

Digital ulcer management in patients with systemic sclerosis

R Gualtierotti^{1*}, G Adorni¹, C Lubatti¹, S Zeni¹, PL Meroni¹, F Ingegnoli¹

Abstract

Introduction

Digital ulcers (DUs) are a major clinical problem for patients with systemic sclerosis (SSc). Almost half of SSc patients experience at least one acral DU during the course of the disease. Patients with DUs may suffer from severe pain and often undergo a limitation of daily life activities, thus resulting in a functional impairment with a significant impact on the patient's health-related quality of life. Prevention of further complications and lesions is possible if the initial evaluation is performed early and correctly and if a treatment is started promptly. Pharmacologic treatment is important, but it is not the only possible approach to patients with DUs. This review provides an overview of the available different treatment options for DUs together with a proposal of a diagnostic-therapeutic approach aimed at a better definition and treatment of patients with SSc and DUs.

Discussion

A correct approach to the patient with DUs begins with a careful examination and evaluation of risk factors and comorbidities in order to cure and prevent complications and further lesions. Then also a correct local treatment of the DU provides a better milieu to foster healing and prevent complications such as infection or gangrene. Different drugs with different mechanisms of action are to date available for the treatment and prevention of DUs in SSc, but it will be swiftly effective only if in combination with good information of the patient and a thorough local treatment of the ulcers.

*Corresponding author

Email: roberta.gualtierotti@unimi.it

¹ Division of Rheumatology, Gaetano Pini Hospital, Department of Clinical Sciences & Community Health, University of the Studies of Milan

Conclusion

A correct therapeutic approach can be based only on a correct education and information of the patient.

Introduction

Digital ulcers (DUs) are a major clinical problem for patients with limited or diffuse systemic sclerosis (SSc) and a recurrent challenge for rheumatologists. About half of patients with SSc experience at least one acral DU during the course of the disease¹. Patients with DUs may suffer from severe pain and often undergo a limitation of daily life activities, thus resulting in a functional impairment with a significant impact on the patient's health-related quality of life (HRQoL)². The aim of this review is to provide the reader with an overview of the currently available approaches for the management of DUs in SSc and to propose a step-by-step diagnostic and therapeutic flow-chart, based on up-to-date evidence and the personal experience of our team.

Characteristics and terminology

Pure DUs are usually punctiform, very painful, they develop mainly in the fingers or toes, usually on the tips, but they may also involve skin creases, over the proximal interphalangeal (PIP) joints³.

The definition of DU has been a problem for a long time, until a very recent consensus approach has attempted to find a more precise classification³ for use in observational studies or randomized clinical trials (RCTs). Based on this classification, a DU is a lesion with loss of continuity of epithelial coverage, which can be denuded, with discernible and measurable depth or covered by a scab or crust (i.e. a hardened covering of dried secretions such as blood, plasma or pus) or necrotic tissue (i.e. a black or dark brown remnant of

normal tissue that has become necrotic because of the ischemia of that area)³. Following this classification, only DUs at or distal to PIP joints and without bone infection or calcinosis are to be assessed. DUs do not include fissures, paronychia, extrusion of calcium, ulcers over calcium nor ulcers over the metacarpophalangeal joints or elbows³. DUs at or distal to PIP joints may be traumatic and the actual contribution of SSc vasculopathy is still to be determined, thus it is up to the designers of the trials to decide whether to include these DUs in the trial or not³.

Active ulcers are those in which denudation is clearly visible at any part of the base and de-epithelialization can be observed. Indeterminate ulcers are those in which the examiner is not able to evaluate the presence of a de-epithelialized base. Healed ulcers are those with a complete re-epithelialization, also in the form of an atrophic hypopigmented area.

Possible complications of DUs are infections, osteomyelitis, gangrene or amputation as shown in figure 1. Gangrene occurs more frequently in diffuse SSc, possibly related to a major vascular involvement⁴. Gangrenous lesions at the fingertip that may be dry,



Figure 1: Multiple digital ulcers of the fingers with associated gangrene and bone exposure leading to auto-amputation.

Competing interests: None declared. Conflict of interests: None declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

Licensee OAPL (UK) 2014. Creative Commons Attribution License (CC-BY)

FOR CITATION PURPOSES: Gualtierotti R, Adorni G, Lubatti C, Zeni S, Meroni PL, Ingegnoli F. Digital ulcer management in patients with systemic sclerosis. *OA Arthritis* 2014 Jan 18;2(1):2.

shrunken and dark or black should not be considered DUs. Even when the lesions do not meet yet the definition of gangrene, but encircle the fingertip (excluding the nail), they should not be considered as DUs in a trial, because the healing of these lesions may be very complicated and perhaps unlikely until the digital tip auto-amputates, thus introducing an unwanted bias (Figure 2).

Etiopathogenesis

DUs are a manifestation of the underlying vasculopathy and fibrosis that characterize SSc. They are almost always associated with Raynaud's phenomenon (RP), a vasospasm in response to cold or emotion resulting in impaired oxygenation of the distal extremities (Figure 3)². The underlying pathogenetic mechanisms of DUs in SSc are multiple, such as microtrauma, sclerodactyly and dry skin, but the vasculopathy that characterizes SSc is believed to play a pivotal role. Although the triggering factors are still unknown², the initial endothelial injury is accompanied by an increase in the levels of endothelin-1 (ET-1), a peptide with vasoconstrictor effects mediated by endothelin type A (ETA) receptors present on vascular smooth-muscle cells (SMCs) causing vasoconstriction and vascular remodelling effects, and by means of endothelin type B (ETB) receptors, present on endothelial cells and SMCs with vasodilating effects^{2,5}. Alternatively, endothelial cells may be injured by the presence of endothelial cell antibodies, which would imply platelet activation with release of thromboxane and eventually intraluminal thrombosis⁵. The subsequent migration of SMCs into the intimal layer of the microvasculature and differentiation into myofibroblasts producing collagen and other extracellular matrix are responsible for the intimal proliferation with fibrosis, thus leading to a fixed narrowing of the intravascular lumen and causing chronic tissue ischemia^{2,5,6}.



Figure 2: Multiple digital ulcers of the fingers (arrows) and a fissure (star).

Discussion

The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies.

Evaluation

As shown in figure 1, the evaluation of a patient with DUs should start from the patient's history, which should be aimed at finding risk factors which may favour the development of DUs such as thrombophilia, dislipidemia, hyperchortisolism, dehydration, traumas, neoplasias, autoimmune pathology, smoke, drugs that may favour vasoconstriction. Physical examination should evaluate localization, depth, boundaries, presence of fibrin, debris, granulation

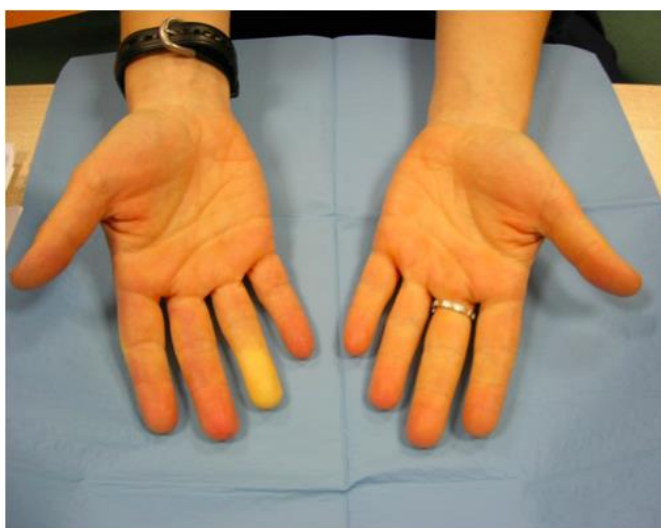


Figure 3: Raynaud's phenomenon: ischemic phase of one digit (middle finger).

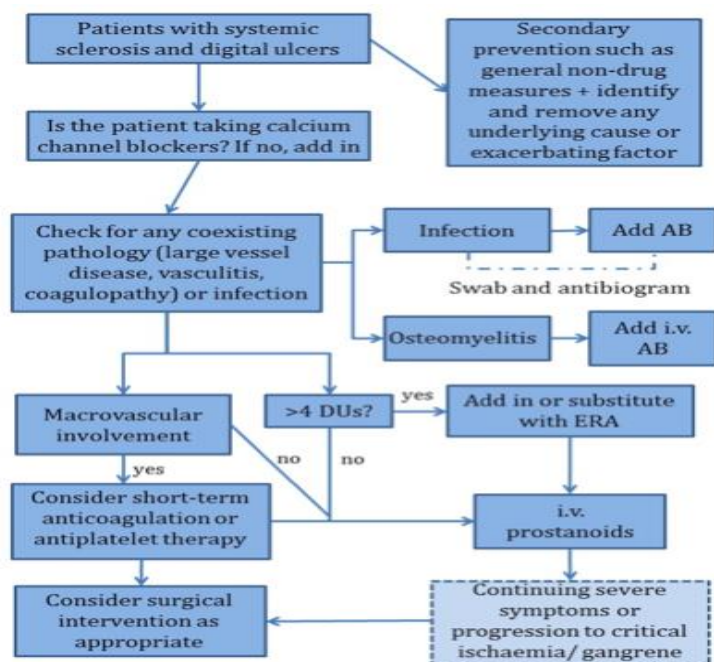


Figure 4: The flow-chart shows the proposed approach to digital ulcers in systemic sclerosis (AB: antibiotic therapy, DU: digital ulcer; ERA: endothelin receptor antagonist; i.v.: intravenous).

tissue, calcinosis, necrosis, gangrene, pus, blood on the de-epithelialized basis. The presence of pus and severe pain is invariably associated with infection. Also severe pain is significantly associated with infection⁴. When associated to gangrene, concomitant DUs may be very deep and accompanied by perilesional oedema, inflammation and presenting, not rarely, with bone and tendon exposure (Figure 1).

Therapeutic approach

The treatment of DUs must parallel the treatment of RP with or without ischaemic complications. A possible approach to treat patients with DUs and/or RP is shown in figure 4. It is pivotal to have a good skin care in order to promote healing, basing the choice of the dressings depending on the presence or absence of infection and other factors (Table 1). To foster DU healing, surgical debridement is often required. The presence of fibrin, oedema or inflammation, necrosis, eschars or gangrene delays significantly the time to healing^{7,8}. Ischaemia involving the whole distal phalanx needs hospitalizations for aggressive treatment^{9,10,11}.

Clinicians should start helping patients in managing pain, which has considerable impact on HRQoL¹² and further triggers vasoconstriction⁵. Secondary prevention, i.e. prevention of further lesions, by minimizing the occurrence of minor trauma as well as prevention of complications is very important. It is important to restore hand function, improve digital circulation, prevent infection and promote healing.

Whenever a macrovascular disease underlying or contributing to the ischaemic digital process is suspected, an ultrasonographic Doppler study of the vessels or an angiography should be performed¹³.

Primary prevention and lifestyle changes

Avoidance of cold temperatures by means of proper garments and gloves, hats, heavy socks, should be sought not only during cold seasons, but in all the cases required by a cold external temperature (e.g. refrigerators in a supermarket; cold temperature in hot seasons due to sudden weather changes, etc.). Stress is another trigger for vasospasm in RP. Although there are not enough data to support the

use of techniques such as conditioning, biofeedback and relaxation techniques in SSc patients¹⁴, the high prevalence of anxiety and depression in these patients requires careful examination of the psychologic conditions of the patients with SSc and, if necessary, the use of anti-depressants or anxiolytics. Patients should also be taught to use topical hydrating creams in order to maintain skin moist.

Whenever possible, trauma to the digits should be avoided, such as working in a cold environment (e.g. fridge aisle, etc) or repetitive hand working (e.g. typing). Smoking should be avoided even if there is a lack of univocal data regarding its pathogenic role in Raynaud's triggering.

Supportive care and local treatment

Pain control should not be overlooked by physicians, not only for improvement of their HRQoL, but also in order to avoid further vasospasm generated by the adreno-receptors that may worsen the ischemic condition⁵. Pain management should be started quickly and adjusted on the patient needs. Acetaminophen and opiates should be preferred⁵. If infection is suspected, a specific antibiotic should be started, based on antibiogram. If osteomyelitis is suspected, prompt treatment with i.v. antibiotics should be started.

Semi-occlusive wound dressings prevent evaporative water loss and retain warmth, which improves wound healing¹⁵. Table 1 shows the most commonly used wound dressings and their different indications. Antiseptics should be avoided because of the known cytotoxic effects on cells and local antibiotics may induce the emergence of resistance to the entire class of antibiotics used topically. Ulcers must be cleaned with physiologic water. The use of systemic antibiotics should be reserved only for clinically infected ulcers and not for bacterial colonization¹⁵. Debridement is important because the removal of necrotic tissue and sloughs have been demonstrated to be effective in accelerating wound healing¹⁵.

Table 1: Wound care dressings and their main indications.

Type of dressing	Healing stage
Hydrocolloids	Mildly exuding ulcer
Alginates	Debridement
Hydrogels	Necrotic ulcer, dry ulcer
Hydrofibers	Infected ulcer, heavily exuding ulcer (debridement stage)
Impregnated or coated meshes	Mildly exuding ulcers, alters peripheral wound skin
Foam dressings	Heavily exuding ulcers, granulating ulcers, altered peripheral wound skin
Hyaluronic acid-based dressings	Mildly exuding ulcer
Charcoal dressings	Foul-smelling ulcer
Silver-coated dressings	Infected ulcer, foul-smelling ulcer
Protease-modulating dressings	Hard-to-heal ulcer

Debridement can be mechanical via curette or scalpel, or chemical, via enzyme-debriding agents such as collagenase, papain, trypsin. D-alpha-tocopheryl acetate (acetic ester of alpha-tocopherol) gel on DUs of SSc patients treated twice a week was shown to induce a faster healing of DUs, with a faster resolution of pain and a lower cost of medications in respect to controls with a lower number of medications¹⁶.

Pharmacological therapy

Despite the substantial impact that SSc-DUs have on function and HRQoL, currently there is no widely accepted therapeutic algorithm.

Prostacyclin analogues

In Europe, cyclic use of i.v. iloprost is the standard of care for the treatment of ischemically threatened digits and severe SSc DUs. The most robust study supporting the use of iloprost is a multicenter trial in patients with SSc and RP¹⁷. After three weeks, 14.6% more patients receiving i.v. 6-hour infusion of iloprost (dose 0.5-2 ng/kg/minute) for five days had 50% or more lesions healed compared with those given placebo. A trend was also observed towards prevention or reduction of the formation of new DUs (25% of the patients had new lesions after iloprost compared with 33% of the patients receiving placebo). A Cochrane review also concluded that i.v. iloprost is effective in the treatment of RP secondary to SSc at decreasing the frequency and severity of the attacks and in preventing or healing DUs. The effect seems to be prolonged after the intravenous

infusion is given. Oral prostanoids may have minimal or no efficacy for the treatment of RP secondary to SSc¹⁸. Other prostacyclin analogues such as epoprostenol and beraprost demonstrated no efficacy in DU healing, although trends towards a decrease in the number of new DUs were observed with both drugs^{19,20}. By contrast, subcutaneous treprostinil showed efficacy in both healing and preventing DUs, but its use is limited by the acute injection site pain²¹. An ongoing phase II double blinded multicenter RCT of oral treprostinil in SSc DUs is currently recruiting.

Calcium channel blockers (CCBs)

CCBs act on vascular SMCs to cause arterial vasodilation. A small RCT compared oral nifedipine at 30 to 60 mg dosage, with i.v. iloprost in patients with SSc and RP, who were severely affected by skin lesions (ulcers, fissures or paronychia), demonstrating a decrease in the mean number of digital lesions. The limitations of this study are the small number of patients, the lack of clear baseline number of DUs per patient and the use of different skin lesions apart from ulcers as outcome measure²².

Endothelin receptor antagonists (ERAs)

Bosentan was initially developed for pulmonary hypertension and was found to be useful in the prevention of the onset of new lesions in SSc patients who had already experienced DUs but seems to have no effect in healing of the existing ulcers^{23,24}. The RAPIDS-2 study confirmed bosentan

effects on prevention of new DUs in SSc patients, particularly in those with multiple DUs (at least four as suggested by the Authors) not receiving i.v. prostacyclin analogues or phosphodiesterase-5 (PDE-5) inhibitors in the previous three months, but also confirmed the absence of efficacy in the healing of pre-existing DUs²⁵. Therefore, the use of bosentan is indicated as secondary prevention in those patients presenting with multiple DUs. The incidence of liver aminotransferase elevation requires tight monitoring of blood tests²⁵.

PDE-5 inhibitors (PDE5I)

PDE5I induce vasodilation by increasing the levels of endogenous nitric oxide (NO). Case reports, case series and a meta-analysis indicate a benefit of sildenafil on SSc-DUs^{24,26,27}. In an open-label study on 19 patients with 49 DUs present at baseline, the number of DUs decreased to 17 after a 6-month therapy with sildenafil, although a total of 9 patients developed 12 new DUs during sildenafil treatment²⁸. The effects of tadalafil on DUs were shown in a study on 25 SSc patients. Although the patients were receiving also other therapies for RP and the healing and prevention of DUs were secondary outcomes, the results were promising: all the 24 digital lesions healed during tadalafil therapy as compared with 3 on 13 during the placebo treatment. One new DU was reported during tadalafil therapy vs 13 during placebo therapy²⁹. Significant adverse events are headache, myalgia, priapism, allergic reactions, chest pain and others²⁴.

Competing interests: None declared. Conflict of interests: None declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

Other drugs

There is a lack of evidence for the efficacy of other drugs such as N-acetylcysteine, angiotensin converting enzyme inhibitors, angiotensin II receptor blocking agents, nitrates and statins. A Cochrane review of prazosin demonstrated efficacy versus placebo, but the efficacy is modest and side effects limit its use. While there is no evidence that aspirin may accelerate DU healing, beneficial effects of low molecular weight heparin were observed in severe RP patients³⁰.

The role of the surgeon for DUs

A surgical consult may be necessary in the case of failure of the medical approaches and thus it is a pivotal intervention not only in the case of macrovascular disease. To foster DU healing, surgical debridement may be required. As shown in figure 1, a surgical opinion should be sought whenever a macrovascular involvement is suspected and, if necessary, also arteriography could be performed, both with diagnostic and therapeutic aims. For patients who do not respond to the above mentioned interventions, a surgical approach in order to inhibit vasoconstriction and to improve blood flow to the fingertips (sympathectomy) should be considered.

Conclusion

Management of DUs in SSc must be based on a complex approach which comprehends the treatment of blood flow reduction, vasculopathy, possible thrombosis of the vessels involved, antibiotic therapy if necessary and local treatment of DUs. Prevention should not be left behind: patients should be taught to refer to their rheumatologist as soon as signs or symptoms of critical digital ischemia present, as well as in case of DU appearance and to lifestyle and hygienic rules that patients should follow even in the case of a mute history for digital ischemia or DUs. A correct therapeutic approach can be based only on a correct education and information of the patient.

References

1. Ferri C, Valentini G, Cozzi F, Sebastiani M, Michelassi C, La Montagna G et al. Systemic sclerosis: demographic, clinical, and serologic features and survival in 1,012 Italian patients. *Medicine (Baltimore)*. 2002;81:139-53.
2. Steen V, Denton CP, Pope JE and Matsuura-Cerinic M. Digital ulcers: overt vascular disease in systemic sclerosis. *Rheumatology (Oxford)*. 2009;48 Suppl 3:iii19-24.
3. Baron M, Chung L, Gyger G, Hummers L, Khanna D, Mayes MD et al. Consensus opinion of a North American Working Group regarding the classification of digital ulcers in systemic sclerosis. *ClinRheumatol*. 2014;33:207-14.
4. Amanzi L, Braschi F, Fiori G, Galluccio F, Miniati I, Guiducci S et al. Digital ulcers in scleroderma: staging, characteristics and sub-setting through observation of 1614 digital lesions. *Rheumatology (Oxford)*. 2010;49:1374-82.
5. Schioppa E, Impens AJ and Phillips K. Digital ischemia in scleroderma spectrum of diseases. *Int J Rheumatol*. 2010;2010.
6. Rodnan GP, Myerowitz RL and Justh GO. Morphologic changes in the digital arteries of patients with progressive systemic sclerosis (scleroderma) and Raynaud phenomenon. *Medicine (Baltimore)*. 1980;59:393-408.
7. Singer AJ and Clark RA. Cutaneous wound healing. *N Engl J Med*. 1999;341:738-46.
8. Ennis H, Vail A, Wragg E, Taylor A, Moore T, Murray A et al. A prospective study of systemic sclerosis-related digital ulcers: prevalence, location, and functional impact. *Scand J Rheumatol*. 2013;42:483-6.
9. Botzoris V and Drosos AA. Management of Raynaud's phenomenon and digital ulcers in systemic sclerosis. *Joint Bone Spine*. 2011;78:341-6.
10. Barr WG and Robinson JA. Systemic sclerosis and digital gangrene without scleroderma. *J Rheumatol*. 1988;15:875-7.
11. Hummers LK and Wigley FM. Management of Raynaud's phenomenon and digital ischemic lesions in scleroderma. *RheumDisClin North Am*. 2003;29:293-313.
12. Gualtierotti R, Scalone L, Ingegnoli F, Cortesi P, Lubatti C, Zeni S et al. [Health related quality of life assessment in patients with systemic sclerosis]. *Reumatismo*. 2010;62:210-4.
13. Frerix M, Stegbauer J, Dragun D, Kreuter A and Weiner SM. Ulnar artery occlusion is predictive of digital ulcers in SSc: a duplex sonography study. *Rheumatology (Oxford)*. 2012;51:735-42.
14. Comparison of sustained-release nifedipine and temperature biofeedback for treatment of primary Raynaud phenomenon. Results from a randomized clinical trial with 1-year follow-up. *Arch Intern Med*. 2000;160:1101-8.
15. Fonder MA, Lazarus GS, Cowan DA, Aronson-Cook B, Kohli AR, Mamelak AJ. Treating the chronic wound: A practical approach to the care of nonhealing wounds and wound care dressings. *J Am Acad Dermatol*. 2008;58:185-206.
16. Fiori G, Galluccio F, Braschi F, Amanzi L, Miniati I, Conforti ML et al. Vitamin E gel reduces time of healing of digital ulcers in systemic sclerosis. *ClinExpRheumatol*. 2009;27:51-4.
17. Wigley FM, Wise RA, Seibold JR, McCloskey DA, Kujala G, Medsger TA, Jr. et al. Intravenous iloprost infusion in patients with Raynaud phenomenon secondary to systemic sclerosis. A multicenter, placebo-controlled, double-blind study. *Ann Intern Med*. 1994;120:199-206.
18. Pope J, Fenlon D, Thompson A, Shea B, Furst D, Wells G et al. Iloprost and cisaprost for Raynaud's phenomenon in progressive systemic sclerosis. *Cochrane Database Syst Rev*. 2000:CD000953.
19. Badesch DB, Tapson VF, McGoan MD, Brundage BH, Rubin LJ, Wigley FM et al. Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. *Ann Intern Med*. 2000;132:425-34.
20. Vayssairat M. Preventive effect of an oral prostacyclin analog, beraprost sodium, on digital necrosis in systemic



sclerosis. French Microcirculation Society Multicenter Group for the Study of Vascular Acrosyndromes. *J Rheumatol.* 1999;26:2173-8.

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

22. Rademaker M, Cooke ED, Almond NE, Beacham JA, Smith RE, Mant TG et al. Comparison of intravenous infusions of iloprost and oral nifedipine in treatment of Raynaud's phenomenon in patients with systemic sclerosis: a double blind randomised study. *BMJ.* 1989;298:561-4.

23. Korn JH, Mayes M, MatucciCerinic M, Rainisio M, Pope J, Hachulla E et al. Digital ulcers in systemic sclerosis: prevention by treatment with bosentan, an oral endothelin receptor antagonist. *ArthritisRheum.* 2004;50:3985-93.

24. Tingey T, Shu J, Smuczek J, Pope J. Meta-analysis of healing and prevention of digital ulcers in systemic sclerosis. *Arthritis Care and Research.* 2013; 65:1460-71.

25. Matucci-Cerinic M, Denton CP, Furst DE, Mayes MD, Hsu VM, Carpentier P et al. Bosentan treatment of digital ulcers related to systemic sclerosis: results from the RAPIDS-2 randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis.* 2011;70:32-8.

26. Della Rossa A, Doveri M, D'Ascanio A, Tavoni A, Consensi A, Neri R et al. Oral sildenafil in skin ulcers secondary to systemic sclerosis. *Scand J Rheumatol.* 2011;40:323-5.

27. Gore J and Silver R. Oral sildenafil for the treatment of Raynaud's phenomenon and digital ulcers secondary to systemic sclerosis. *Ann Rheum Dis.* 2005;64:1387.

28. Brueckner CS, Becker MO, Kroencke T, Huscher D, Scherer HU, Worm M et al. Effect of sildenafil on digital ulcers in systemic sclerosis: analysis from a single centre pilot study. *Ann Rheum Dis.* 2010;69:1475-8.

29. Shenoy PD, Kumar S, Jha LK, Choudhary SK, Singh U, Misra R et al. Efficacy of tadalafil in secondary

Raynaud's phenomenon resistant to vasodilator therapy: a double-blind randomized cross-over trial. *Rheumatology.* 2010;49:2420-8.

30. Denton CP, Howell K, Stratton RJ and Black CM. Long-term low molecular weight heparin therapy for severe Raynaud's phenomenon: a pilot study. *ClinExpRheumatol.* 2000;18:499-502.

Competing interests: None declared. Conflict of interests: None declared. All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript. All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

Licensee OAPL (UK) 2014. Creative Commons Attribution License (CC-BY)

FOR CITATION PURPOSES: Gualtierotti R, Adorni G, Lubatti C, Zeni S, Meroni PL, Ingegnoli F. Digital ulcer management in patients with systemic sclerosis. *OA Arthritis* 2014 Jan 18;2(1):2.