

Optimal management of digital ulcers in systemic sclerosis

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Abstract: Raynaud's phenomenon and digital ulcerations are two common clinical features seen in patients with systemic sclerosis. They are painful and lead to significant morbidity and altered hand function within this patient population. While currently there are no US Food and Drug Administration (FDA)-approved medications for the treatment of digital ulcerations in the United States, clinical trials have supported the use of pharmacologic and nonpharmacologic modalities in facilitating healing of existing digital ulcers and preventing formation of new ulcers. This article reviews the published data on these therapeutic options.

Keywords: scleroderma, systemic sclerosis, Raynaud's phenomenon, digital ulcers, treatment

Introduction

Systemic sclerosis (SSc) is a rare connective tissue disorder that is marked by fibrosis, vascular damage, and immunologic abnormalities with varying degrees of internal organ involvement. Although SSc is often clinically divided into two subtypes, diffuse cutaneous and limited cutaneous, based upon the extent of skin involvement, Raynaud's phenomenon (RP) and its complications are universal features of the disease affecting more than 95% of patients.¹

RP in scleroderma results from both functional and structural vascular abnormalities with marked intimal proliferation of the digital arteries. The structural component is twofold. The first marker is intimal proliferation and fibrosis causing significant compromise of the vessel lumen. The resultant endothelial damage leads to the upregulation of vasoconstrictive mediators while simultaneously lowering the levels of vasodilatory molecules. This coupled with intraluminal narrowing of digital arteries sets up a milieu against which digital ulcers (DUs) may arise. The functional aberration results from frequent vasospasm, which ultimately leads to progressive tissue ischemia and the formation of oxygen-free radicals, which further perpetuates this cycle. Treatment has been challenging because we have focused primarily on vasodilating these vessels which may not be possible when they are inherently so structurally damaged.

RP symptoms occur in almost all scleroderma patients, while digital ulcerations are present in approximately 30% of these patients yearly. DUs are defined as a denuded area of tissue with well-demarcated borders involving loss of both the dermis and epidermis.² These ischemic lesions are typically found on the fingertips. Ulcers may occur over bony protuberances, such as the proximal phalanges or the elbows but these are more likely to be secondary to taut skin and trauma and are not likely to be responsive to vasodilatory therapy. All ulcers are characteristically very painful and often result in impaired hand function. Clinical features associated with an increased

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risk of digital ulcerations include male sex, early onset of RP, anti-scl-70 antibodies, presence of pulmonary arterial hypertension, smoking, and elevated acute-phase reactants.³ DUs tend to recur, with 66% of patients having more than one episode despite use of vasodilators.⁴ They hold the possibility of resulting in irreversible tissue loss, as well as other significant complications including osteomyelitis, gangrene, and amputation.

In addition to the potential for tissue loss, the degree of functional impairment is considerable as well. The disability in patients with persistent digital ulcerations is significantly greater than those without DUs. The financial burden is substantial as well, as patients with digital ulcerations require more hospitalizations including those for antibiotics than those without.⁵

Despite these findings, recent data published by Ferri et al⁶ show that DUs may in fact be becoming less prevalent. When they compared their scleroderma cohort enlisted from 2000 to 2011 with patient groups from older studies, there was a significant reduction in skin ulcers (from 54% to 16.5%; $P < 0.0001$). This might point to an increased physician awareness of the disease process and speak of the effectiveness of the myriad of treatment options that can potentially be used in these patients.⁶

Management of DUs in scleroderma includes nonpharmacologic, pharmacologic, and surgical intervention. Nonpharmacologic modalities employed include avoidance of RP triggers including cold exposure, emotional stress, or medications that promote vasoconstriction, including beta blockers, migraine medications such as sumatriptan and ergotamine, birth control pills, certain chemotherapeutic agents such as cisplatin and vinblastine and amphetamines including those used for attention deficit hyperactivity disorder (ADHD). Smoking cessation is absolutely necessary to prevent further vascular insult to already vulnerable tissue.

Multiple agents have been employed to counteract RP and prevent/reduce the burden of digital ulcerations (Table 1), although none are approved in the United States. There have been major challenges in performing clinical trials in RP and DUs. Some are related to trial design, some related to the difficulty in defining active DUs², and some are related to the lack of pharmaceutical commitment to RP and DUs in scleroderma. The major drugs that we will review are calcium channel blockers (CCBs), phosphodiesterase inhibitors, prostacyclin analogs, and endothelin receptor antagonists. We performed a PubMed search for articles detailing treatment modalities employed for management of RP and DUs in the scleroderma patient population.

Table 1 Therapies for RP and DUs in scleroderma

Type of therapy	References
Nonpharmacologic treatment	
Smoking cessation	
Avoidance of precipitants, including cold, stress, and vasoconstrictive agents such as beta blockers and amphetamines	
Use of hand warmers and protective clothing	
Pharmacologic treatment of RP	
Calcium channel blockers	7–9
Angiotensin receptor blockers	35
Alpha-adrenergic blockers	36
Digital ulcer treatment	
Phosphodiesterase inhibitors	10–21
Prostacyclin analogs	22–25
Endothelin receptor antagonists	26–28
Nitrates	29–32
N-acetylcysteine	33, 34
Statins	38
Local management of ulcers	
Intermittent wet soaks, occlusive dressings, vitamin E gel	39
Topical/systemic antibiotics for concurrent infection	
Adequate pain control	
Debridement as indicated	
Surgical management of RP and DUs	
Central sympathectomy (endoscopic thoracic sympathectomy)	41
Digital sympathectomy	42–44
Botulinum a toxin injection	45, 46
Autologous fat grafting	47, 48
Surgical amputation	

Abbreviation: DUs, digital ulcers; RP, Raynaud's phenomenon.

The articles reviewed independently by the authors were included in the review article if they were determined to clearly describe study methods and subsequent results within their trials.

Pharmacological intervention

Calcium channel blockers

CCBs are considered first-line treatment for RP in patients with scleroderma. Nifedipine and amlodipine which have the greatest peripheral effects seem to be most helpful. They work upon the vascular smooth muscle to produce vasodilation. CCB also portend antiplatelet and antithrombotic features. Thompson and Pope in a meta analysis of six studies were able to show a 2.8%–5% reduction in weekly RP episodes as well as a 33% reduction in RP severity with use of CCB.⁷ The efficacy of CCBs in the patients with digital ulcerations is less clear. A 16-week randomized study comparing oral nifedipine with intravenous iloprost in patients with RP-associated skin lesions secondary to scleroderma showed that both drugs appeared to reduce the number of skin ulcers.⁷ Common side effects from CCB result from the nonspecific systemic vasodilation and include flushing,

hypotension, headache, and peripheral edema, which can limit the up titration of this class of drugs.⁸ To combat the peripheral edema seen with use of CCBs, venodilators such as ACE-Inhibitors or angiotensin receptor blockers have been periodically used to reduce the postulated venous hypertension driving this phenomenon. In addition, CCBs, with dihydropyridines in particular, have been noted to precipitate or exacerbate reflux symptoms which can potentially limit their use within this patient population as well.⁹ Historically, CCBs tend to serve as the framework against which further treatment options are added, and their dose should be maximized before other agents are tried.

Phosphodiesterase inhibitors

Phosphodiesterases are isoenzymes that regulate the intracellular concentrations of cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP). cGMP has direct effects on smooth muscle tone. Nitric oxide works to increase levels of cGMP by directing the conversion of GMP to cGMP. This in turn leads to a dilation of the vessel wall. Phosphodiesterase isoenzyme 5 (PDE 5) is involved in the breakdown of cGMP; and therefore, its inhibition can lead to a continued vessel dilatation.

This pathophysiologic feature has led to an approval of PDE 5 inhibitors for the treatment of pulmonary arterial hypertension. Although its use in refractory RP and digital ulcerations has also been studied, no drug has been submitted to the US Food and Drug Administration (FDA) for approval and thus, insurance approval can be very challenging. The three commercially available PDE 5 inhibitors include sildenafil, vardenafil, and tadalafil. Sildenafil and vardenafil have shorter half-lives of around 4 hours while tadalafil's half-life is much longer at close to 18 hours.

Sildenafil

There have been multiple anecdotal reports and small series of patients with improvement in RP and digital ulcerations with the use of sildenafil. A 2005 retrospective single-center chart review looking at ten scleroderma patients treated with varying doses of sildenafil (from 12.5 mg to 100 mg daily) showed that there was a significant reduction in the frequency and severity of RP seen in eight of the ten study patients. Complete healing was reported in the eight patients with digital ulcerations.¹⁰

Reports of improvements in digital temperature were noted in a small study involving five scleroderma patients published in 2006. Sequential thermal images of the hands of scleroderma patients subjected to a mild cold challenge

were obtained every minute for a total of 15 minutes after a dose of 50 mg of sildenafil was administered. The authors reported that in three of the five patients, there was a significant improvement in temperature responses post-drug administration.¹¹

A double-blinded, placebo-controlled, fixed-dose, crossover study looked into the effectiveness of sildenafil for the treatment of RP. Sixteen patients were divided into receiving 50 mg sildenafil twice daily versus placebo for a 4-week duration. The majority of these patients (88%) had secondary RP of which 38% had complications of digital ulcerations. The primary endpoints evaluated in the study were frequency and duration of RP, a validated composite measure, Raynaud's Condition Score (RCS), capillary flow velocity by laser Doppler anemometry, and healing of digital ulcerations. The authors were able to show that there was a significant improvement in duration (581 versus 1,046 minutes, $P=0.0038$) and frequency (35 versus 52, $P=0.0064$) of RP episodes in patients treated with sildenafil. The RCS were lower (2.2 versus 3.0, $P=0.0386$), and the mean capillary blood flow velocities were increased significantly ($P=0.00004$). Of the six patients with DUs, two had complete healing, while the remaining four noted interval improvement.¹² This study highlights the augmentation in peripheral vascular blood flow seen with use of the drug.

Brueckner et al¹³ reported their single-center open-label study on the effect of sildenafil on DUs. In their cohort of 19 patients treated with a mean dose of sildenafil 114 mg/day for a mean duration of 5.2 months, there was a statistically significant reduction in the number of DUs at the end of the study (1.1 per patient) when compared to the outset (3.1 per patient). The number of DUs decreased from 49 at the initiation of the study to 17 at the study end. The reduction in DU burden was seen most prominently at the 3-month mark. Of note, during the study period, there were 12 DUs that developed within nine patients.¹³ This study highlights the fact that sildenafil is generally well tolerated and should be a good option for the treatment of scleroderma-associated digital ulcerations particularly now that a generic sildenafil (20 mg three times a day) is available.

Vardenafil

Vardenafil shares a similar bioavailability profile to sildenafil, with maximal therapeutic levels reached at 1 hour with a half-life of approximately 4 hours. In 2006, Caglayan et al¹⁴ reported the sole open-label study of vardenafil in patients with RP. The dosing of the drug was 10 mg twice daily for a 2-week study period. A total of 33 of the 40

patients enlisted in the study had secondary RP. In this study, there was an obligatory 1-week washout period of all other vasoactive medications prior to recruitment for the trial. The primary endpoints studied were frequency and duration of RP attacks, RCS as well as laser Doppler measurements of peripheral blood flow in both colder and room temperature rooms. The Doppler study analysis revealed that 28 of the patients had signs of increased blood flow at room temperature readings, with increases of 21% and 30% noted at the 1 hour and 2-week interval, respectively, when compared to baseline ($P < 0.001$). The RCSs improved significantly from baseline to the 2-week mark (5.05 versus 3.54, $P < 0.001$).¹⁴ These patients did not have DUs. These findings are encouraging, but an open-label prospective trial in patients with DUs is needed to see if any clinically meaningful endpoints in ulcer healing or prevention are met.

Tadalafil

Results on the use of tadalafil in patients with scleroderma with associated RP with or without digital ulcerations have been quite varied. A 2007 double-blind, placebo-controlled crossover study looked into the mechanistic properties of tadalafil in 20 patients with primary RP. Laser Doppler flowmetry was performed to see if blood flow improved during exposure to cooling and heating progressions 90 minutes after a 10 mg dose of tadalafil was administered. There were no significant differences in skin blood flow or skin temperature noted.¹⁵ Schioppa et al¹⁶ described their experience in a randomized, double-blinded, placebo-controlled, crossover trial of tadalafil 20 mg daily versus placebo in 39 patients with scleroderma-related RP. The study consisted of a 4-week treatment trial followed by a 2-week washout period. Patients enrolled in the study were nonsmokers and were not allowed to use concomitant vasodilator therapy. The study failed to show any statistical differences between tadalafil and placebo in RCS, frequency or duration of attacks.¹⁶

Despite these unexciting early studies, three more recent studies published in 2010 have shown promise in the use of tadalafil in patients with scleroderma-related RP. Rosato et al¹⁷ in an open-label study of 20 males with scleroderma-associated RP showed that there were improvements in the RCS, reduction in frequency of attacks, and lower endothelin 1 (ET-1) levels compared to baseline. These patients were treated with tadalafil 10 mg daily for a 12-week study period.¹⁷

Shenoy et al¹⁸ reported their findings of a single-center, randomized, double-blind crossover trial from India on the

use of tadalafil 20 mg on alternate days versus placebo. This study's design closely mirrored Schioppa et al's study¹⁶ but allowed patients to continue on their preexisting vasodilatory RP medications and had a longer trial period of 6 weeks on the drug followed by a shorter 1-week washout period. Patients in this study were only required to have at least four episodes of RP a week for inclusion and were a relatively younger cohort in comparison to Schioppa et al's study.¹⁶ The results of the study showed that the primary endpoints of RP frequency and duration were statistically and substantially better when compared to the placebo arm (2.29 versus 3.37, $P < 0.0001$) and (33.81 versus 54.89, $P = 0.0023$), respectively. The RCS scores were also significantly better (3.86 versus 5.20, $P < 0.0005$). Remarkably, all 24 DUs healed within the tadalafil arm compared to only 3 of the 13 lesions in the placebo group.¹⁸

A second multicenter randomized, double-blinded, placebo-controlled study from India compared the use of tadalafil 20 mg every other day versus placebo. Subjects were again younger than those enlisted within the Schioppa's trial.¹⁶ Patients were given a 2-week run-in period followed by randomization to either the tadalafil or placebo subgroup for 8 weeks. The results showed a statistical improvement in RP clinical score, duration, and frequency of RP attacks. Also, a considerable amount of preexisting digital ulcerations healed in the tadalafil group (14 out of 18 patients) compared to the placebo arm (only 5 out of 13).¹⁹ These two latter studies seem to highlight that the use of tadalafil appears to have better outcomes when used (a) in younger patients and (b) concomitantly with other vasodilators.

Only one study has compared amlodipine to a PDE 5 inhibitor, udenafil, which were both effective in improving RP symptoms but only the PDE 5 inhibitor actually improved blood flow.²⁰ A recent meta analysis of six randomized controlled trials was reported (one with sildenafil, one with modified-release sildenafil, three with tadalafil, and one with vardenafil). PDE 5 inhibitors significantly decreased mean RCS by -0.46 (-0.74 to -0.17) ($P = 0.002$), the daily frequency of ischemic attacks by -0.49 (-0.71 to -0.28) ($P < 0.0001$), and daily duration of RP attacks by -14.62 (-20.25 to -9.00) minutes ($P < 0.0001$).²¹ Unfortunately, no Phase III industry-sponsored trial of PDE 5s has been submitted to the FDA for approval, so getting insurance approval is uncommon, although with vigorous appeals, we may be successful about half the time. The use of these drugs continues to be challenging.

Prostacyclin analogs

Prostaglandin serves as a potent vasodilator. Iloprost, approved in Europe for the treatment of digital ulcerations

associated with scleroderma, is a chemically stable prostacyclin analog with dual vasodilatory and platelet inhibitory effects.⁸ In a multicenter, placebo-controlled, double-blind study by Wigley et al²² Iloprost was administered as a 6-hour intravenous infusion, titrating up as tolerated from 0.5 to 2 ng/kg/minutes for 5 or more days. They found a mean reduction in weekly RP attacks of 39% (compared with 22% within the placebo arm, $P=0.005$). There were also statistically significant improvements in RP clinical scores and degree of DU healing. Although much of the healing of preexisting ulcers occurred in the first few of the study, the effect of the Iloprost was still present at 9 weeks. There was also a trend toward a prevention of new DU formation in the study.²² This was not submitted for approval in the United States and is therefore not commercially available in the United States, as the pharmaceutical company rather pursued oral iloprost preparations. Infusions every 1–2 months have been the standard of care in Europe, particularly for scleroderma patients with DUs. Similar results were found in patients treated with epoprostenol, another IV prostacyclin which is approved for the treatment of pulmonary arterial hypertension. In a randomized controlled trial on the effect of epoprostenol in patients with scleroderma-related pulmonary arterial hypertension, patients treated with the drug were noted to have 50% fewer new digital ulcerations in comparison to those treated without this therapy. However, no effects on healing of preexisting ulcerations were noted, although the study was not to be designed to look into this aspect of scleroderma.²³ Oral preparations of iloprost have been researched but have failed to show any meaningful improvements in RP or DU burden, but inadequate dosage and toxicity profile were potential limiting factors.²⁴ An oral preparation of treprostinil, another prostacyclin, has recently been studied. Although the short-term study did not show statistically fewer ulcers, the long-term open extension and a withdrawal study suggested that there may be beneficial use of this agent.²⁵

Endothelial receptor antagonists

Bosentan

Endothelin is a potent vasoconstrictor that also stimulates smooth muscle cell and fibroblast proliferation, thereby making it an integral player in the vascular damage seen in patients with scleroderma. Bosentan blocks the interaction of ET-1 with its receptors ETA and ETB and is approved for the treatment of pulmonary arterial hypertension. Based on the two pivotal double-blind placebo-controlled studies with bosentan on healing and prevention of ischemic DUs in patients with SSc (RAPIDS) trials described below, it was approved in Europe (but not in the United States) for

the prevention of DUs in scleroderma. These studies have suggested a trend toward efficacy in a number of healed ulcers.²⁶

Two key studies, the RAPIDS-1 and follow-up RAPIDS-2 trial, assessed the efficacy of bosentan in the management of DUs. RAPIDS-1 was a large, multicenter, randomized, placebo-controlled study of 122 patients with SSc with pre-existing digital ulcerations. The study subjects were given bosentan 62.5 mg twice daily for 4 weeks followed by 125 mg twice daily for 12 weeks. Bosentan had no effect on healing of the ulcers, but it appeared to be effective in preventing new ulcer formation and in turn improving hand function. Patients were noted to have a 48% reduction in the mean number of new ulcers developed during the study period.

RAPIDS-2 was the follow-up study with a longer treatment period that was designed to reinforce the results of the RAPIDS-1 trial. This was a 24-week, randomized, double-blind, multicenter study in which scleroderma patients were administered 62.5 mg twice daily for 4 weeks which was then increased to 125 mg twice daily for 20 weeks. The primary endpoints were to assess the effect of bosentan on the reduction in new ulcer formation as well as time to complete healing of existing ulcers. Again, the existing digital ulcerations did not heal more quickly while on bosentan compared to placebo. There was a 30% reduction in formation of new ulcers in bosentan-treated patients in comparison to the placebo group and particularly in patients with more than three DUs. During the study period, patients receiving bosentan developed a mean of 1.9 new ulcers compared with 2.7 in those receiving placebo ($P=0.035$). Secondary outcomes in RAPIDS-2 trial showed an improvement in patient function as well, particularly within the dressing domain. Adverse events associated with the use of bosentan included elevated liver function tests and fluid retention.^{27,28} This drug was approved in Europe for prevention of DUs in scleroderma, but the FDA, after careful review, did not approve it. Bosentan may be an important treatment modality, given its oral preparation and its potentially unique ability to prevent new DU formation.

Nitrates

Topical nitrates have been used to try and improve blood flow, but given its relatively cumbersome application in between the interdigital web spaces, and potential for side effects due to variable systemic absorption, less enthusiasm about its regular use exists. Anderson et al examined the effects of topical glyceryl trinitrate (GTN) on blood flow measured via scanning laser Doppler imaging in patients with both primary and secondary RP related to limited

scleroderma. After a 1-minute application of 2% GTN, there were statistically significant improvements in blood flow noted when compared to fingers where placebo gel was applied ($P=0.004$). There was a lack of systemic side effects from local application of the drug in this small cohort of patients, which may make it a viable option for patients who cannot tolerate oral vasodilators.²⁹ Two other randomized control trials have looked at a relatively new topical preparation of nitroglycerin, MQX-503, for the treatment of RP. The first study showed improvements in RCS in relation to the placebo group but failed to show statistical differences in frequency or duration of RP episodes.³⁰ The second study showed improvements in blood flow measured by laser Doppler but lacked any change in pain scores or skin temperature readings.³¹ In an attempt to find a more user-friendly mode of application, Teh et al³² performed a randomized placebo-controlled trial, looking at the efficacy of GTN patches for treatment of RP, again in patients with both primary and scleroderma-related RP. They found that the use of the 0.2 mg/h patches worn daily for 12-hour intervals for 1 week reduced the frequency and severity of RP episodes (both P -values <0.05). However, patient adherence was limited by adverse events of headaches, which caused a considerable portion of the patient cohort to discontinue use of the patch. Also, objective data showed no differences in the thermographic imaging between the drug and placebo group after the study week.³² All these trials must be taken with the caveat that DU data were not included.

N-acetylcysteine

The use of *N*-acetylcysteine (NAC) infusions has been reported for use in scleroderma patients with RP and DUs. It is postulated that the antioxidant properties of NAC, in addition to its potential effects on smooth muscle vasodilation and platelet inhibition, are its primary mechanism of action. Sambo et al³³ performed an 11-week open clinical trial on 22 patients. The study subjects received a 5-day continuous intravenous infusion of NAC, initially a loading dose of 150 mg/kg followed 2 hours later by a maintenance dose of 15 mg/kg/h. The infusions were well tolerated in all patients. The frequency and severity of RP attacks reduced significantly when patients were seen in follow-up. They also had 25.18% less active DUs 33 days out from start of treatment.³³ This was mainly a safety trial which showed no serious adverse events in patients receiving the drug. Rosato et al³⁴ performed a prospective study on 50 scleroderma patients who received NAC infusions every 2 weeks for a median follow-up of 3 years. The authors found a reduction of DU/patient/year

(4.5 ± 3.1 versus 0.81 ± 0.79) and DU ulcer visual analog scale (VAS) (6.88 ± 2.62 versus 3.20 ± 1.80) and a decrease of the RP number attacks (7.18 ± 3.87 versus 3 ± 1.92) and a RP VAS (6.24 ± 1.92 versus 3.62 ± 1.48).³⁴ Further trials are needed to correlate the findings shown in these two studies.

Other medications

Angiotensin enzyme inhibitors and receptor blocking agents have been employed in the treatment of secondary RP, mainly due to their deterrent effect on angiotensin II, a potent vasoconstrictor that also has profibrotic effects.³⁵ They have not been studied in DUs and clinically do not seem to be as effective as CCBs. Alpha-adrenergic blockers, particularly prazosin, whose mechanism of action is through inhibition of the alpha one postsynaptic adrenergic receptors, and selective serotonin reuptake inhibition, by blocking serotonin (a potent vasoconstrictor) have been shown in studies to reduce the severity and frequency of RP episodes.^{36,37} But, again, there is a lack of published data of their effect on digital ulcerations.

Addition of low dose aspirin has been suggested in patients with RP, but studies have not shown that it is helpful. Aspirin serves to inhibit cyclooxygenase formation in platelets and endothelial cells, therefore, precluding the formation of thromboxane A₂, which serves as a potent vasoconstrictor.

Clinical benefits in patients with SSc-related RP taking statins have been reported. In a study of 84 such patients, the 56 patients receiving atorvastatin 40 mg daily for 4 months had significantly better clinical outcomes compared to the 28 patients receiving placebo. These benefits included the development of fewer DUs (1.6 versus 2.5 new ulcers per patient in the placebo arm), improvements in health assessment questionnaire (HAQ) scores, analog scales for RP, pain scales, severity of digital ulcerations, and physician global assessments.³⁸

Local and surgical intervention

Local wound care

Local wound care measures include the application of topical hydrocolloid and occlusive dressings to protect the affected skin and prevent further risk of microtrauma. Topical hydrocolloid dressings have been shown to promote healing of DUs in randomized control trials. Vitamin E gel improves time of healing in scleroderma patients with DUs, 13 weeks versus 20 weeks in comparison to patients treated without vitamin E gel ($P<0.0001$).³⁹ Creams to keep the skin well moisturized are also recommended. Necrotic tissue should be debrided to avoid systemic infection and promote ulcer

healing. Deposits of calcinosis embedded under the ulcer should also be extracted for the same reason. Debridement should ideally be performed at facilities with wound care expertise who have experience with managing these types of ulcers, particularly plastic hand surgeons, as often wound centers focus more on lower extremity ulcers. Digital amputation is reserved for clinical scenarios where there are no other options. Although these ulcers take a very long time to heal, if pain and infection can be controlled, this will lead to better outcomes, more function, and more preserved tissue than resorting to amputations.

It is imperative to provide patients who develop digital ulcerations prompt and ample pain relief given the severity of pain associated with these lesions. A short-term course of opioids is generally acceptable until lesions begin to heal. If there is a suspicion for infection, empiric antibiotics coupled with aggressive local wound care is mandated to prevent further tissue compromise.⁴⁰

Sympathectomy

Sympathectomies intend to block the sympathetic nerve-driven vasospasm thought to play a significant role in scleroderma-associated vasculopathy. Historically, invasive thoracic sympathectomies were done with lots of risks and variable duration of benefit. Less invasive approaches using endoscopic thoracic sympathectomy have been useful, but most recently, the use of digital sympathectomies has been used to salvage ischemic and ulcerated digits.⁴¹ The surgeon skillfully and carefully removes the adventitia and, therefore, disrupts the sympathetic fibers contained within them. The disruption of the adventitia ultimately leads to arterial dilatation as the smooth muscle cells relax. Assessing vessel patency typically follows this process, with the surgeon performing revascularization of occluded regions if distal anastomosis sites are available. Local digital sympathectomies have been shown to provide pain relief, contribute to ulcer healing, and prevent formation of new DUs in two separate small studies.^{42,43} In a retrospective chart review, 26 peripheral sympathectomies were performed on 17 patients. The authors noted that no significant postoperative complications occurred in their cohort. Also, there was a 92.3% improvement in pain scores after the procedure. All patients with digital ulcerations had complete healing with only two having recurrence of new lesions during a follow-up period. This study served to display that digital sympathectomies are well tolerated and can have significant clinical benefits in terms of healing of preexisting ulcers, possible prevention of ulcer recurrence, and overall improvement in

hand function. Although these procedures have been reserved for when traditional modalities have failed, there may be an added clinical benefit for early intervention prior to the development of fixed stenotic defects and limited areas for revascularization.⁴⁴

Botulinum toxin

Case series have reported on the potential beneficial effects of botulinum toxin in patients with digital ischemia/ulceration, including those with scleroderma. The mechanism of action of botulinum toxin is through inhibition of the release of acetylcholine vesicles at the neuromuscular endplate, thus blocking smooth muscle vasoconstriction and leading to arterial vasodilation.⁴⁵ It also works to inhibit norepinephrine transmission as well as blunting the effect of nociceptors. There have been several studies that looked at the effect of botulinum toxin in treatment of ischemic lesions. There are no prospective controlled trials to date. A systematic review of the literature by Iorio et al⁴⁶ reported on five articles that commented on use of the drug in Raynaud's Disease or associated vasoconstrictive diseases. The common endpoints to all these studies were that there were considerable improvements in pain levels, healing of existing ulcers, with improvements in blood flow post-procedure noted on Doppler imaging. The difficulty lies in the fact that patients in these studies have received heterogeneous concentrations and locations of drug placement, so the optimal patient cohort for this procedure is not well delineated.⁴⁶ Uppal et al⁴⁵ were able to report on the improvement in hand function after botulinum toxin. In their study, 20 patients underwent administration of 100 units of the drug. When compared to the noninjected hand, there were statistically significant improvements in hand function characterized by improved pinch and grip strength (all *P*-values less than 0.01). Subjective indicators of disability, hand function, pain scores, digit color, and cold tolerance all improved, but not to statistically significant levels in the study.⁴⁵

Autologous fat grafting

New literature suggests some promise for a technique known as autologous fat grafting. In it, purified fat tissue is injected into the border of refractory ulcers. The proposed mechanism of this procedure is that the fat graft includes adipose-derived stem cells, which secrete a favorable cytokine profile that promotes neovascularization. These cytokines include upregulation of antifibrotic factors such as interferon gamma and matrix metalloproteinases while downregulating profibrotic factors such as transforming growth factor beta. The relative ease in procurement of these samples as opposed

to bone marrow stem cells makes this modality one that is gaining more interest. A single-site open-label Phase I study reported on the safety, tolerance, and efficacy of autologous fat grafting was performed in a cohort of 12 patients. None of the patients suffered any serious adverse events from the procedure. There were close to 50% improvements noted in the RCS, general health status, hand pain, and hand function. There was a reduction of total DU burden from 15 at the beginning of the study to seven at the end of the 6-month study trial.⁴⁷ Del Bene et al reported their experience with the procedure in a cohort of nine scleroderma patients with 15 ulcers. These patients were also concomitantly treated with IV iloprost. The fat graft was performed between 2 and 8 weeks from the onset of ulcer formation and resulted in complete healing of ten ulcers with a >50% reduction in the size in two ulcers within 8–12 weeks of the procedure.⁴⁸ This may serve as an adjunct to other treatment modalities in cases of severe, refractory ulcerations.

Surgical indications

There have been reports in the literature of macrovascular involvement noted in patients with scleroderma. Although the digital arteries are the most severely affected arteries in scleroderma, in some patients, the radial and ulnar arteries can be occluded. A retrospective study of 15 patients with scleroderma-related digital ulcerations with angiographically confirmed ulnar artery occlusion showed that eight patients who underwent ulnar artery revascularization with digital sympathectomy had improvement in healing of their ulcers.⁴⁹

Conclusion

Scleroderma-related vasculopathy is a serious and problematic issue that adds significant morbidity to patient's lives. The search for well-tolerated, inexpensive therapeutic options for scleroderma-related RP and associated digital ulcerations remain a high priority. The lack of FDA-approved therapies for digital ulcerations warrants renewed focus and attention to find meaningful treatment options. The existing fund of knowledge on current therapeutics has laid a foundation on which future research studies can be devised. Ultimately, physicians will need to employ a multifaceted therapeutic approach to optimize existing DU management and prevent formation of new lesions to provide our patients with the best quality of life.

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