Ulcer Healing and Prevention in Systemic Sclerosis

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Digital ulcers (DU) are common in systemic sclerosis (SSc) and have a major clinical impact. Whilst treating established ulcers is important, the most logical and effective approach to DU is to prevent their formation, as this will immediately remove the risk of severe complications and avoid the morbidity that is otherwise inevitable and substantial. Thus, the best therapeutic strategy for DU is *prevention of their occurrence or recurrence*, which is strategically linked to the frequency and severity of Raynaud's phenomenon (RP) episodes. For this reason, it is necessary to achieve RP control and to educate patients regarding its non-pharmacological management [1]. Patients should be taught to avoid cold temperatures by means of proper garments and gloves, hats and heavy socks, whenever there is exposure to different external temperature (e.g., cold temperature in hot seasons due to sudden weather changes, conditionated air, refrigerators in a supermarket, etc.). Stress is also an impacting trigger for vasospasm in RP [2], requiring careful examination of the psychologic conditions of SSc patients and, if necessary, counseling or prescription for antidepressants or anxiolytics. Patients should also be taught to treat dry skin with simple topical lubricating products and emulsifying ointments, in order to prevent dry skin from cracking or fissuring. Patients should be suggested to avoid nicotine [3] and any substances that cause vasoconstriction (caffeine, cephalosporins, b-blockers), and whenever possible, also to avoid trauma to the digits, such as those related to repetitive hand actions (e.g. typing or manual work) [1].

Given the impossibility to primarily prevent SSc and DU onset, DU secondary prevention begins with the identification and detection of risk factors. A recent systematic literature review identified male gender, early diffuse cutaneous SSc, in particular associated with anti-topoisomerase I antibody positivity and previous history of DU, as the predominant SSc-related features increasing the risk for DU appearance [4]. Moreover, circulating biomarkers studies identified high placental growth factor levels and low endothelial progenitor cells levels were associated with increased risk for future DU appearance, in particular for patients with history of previous digital ulcers [5]. Another study also identified Interleukin-6 levels as a predictor for future DU development, representing systemic inflammation [6]. Nail fold video capillaroscopy has an additional value in identifying patients at risk for vascular worsening: this was demonstrated for both qualitative evaluation with the late scleroderma pattern or evolution in the microvascular signs of vasculopathy [7] and for a composite videocapillaroscopic parameters score, named CSURI, derived from the combination of capillary number, maximum loop diameter and the number of giant capillaries, with a 2.9 score cut-off predicting high risk for DU development at 3 months [8].

Given these early high-impact disease-related features, the prompt initiation of background treatment could prevent new DU onset, which is strongly based on immunosuppression [9] and vasoactive-vasodilating treatments [10].

It is pivotal to understand how the concepts of healing and prevention are strongly linked and imbricated when taking care of SSc-DU patients. In fact, tertiary prevention starts once DU are manifested, in order to promote and determine their

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healing, avoid recurrency and positively influence patient reintroduction in daily social, working and family life. Therefore, a drug that helps DU healing can still also be practically considered as a preventive drug (see overview in Table 20.1).

Among vasoactive drugs, Bosentan, a dual endothelin-1 receptor antagonist, was approved for DU *prevention* after two randomized clinical trials (RCT). Its use determined a 30–48% reduction in new DU appearance at 16–24 weeks, more effectively in patients entering the trial with ≥3 DU, although no effect was shown in healing rates of already present DU [29, 30]. The positive short-term RCT results were also confirmed in various real-life studies: in particular, drug effects were evident also when the drug was primarily prescribed for pulmonary arterial hypertension treatment [18], and these effects maintained for at least 12 months [17] up to 3 years for both safety [15] and efficacy [14]. Moreover, Fanauchi et al. hypothesized possible extravascular effects on the drug, in particular antifibrotic properties [16].

The DU-preventing properties of anti-ET1 bosentan could be at least partially explained by its effect on microvasculature: in particular, it was shown to determine deremodeling effects of nailfold videocapillaroscopy changes, both alone [31] and when used in combination with prostanoids [32].

These results have not been reproduced for other members of this pharmacological class, such as macitentan [33] and ambrisentan. Conversely, ambrisentan has shown efficacy in DU healing, both in combination with iloprost [11] and alone: although a definite placebo-controlled study has not been fully performed, Chung et al. showed a complete healing of all baseline DUs in 14/20 patients [12].

Healing of DUs is possible and easier if early detected. Treatment should be started promptly, and, although pharmacologic systemic treatment is pivotal, it is not the only possible approach. DU treatment is mostly based on vasodilating agents, which take into account various pharmacological entities, characterized by different mechanisms of action, routes of administration and direct/indirect costs. Calcium-channel blockers are commonly used for the treatment of both primary and secondary RP and have been anecdotally used for treating DUs [34]. Intravenous prostaglandin analogue alprostadil has shown effect in treating SSc-DU [35] and is still commonly used, in particular, when other treatments are not easily available [36]. Prostacyclin analogues are frequently prescribed for treating pulmonary arterial hypertension, and, given the pathogenetic link with DU, their use has been exported to DU treatment. Intravenous iloprost, infused continuously for 6 h 0.5–2.0 ng/kg/min on 5 consecutive days, has been extensively used for RP and DU treatment: it was shown to determine DU healing in both open-label [21] and double-blinded [19] studies. Iloprost has shown to be comparably effective for both low and high dosages (0.5 and 2.0 ng/kg/min) [20] also characterized by long-term efficacy in preventing new DU appearance [37]. Recent data have also shown the possibility of avoiding hospitalization using a portable siring pump [38]. Among other prostacyclin analogues, treprostenil showed initial significant impact on DU healing in a small open-label pilot study [39] and the worsening of the DU status after its withdrawal [40]. A recent double-blind RCT did not show any significant effect in reducing DU net burden and impacting healing and prevention [41]. Similarly, oral beraprost and intravenous epoprostenol showed only a trend to improvement of DU prevention and healing, although data seem to be less supportive compared to iloprost [42, 43].

Table 20.1 Summary of available positive evidences for DU healing and preventing drugs

Drug	Study	Year	n	Description
Ambrisentan	Parisi et al. [11]	2013	6	Preliminary, open-label
	Chung et al. [12]	2014	20	Prospective, open-label
Atorvastatin	Abou-Raya et al. [13]	2008	84	Single centre, placebo-controlled
Bosentan	RAPIDS-1 [11]	2004	122	*Double-blind*, placebo-controlled, multicentre
	RAPIDS-2 [12]	2010	188	*Double-blind*, placebo-controlled, multicentre
	Tsifetaki et al. [14]	2009	26	Prospective, 3-year follow-up
	Garcia de la Pena Lefebvre et al. [15]	2008	15	Prospective, observational
	Funauchi et al. [16]	2009	8	Single centre, observational
	Roman Ivorra et al. [17]	2011	67	Multicentre, retrospective cohort
	Cozzi et al. [18]	2013	30	Retrospective, case control
Iloprost	Wigley et al. [19]	1992	35	*Double-blind*, placebo-controlled
	Kawald et al. [20]	2008	50	Randomized, open label
	Zachariae et al. [21]	2009	14	Open label, observational
N-acetylcysteine	Sambo et al. [22]	2001	22	Multicentre, open-label
	Rosato et al. [23]	2009	50	Prospective, observational
Sildenafil	Brueckner et al. [24]	2010	19	Single centre, pilot study
	Kumar et al. [25]	2012	16	Prospective, open label, uncontrolled
	SEDUCE [26]	2015	83	*Double-blind*, placebo-controlled, multicentre
Tadalafil	Agarwal et al. [27]	2010	53	Placebo-controlled, multicentre
	Shenoy et al. [28]	2010	25	Placebo-controlled, single centre

Phosphodiesterase 5 inhibitors are also commonly prescribed vasodilators in SSc-related RP and DU, in particular sildenafil, supporting initial promising results in case series [24, 25]. The SEDUCE study showed a trend for higher DU healing rate and a significantly lower DU number after 8 and 12 weeks of treatment with sildenafil vs placebo [26]. In this RCT, 28 patients received bosentan concomitantly with sildenafil: in this subgroup *time to healing was shorter in the sildenafil group* than in the placebo group [26]. From the same class, Tadalafil also proved some beneficial effect on RP and DU in two small double-blinded placebo-controlled studies [27, 28].

Among other IV treatments, intravenous administration of N-acetyl cysteine has shown beneficial effects on both SSc-related RP and DU, both in short-term [22] and long-term [23] treatment duration.

Combined with above-mentioned systemic treatments, *local topical treatment* is also crucial: in fact, a careful management is important to prevent further complications, i.e. infection, osteomyelitis and/or gangrene needing amputation. Among wound healing procedures, the use of different advanced dressings is supported and needs to be adapted to the changing DU status [44]. Vitamin E gel application, in combination with local wound healing procedures and dressings, was shown to significantly reduce time to DU healing [45].

The association of local and systemic treatment is of pivotal importance, and the combination of vasoactive and vasodilating drugs is frequently used to have higher impact on DU healing [46].

Case reports and case series also show promising positive effect of other medical or surgical treatments. Botulin A toxin injection, for example, is a minimally invasive and relatively safe local vasodilating treatment: it has shown beneficial effects in improving blood flow and RP and promoting DU healing in both a case series [47] and a single-blinded placebo-controlled study [48]. Beneficial effects were also demonstrated in a placebo-controlled double-blind trial of atorvastatin for 4 months, determining significant reduction in overall DU number and new DU development [13].

Regenerative medicine is also a possible approach for treating patients who are resistant to medical treatment. Autologous platelet-rich gel is a hemo-component containing numerous growth factors, which has been shown to determine improvement to healing in few case reports and an Italian case series [49]. Bone-marrow mononuclear cells have also been administered into the DU affected limb, improving pain and reducing risk of amputation/ischaemia recurrence [50, 51]. Autologous adipose-derived stromal vascular fraction and autologous adipose tissue-derived cells fractions are other source of regenerative factors: fat can be derived from patient body and then reinjected after an extraction procedure. Their use has been tested in some case series with interesting reports regarding DU number decrease [52] and reduced time to healing, also associated with pain reduction and increase in capillary number on nailfold videocapillaroscopy [53]. RCTs are currently ongoing to definitively support fat grafting use in clinical practice.

Among other medical options, tocilizumab [54], rituximab [55], recombinant human erythropoietin [56], hyperbaric oxygen therapy [57], vacuum-assisted closure therapy [58] and extracorporeal shock wave therapy [59] can be listed. Regarding surgical approaches, digital sympathectomy [60] and skin grafting [61] could be also considered but further studies are needed before being routinely performed. They can however be used for refractory DU cases or when conventional treatments are contraindicated.

Whatever the treatment choice, chronic wounds management requires full patient participation. It is therefore crucial to provide therapeutic educational interventions to increase and ensure treatment adherence and compliance. This starts from either DU-related [62] and procedures-related [63] pain control, as among the most patient perceived DU features. Patient collaboration is indeed a key aspect for achieving maximum results.

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