS) and the steering committee (TS, CD, VCR, AC). The research fellows were selected based on their curriculum vitae and letter of intent after a national call was sent by the Portuguese Society of Rheumatology and the Steering Committee.

Step 2: Formulation of overarching principles and recommendation statements

The results of the SLR[8] and expert opinion formed the basis for the overarching principles and recommendation statements proposed by the steering committee. These were then presented and discussed with the task force members at two consecutive meetings in January 2024 (in-person) and February 2024 (online). In these meetings, 23 and 20 of the 25 task force members participated, respectively.

The discussion with the taskforce led to the amendment of the overarching principles and recommendation statements, following a voting process. Statements achieving at least 75% approval were approved. An agreement of 67% or 50% was required for approval in the second and third rounds, respectively. Notes were taken to capture the content of the discussion and inform the comments accompanying the individual items below. After the two task force meetings, the level of agreement among the task force members was assessed via an anonymized online voting platform, using a 0–10 scale (with 10 meaning full agreement). The mean and standard difference (SD) of the level of agreement, as well as the percentage of task force members with an agreement ≥8, were determined. The level of evidence and strength of recommendations was assessed for each item of the recommendations, according to the Oxford evidence-based medicine categorization[9].

Target audience

The target users of these recommendations include various stakeholders: (1) all healthcare professionals taking care of patients with SSc/CTDs, including rheumatologists and other healthcare professionals (rheumatology nurses, vascular/plastic surgeons, physiatrists, and physical/occupational therapists); (2) patients with SSc/CTDs, to be better informed for optimal shared decision making; and (3) other stakeholders, including patient organizations.

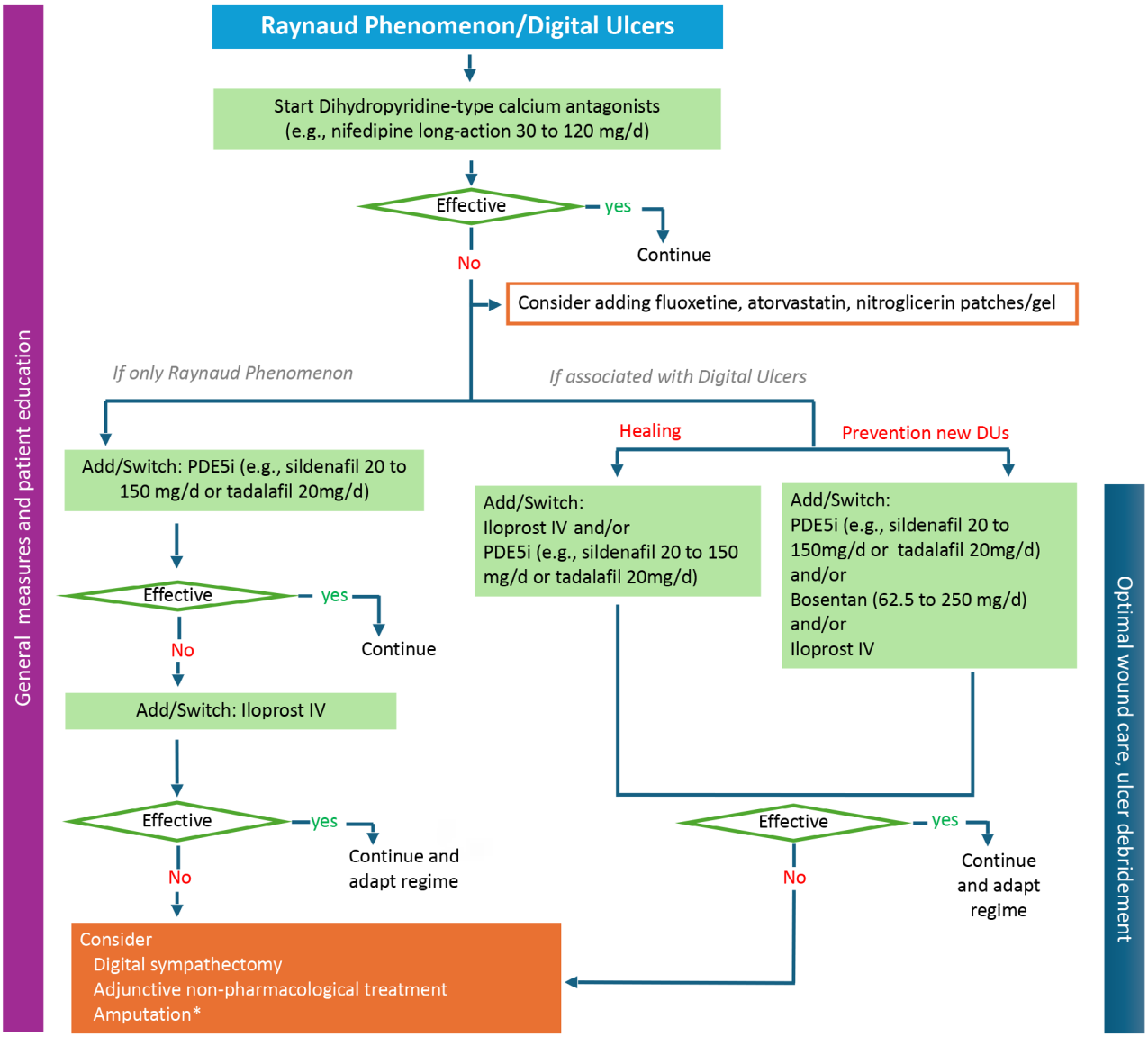
RESULTS

The results of the SLR[8] informing these recommendations are published separately and should be considered as part of this report. Based on the SLR[8] results and expert opinion,5 overarching principles and 13 recommendations for the management of RP and DUs were formulated. Figure 1 depicts the algorithm summarising the recommendations, which requires the explanatory text below.

Overarching principles (A to E)

A-Patient education and general measures, such as cold, trauma and stress eviction, smoking cessation, and skin care, are the cornerstone of the management of RP and DUs in patients with SSc and other CTDs.

Cold exposure and sudden temperature changes can trigger episodes of RP. In a qualitative study, patients with SSc identified cold as the main exacerbating factor for RP[10]. The task force emphasizes that practical



This algorithm should be interpreted in the light of the clarifications provided in the body of the text and by the supporting SLR.
*In the case of irreversible ischemia
d, day; IV, Intravenous; PDE5i, Phosphodiesterase type 5 inhibitor.

Figure 1. Algorithm based on the Portuguese recommendations for the management of Raynaud's phenomenon and digital ulcers in SSc and other CTDs.

advice to people with SSc/CTDs suffering from RP may include the use of gloves and heating devices for the hands and avoidance of direct contact with cold surfaces or substances[11]. A recent RCT corroborated that gloves decrease the burden of RP, but silver fibre gloves yielded no difference versus conventional ones[12].Despite the lack of evidence specifically assessing the efficacy of smoking cessation strategies, it was unanimous among the task force members that smoking cessation should be encouraged and facilitated in smokers with SSc/CTDs[13]. The task force finds relevant to use a generic term that would highlight and encompass, in general, skin care measures, particularly for the hands, to prevent digital fissures and/or ulcers, such as the use of moisturizers and avoiding cutting the nails too short.

B-Rheumatologists should coordinate the care of patients with SSc/CTD-associated RP, and, particularly, DUs, within a multidisciplinary team, including specialist nurses, vascular/plastic surgeons, physical/occupational therapist, and other health professionals.
The task force reinforces that the care of patients with SSc/CTD-associated RP, and, particularly, DUs, should be led by rheumatologists, the specialists in the care of patients with CTDs. A comprehensive, thorough, and multidisciplinary approach is vital for the management of patients with SSc and other CTDs, in particular those with RP and DUs.

C-Early detection and optimal wound care, including debridement, are essential components in the management of DUs within the context of specialized DU clinics.
Recommendations about wound management could not be derived based on current evidence, but the task force highlighted that local wound care and surgical debridement (to be considered in patients with necrotic tissue or underlying calcinosis) were essential components of treating DUs[14]. There is a need for further studies within this area, which is particularly important for patients with SSc.

D-A combination of non-pharmacological and pharmacological interventions should be adopted to treat RP and DUs in patients with SSc and other CTDs.
Non-pharmacological and pharmacological interventions should be provided as combinations of treatments. Non-pharmacological management should not substitute pharmacological treatment when the latter is required, which is often the case.

E-Management of RP and DUs should be conducted on a shared-care basis, involving patients in decision-making.
The task force felt that it was important to underline that non-pharmacological and pharmacological management of RP and DUs associated with SSc/CTDs should be tailored to patients' needs, if possible, within their expectations and preferences and should be based on a shared decision process. Additionally, the task force emphasized the importance of the patients' involvement in their care, as well as individually tailored strategies towards optimized outcomes.

Recommendations

I-Dihydropyridine-type calcium antagonists, namely nifedipine, should be considered as first-line treatment to reduce the frequency and severity of RP.
Five RCTs (4 with nifedipine[15–18] and 1 with nicardipine[19]) demonstrated that dihydropyridine-class calcium antagonists reduce the frequency[15,16,18]and severity[16,18]of RP. One study[17]also demonstrated that nifedipine was associated with a reduction in the duration of RP episodes. Non-dihydropyridine calcium antagonists (i.e., diltiazem) have shown no benefit in RP management[20]. Headaches and nausea were common adverse events (AE) of these drugs, although no serious adverse events were reported. Considering their cost-effectiveness profile and the fact that they have been more extensively studied, the taskforce recommends the use of dihydropyridine-type calcium antagonists, in particular nifedipine long-acting formulations, as first-line treatment for RP. It is noteworthy that there are no studies directly comparing dihydropyridine-type calcium antagonists for RP.

II-Phosphodiesterase-5 inhibitors should be considered to reduce the frequency, severity, and duration of RP in patients refractory and/or intolerant to first-line therapy.
Nine RCTs[21–29](5 with sildenafil[21-23,25,26], 2 with tadalafil[27,28], 1 with vardenafil[24], and 1 with udenafil[29]) evaluating the efficacy and safety of phosphodiesterase-5 inhibitors (PDE5i) in RP, showed that these drugs improve the frequency, severity and duration of RP attacks. Common AE reported with the use of PDE5i were vasomotor reactions/flushing and headaches, which led to drug discontinuation in some patients. In patients refractory and/or intolerant to dihydropyridine-type calcium antagonists, PDE5i should be considered for RP management. Therefore, the task force supported sildenafil as a second-line therapy, as this drug is usually more expensive than calcium antagonists, and the majority of the published studies evaluated sildenafil

(100mg/day). Tadalafil (20mg/day) may be an alternative. No studies comparing different PDE5i met the SLR inclusion criteria.

III-Phosphodiesterase-5 inhibitors should be considered for the healing and prevention of new DUs.
Four studies (3 with sildenafil[21,23,25], 1 with tadalafil[28]) demonstrated that PDE5i can improve DUs healing and reduce the occurrence of new DUs. Therefore, the taskforce recommends the use of PDE5i, in particular sildenafil, for both healing of existing DUs and prevention of new ones. Importantly, in a patient with DUs who has not previously received first-line therapy for RP, the task force suggested that a dihydropyridine-class calcium antagonists (nifedipine) should be started, usually in combination with PDE5i.

IV-Intravenous (IV) prostacyclin analogues, namely iloprost, can be considered for reducing the frequency and severity of RP, in patients refractory and/or intolerant to first-line therapy.
IV prostacyclin analogues, namely iloprost, can be considered for the healing of DUs.
Eight RCTs[30–37] demonstrated that IV iloprost reduces the frequency and severity of RP. One RCT[34] showed that there was no significant difference between low dose (0.5 ng/kg/min) and high dose (2 ng/kg/min) IV iloprost. Two RCTs[30,31] demonstrated that IV iloprost was effective in healing DUs in patients with SSc and reduced the number of DUs. The most frequently reported AEs were headache and nausea, which tend to be mild to moderate. Reducing the infusion rate could improve symptoms[38].

For patients with RP who have failed or are not tolerant to previously mentioned oral therapies (dihydropyridine-type calcium antagonists and PDE5i), the taskforce recommends the use of IV iloprost.

For DUs healing, sildenafil and IV iloprost can be equally used. The choice between the two must take into consideration the patient's profile or/and hospital constraints. IV iloprost had no proved benefit in preventing new DUs. Considering the heterogeneity of protocols regarding IV iloprost administration, the taskforce decided not to make any specific recommendation on this topic.

However, based on expert experience, preference should be given to administration of IV iloprost in an outpatient setting, as long as tolerance to the drug and easy access to a health service in case of AEs are ensured. The latter approach is used for administering IV iloprost in most Portuguese Rheumatology centers[39]. The regime and regularity of administration of this treatment is not homogeneous across national Rheumatology centers. Iloprost infusion through elastomeric pump in an outpatient setting can be an alternative to inpatient intravenous iloprost infusions.[39]

V-Oral prostacyclin analogues and prostacyclin receptor agonists* are not recommended for the treatment of RP and DUs.
*** Only for RP; no data on DUs.**
Oral prostacyclin analogues showed no benefit in the treatment of RP and DUs[30,31,40].Therefore, their use is not recommended.
Prostacyclin receptor agonist (selexipag) also demonstrated no benefit in RP treatment[41] and the taskforce considers it an inappropriate alternative in the treatment of RP.

VI- The endothelin receptor antagonist (ERA) bosentan should be considered for the prevention of new DUs. Endothelin receptor antagonists are not recommended for the treatment of RP or the healing of DUs.
Two RCTs[42,43]have shown that bosentan can reduce the number of new DUs, although it had no effect on DU healing. On the other hand, macitentan showed no benefit in the prevention of new DUs[44]. Bosentan did not show any benefit in reducing the frequency, severity, or duration of RP[45].

The major concerns related to the use of bosentan and other ERA include potential liver injury and teratogenicity. Headache was also reported as a frequent AE.

The taskforce recommends the use of bosentan for the prevention of new DUs, particularly in patients who have multiple DUs despite treatment with other vasodilators, including oral dihydropyridine-type calcium antagonists, PDE5i, and IV iloprost. There aren´t head-to-head comparative studies between PDE5i and bosentan. Therefore, the task force suggests that the decision should be based on costs, time to hospital authorization, and patient comorbidities such as acute heart failure and hepatic disease, among others. Special attention should be given to liver enzyme monitoring in patients treated with ERA, as well as the use of contraceptive measures. Bosentan should not be used to treat RP.

VII-Nitroglycerin patches can be considered for reducing the frequency and severity of RP attacks and management of DUs.
One RTC[46] demonstrated that nitroglycerin patches reduce the frequency and severity of RP. Headache was the most frequent AE.

Despite the paucity of available evidence (only one study on this drug formulation[46]), several members of the taskforce use this therapy in their daily clinical practice for RP management and in the initial approach of

DUs. This collective experience is mostly as an add-on therapy to oral/IV vasodilators. Therefore, the taskforce recommends their use, mostly as an add-on treatment.

The same applies to nitroglycerin gel, which is also used as an alternative for some members of the taskforce, although no evidence was found for its use in the SLR.

VIII-Angiotensin-converting-enzyme inhibitors and angiotensin receptor blockers are not recommended for the treatment of RP and DUs.

Angiotensin-converting-enzyme inhibitors, namely quinapril, and angiotensin receptor blockers, namely losartan, showed no benefit in RP outcomes, according to two RCTs[47,48].

Therefore, the taskforce does not recommend their use in either RP or DUs.

IX-Statins, namely atorvastatin, can be considered as a complement to standard vasodilator treatment for RP and DUs.

According to twoRCTs[49,50], the addition of atorvastatin (40mg/day) to standard vasodilator therapy can reduce RP severity. Additionally, one of these studies[49] reported a significant reduction in the number, severity, and pain associated with DUs with atorvastatin. No significant AEs were reported.

X- Selective serotonin reuptake inhibitors, namely fluoxetine, can be considered as a complement to standard vasodilator treatment for RP.

One small RCT[51] demonstrated that fluoxetine (20mg/day) was more effective than nifedipine in reducing the severity and comparable in reducing the frequency of RP attacks.

The taskforce recommends the use of fluoxetine for the treatment of RP in patients with low blood pressure who cannot tolerate vasodilators or in patients who require antidepressant therapy.

XI-Local oxygen-ozone therapy can be considered as an add-on therapy for the treatment of refractory DUs.

A single RCT with low risk of bias (RoB) indicated that local oxygen-ozone therapy improved the RP outcome measures as an add-on therapy[58].The experts recognize that local oxygen-ozone therapy may be part of the management of DUs in SSc.

The task force felt that it was important to underline that none of the experts had experience with local oxygen-ozone therapy.

XII-Periarterial sympathectomy with or without concomitant vascular bypass can be considered for the treatment of refractory DUs in selected patients.

Evidence of periarterial sympathectomy derives from two retrospective cohort studies that were at critical RoB[52,53]. Based on this evidence and expert opinion within the task force, periarterial sympathectomy should be considered only for refractory DUs in selected patients (i.e., patients with DUs with contraindication or inefficacy of previous pharmacological treatment). The task force emphasized the importance of weighing risks and benefits, as this intervention may have significant AEs, including reflex sweating and infections. This item had the lowest level of agreement among the task force members (i.e., agreement ≥8 of 73.9%).

XIII - Other non-pharmacological interventions might be considered as add-on treatments to improve RP and DU in selected patients.

Based on the limited or lack of evidence found in the SLR[8], the task force deems it crucial to explore research avenues beyond pharmacological interventions. These include laser therapy, physiotherapy, bone marrow mononuclear cell implantation, and hyperbaric chamber treatments. During the taskforce meeting, one of the members (IV) shared limited experience with hyperbaric chamber treatments in patients with CTD-associated DUs, which may be considered as a last resort to be offered to the patient.

Regarding other treatments, namely botulinum toxin injections[54,55] and prazosin[56,57] for RP, as well as regional grafting of autologous adipose tissue[58]and vitamin E gel[59] for DUs, the task force opted not to provide specific recommendations due to the lack or absence of experience in clinical practice.

Lastly, the task force considered that evidence and expert experience do not favour the use of ischemic preconditioning for the management of CTD-associated RP or DUs.

Research agenda

Table II presents the research agenda proposed by the task force based on areas with only weak or limited evidence.

DISCUSSION

These are the first Portuguese Recommendations on the management of RP and DUs associated with SSc/CTDs. A multidisciplinary task force convened and formulated the overarching principles and recommendations presented herein following the EULAR standardized operating procedures[60].These were based on an associatedSLR[8]and multidisciplinary expert opinion.

These recommendations intend not only to guide

TABLE I. OVERARCHING PRINCIPLES AND RECOMMENDATIONS FOR THE MANAGEMENT OF RAYNAUD'S PHENOMENON AND DIGITAL ULCERS IN CONNECTIVE TISSUE DISEASES

Overarching principles (A to E)	LoE	GoR	LoA (% LoA≥8)
A - Patient education and general measures, such as cold, trauma, and stress eviction, smoking cessation, and skin care, are the cornerstone of the management of RP and DUs and digital ulcers in patients with SSc and other CTDs.	n.a	n.a	9.61±0.50 (100%)
B - Rheumatologists should coordinate the care of patients with SSc/CTD-associated RP, and, particularly, digital ulcers, within a multidisciplinary team, including specialist nurses, vascular/plastic surgeons, physical/occupational therapists, and other health professionals.	n.a	n.a	9.74±0.54 (100%)
C - Early detection and optimal wound care, including debridement, are essential components in the management of DUs within the context of specialized DU clinics.	n.a	n.a	9.43±1.20 (91%)
D - A combination of non-pharmacological and pharmacological interventions should be adopted to treat RP and DUs in patients with SSc and other CTDs.	n.a	n.a	9.83±0.49 (100%)
E - Management of RP and DUs should be conducted on a shared-care basis, involving patients in decision-making.	n.a	n.a	9.78±0.52 (100%)
Recommendations (I to XIII)			
I - Dihydropyridine-type calcium antagonists, namely nifedipine, should be considered as first-line treatment to reduce the frequency and severity of RP.	LoE 1a	A	9.83±0.39 (100%)
II - PDE5i should be considered to reduce the frequency, severity, and duration of RP in patients refractory and/or intolerant to first-line therapy.	LoE 1a	A	9.70±0.47 (100%)
III - PDE5i should be considered for the healing and prevention of new DUs.	LoE 1a	A	9.65±0.71 (96%)
IV-IVa - prostacyclin analogues, namely iloprost, can be considered for reducing the frequency and severity of RP in patients refractory and/or intolerant to first-line therapy. IVb - prostacyclin analogues, namely iloprost, can be considered for the healing of DUs.	LoE 1a	A	9.48±1.16 (100%)
V - Oral prostacyclins analogues and prostacyclin receptor agonists* are not recommended for the treatment of RP and DUs. * Only for RP; no data on DUs.	LoE 1a	A	9.39±0.94 (91%)
VI - The ERA bosentan should be considered for the prevention of new DUs. ERA are not recommended for the treatment of RP or healing of DUs.	LoE 1b	B	9.65±0.71 (96%)
VII - Nitroglycerin patches can be considered for reducing the frequency and severity of RP and management of DUs.	LoE 2b	C	8.65±.1.77 (83%)
VIII - Angiotensin-converting-enzyme inhibitors and angiotensin receptor blockers are not recommended for the treatment of RP and DUs.	LoE 1b	B	9.43±0.73 (100%)
IX - Statins, namely atorvastatin, can be considered as a complement to standard vasodilator treatment for RP and DUs.	LoE 1b	C	8.96±1.15 (91%)
X - Selective serotonin reuptake inhibitors, namely fluoxetine, can be considered as a complement to standard vasodilator treatment for RP.	LoE 2b	C	8.39±1.90 (78%)
XI - Local oxygen-ozone therapy can be considered as an add-on therapy for the treatment of refractory DUs.	LoE 1b	B	8.48±1.70 (83%)
XII - Periarterial sympathectomy with or without concomitant vascular bypass can be considered for the treatment of refractory DUs in selected patients.	LoE 4	D	7.83±2.08 (74%)
XIII - Other non-pharmacological interventions might be considered as add-on treatments to improve RP and DUs in selected patients.	LoE 4	D	9.00±1.41 (87%)

Legend: RP – Raynaud phenomenon; DU – digital ulcer; SSc – systemic sclerosis; CTD – connective tissue disease; PDE5i - phosphodiesterase-5 inhibitors; IV – intravenous; ERA – endothelin receptor antagonist
These recommendations should be interpreted in the light of the clarifications provided in the body of the text and by the supporting SLR. *Numbers in column 'LoA' indicate the mean and SD (in parentheses) of the LoA, as well as the percentage of task force members with an agreement ≥8. GoR, grade of recommendation; LoA, level of agreement; LoE, level of evidence; n.a, not applicable.

TABLE II - RESEARCH AGENDA.

Understanding the efficacy and safety of prophylactic treatment with iloprost in the management/prevention of DUs
Understanding the efficacy and safety of combination therapies management and prevention of DUs
Establishing a standardized protocol for the administration of intravenous iloprost
Understanding the efficacy and safety of non-pharmacological interventions in RP and DUs for which evidence is still scarce
Need for innovative and high-quality trials and designs that can provide insights into the effect of tailored interventions.

Legend: DU – digital ulcer; RP - Raynaud phenomenon

the non-pharmacological and pharmacological management of RP and DUs but also to increase awareness of the importance of interprofessional and multidisciplinary teams in managing these conditions.

Regarding pharmacological treatment, 59 studies were identified (58 RCTs and one CCT). Fifty-one were placebo-controlled trials, six were head-to-head trials and two compared the same intervention at a different posology. Most RTCs (31) had an unclear RoB, and 7 had a high RoB.

Based on the published evidence, the taskforce recommends the use of dihydropyridine-type calcium antagonists, namely nifedipine, as a first-line option for the treatment of RP, with PDE5iand intravenous prostacyclin analogues being considered for patients refractory and/or intolerant to first-line therapy. PDE5iand intravenous prostacyclin analogues should be considered for DU healing, while PDE5i and endothelin receptor antagonist bosentan are recommended for the prevention of new DUs. Nitroglycerin patches can also be considered for the management of RP and, in the initial approach to DUs, as an add-on treatment. The drugs proposed in these recommendations regarding RF/DU have known risks and may interfere or aggravate other manifestations of the CTDs or other underlying conditions. Therefore, adequate knowledge and experience is warranted before its use. Also, prescription of these drugs should be managed by rheumatologists with expertise in the management of SSc and other CTDs and tailored to the individual patient, according to disease manifestations and patient comorbidities. Special attention should be given to cardiac, pulmonary, and gastrointestinal involvement, liver/renal function, and presence and characterisation of pulmonary hypertension.

Regarding the published evidence of non-pharmacological treatments, 12 studies (including four RCTs, three retrospective cohorts, three prospective cohorts, and two CCTs) were identified. The studies had heterogeneity in study design, content of interventions, and outcome measures. The four RCTs had high[61–63] or unclear RoB[12]. Therefore, evidence remains limited in quantity and quality concerning non-pharmacological interventions. Recently, an EULAR task force[64] formulated recommendations for the non-pharmacological management of people living with SSc, emphasizing that their implementation can help manage pain, reduce fatigue, improve mobility, and function, and address the psychological impact of living with a chronic illness.

Based on the results of the SLR[8], the task force was of the opinion that formulation of evidence-based recommendations for physiotherapy, and skin and wound care for patients with SSc and other CTDs was not possible at this time.

We hope that these recommendations will inspire and be widely adopted by rheumatologists and healthcare professionals taking care of patients with CTDs. This is a landmark step forward in the much-needed progress in the better care of RP and/or DUs associated with CTDs. Implementation into clinical practice can be facilitated by the dissemination of the recommendations using online media, by presentations in national and international events, development of workshops or educational lectures in meetings of different specialties involved in RP and/or DUs management. We believe that the implementation of these recommendations will ultimately improve clinical practice and patients' quality of life. Also, efforts should be applied to educating healthcare professionals and patients alike on the potential and importance of different non-pharmacological strategies. The rarity of SSc calls for global collaborative efforts in the design of studies, especially investigator-initiated efforts that warrant better funding. Efforts should be applied to reinforce patient needs and priorities and identify barriers and means for overcoming them.

In summary, we have developed 13 recommendations on various aspects of the pharmacological and non-pharmacological management of patients with RPand/or DUs associated with CTDs. They were based on the best available evidence along with hands-on expertise. We will carefully follow developments and implementation, expecting that an update of these recommendations may be needed within a few years.

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