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Pharmacotherapy Options in the Management of Raynaud's Phenomenon

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Abstract

Purpose of review: Multiple classes of medications have been studied for the treatment of Raynaud's phenomenon (RP) with or without digital ischemia. The goal of this review is to discuss the outcomes of recent studies and to report on our approach to the management of RP in light of the available evidence.

Recent findings: Comparing treatments for RP remains a challenge as efficacy endpoint vary widely among trials. While calcium channel blockers are used first-line in the pharmacologic management of RP, phosphodiesterase 5 inhibitors have also been shown to be beneficial in reducing symptoms. In the setting of digital ischemia, administration of intravenous prostanoids is the standard of care. Bosentan has shown benefit in the prevention of future ulcers in patients with scleroderma. Botulinum toxin therapy was ineffective in a clinical trial involving scleroderma patients; more controlled studies are needed in other subsets of patients. Digital sympathectomy may be beneficial in cases of critical digital ischemia, though recurrence of symptoms is common.

Summary: Comparative effectiveness studies are needed to determine which therapeutic interventions are most beneficial in patients with RP. Based on the available evidence, we start with CCBs and add a phosphodiesterase inhibitor if symptoms are not controlled, or intravenous prostacyclin in the setting of severe critical digital ischemia. We may additionally add an endothelial receptor antagonist in cases of recurrent digital ulcers. A surgical sympathectomy may be used in refractory cases of digital ischemia. A digital block may also be a less invasive, but temporary, intervention allowing for titration of medical therapy.

Keywords

Raynaud's; outcomes; treatment; procedures; scleroderma; review

Introduction

Cold exposure increases the sympathetic tone of unique thermoregulatory vessels in the skin, triggering vasoconstriction and subsequent decreased cutaneous blood flow. In Raynaud's

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phenomenon (RP), there is an exaggerated vasoconstrictive response to cold stimulation, resulting in the classic white and/or blue color changes in the fingers and toes. The nose, ears, nipples and rarely the tongue can also be involved in some patients. In addition to cold exposure, emotional stress can trigger RP attacks [1,2].

Primary RP is a benign condition that is not associated with a defined disease. It typically arises in the second or third decade of life and about 25% of patients have first-degree relatives with the same condition [3]. Symptoms are usually mild and often non-pharmacologic measures, including educating the patient about the problem and instructing on cold avoidance, can appropriately manage the condition. Generally, the frequency and severity of primary RP symptoms lessen with increasing years of age.

Secondary RP occurs in association with several secondary disorders including underlying autoimmune diseases. Scleroderma is the most common autoimmune connective tissue disease associated with secondary RP, with over 95% of patients with scleroderma experiencing RP [4]. Symptoms in secondary RP are typically more severe than in primary RP, with, for example, painful dermal ulcerations occurring in approximately 50% of patients with scleroderma [4]. Critical digital ischemia with resulting gangrene and loss of digits is the most severe complication and immediate aggressive pharmacologic management is warranted.

While maintaining a warm core body temperature and protecting the extremities from cold temperatures are the essential and fundamental strategies in the management of RP in all patients [5], pharmacologic treatment may still be needed particularly in secondary RP in which digital ischemia is occurring.

In this present article, we will review the major classes of medications used to treat RP. We will focus on studies released over the last 10 years that have impacted the management, or hold promise in impacting the future management, of RP (Tables 1 and 2). Finally, we will discuss our approach to managing RP in the context of the available evidence (Figure 1).

Outcomes Measures

Perhaps one of the most challenging aspects of comparing the effectiveness of treatments among the available therapeutic options is the heterogeneity of outcome measures utilized in studies. Patient reported outcomes measures, as well as laboratory-based physiologic outcomes measures, have been variably used in clinical studies to assess treatment efficacy. We will briefly review these measures to provide context for the review of treatment options.

Clinical Outcomes Measures

Visual Analog Scores (VAS): VAS have been used to assess pain, tingling, and numbness during an attack. It ranges in scale from 0–10 or 0–100. Global patient and physician appraisal of overall RP activity has also been assessed using VAS. While VAS for pain, tingling, and numbness has shown satisfactory reliability with an intraclass coefficient of 0.70, global patient and physician VAS reliability was poor with intraclass coefficients 0.55 [6].

Frequency and duration of attacks: A diary of the frequency and duration of daily attacks is often used in trials. These measures rely on patients' recall, which may be particularly challenging in the setting of frequent attacks throughout a day. Duration of attacks may also be difficult to assess, since some attacks never fully resolve while others can last for mere seconds. An assessment of the reliability of these measures revealed a satisfactory intraclass coefficient of 0.75 for average frequency of attacks, but poor reliability for duration of attacks with an intraclass coefficient of 0.55 [6].

Raynaud's Condition Score (RCS): The RCS is a validated, patient reported outcomes measure assessing the patient's perceived impact of the frequency, duration, pain, disability and severity of Raynaud's attacks on a summary ordinal 10-point scale [7]. It is completed on a daily basis, with daily scores typically averaged over 1–2 weeks. The patient acceptable state, defined as “very mild” or “mild” RP activity, and the minimally clinically important difference, was found to be 3.4 and 1.4–1.5 in a clinical trial [8]. The RCS correlates well with the Health Assessment Questionnaire (HAQ) disability and pain and differs between patients with and without digital ulcers [7], offering a dimension of measurement not inherent in the somewhat variable VAS scores.

A high placebo response for all the aforementioned clinical outcomes measures (RCS, patient and physician global VAS, frequency, duration, and pain, numbness, and tingling) has been shown, with up to 56% of patients in placebo arms reporting at least a 10% improvement and up to 19.5% reporting at least a 60% improvement [6]. Combining measures was shown to decrease the placebo response. Despite these findings, no consensus has been reached regarding standardization of these measures for use as clinical trial endpoints. Unfortunately, a high placebo response leads to difficulty with detecting improvements from a therapeutic agent in intervention trials. In addition to the inherent effect of a placebo, weather changes, levels of stress, and lifestyle adjustments can all lead to variability in RP symptoms that are not yet captured by any of the current patient reported outcomes measures, and may account for the poor reliability seen with some instruments [9]. We do not routinely use these measures in clinical practice to determine adjustments in medical therapy.

Laboratory Based Outcomes Measures

Infrared thermography (IRT): Changes in skin temperature due to cutaneous perfusion can be measured by IRT. IRT is often used in conjunction with a *cold stress test*, in which a subject's gloved hand is submerged in a cold-water bath for a pre-specified time, then rewarming time monitored pre- and post-intervention. A wide variety of protocols using IRT have been used, rendering direct comparisons between studies difficult [10].

Laser Doppler flowmetry (LDF): In LDF, light penetrating the skin from a single probe reaches moving erythrocytes in the blood and is scattered back to a photodetector. Light scattered from moving cells undergoes a small frequency change; this change in frequency is directly proportional to the speed and concentration of erythrocytes and thus allows for measurement of blood flow [11]. This technique is prone to movement artifact and has poor reproducibility.

Laser Doppler imaging (LDI): LDI overcomes limitation of LDF in that an area is scanned, rather than a single point, and blood cell velocity is measured at several points to construct a map of tissue perfusion [11]. This technique takes longer than LDF, though faster imagers have been developed at the cost of lower resolution images.

Laser speckle contrast imaging (LSCI): LSCI allows simultaneous full field dynamic vascular assessment using optics. By directing a two-dimensional laser beam generated by optics, at an optically rough surface, a speckle pattern of reflections from the uneven surface is detected at the focal plane of the imaging lens [11]. If the laser is directed at areas where there is movement due to perfusion, the speckle contrast pattern will change, and changes in accordance to the velocity of blood flow. Good inter-rater reliability in scleroderma has been shown [12].

While laboratory assessments provide objective measures of temperature and digital blood flow that can be tracked in a controlled environment following an intervention, they do not always translate into improvements that may occur in a real life ambulatory setting [13]. The role of laboratory-based measurements in assessing success of interventions in RP trials remains a topic of significant interest among researchers; certainly, further research needs to be performed to determine relevance of laboratory based measurements on clinical outcomes in order to employ this technology in the routine clinical care of patients with RP.

Pharmacologic Treatment: Topical Therapy

RP treatments given systemically may cause intolerable side effects in some patients. Theoretically, topical agents may at least partially circumvent this issue by maximizing therapy at the distal extremities that are most affected while limiting the amount of systemic absorption.

The efficacy of topical glyceryl trinitrate was first demonstrated in a double-blind, placebo-controlled, crossover trial in 17 subjects with secondary RP, which showed a reduction in the frequency and severity of attacks and size of ulcers in the glycerol trinitrate arm [14]. Using LDI, topical glyceryl trinitrate was also found to increase perfusion at both distal digital ulcer and extensor digital ulcer cores as compared to placebo [15]. MXQ-503 is a topical microemulsion formulation of nitroglycerine with little to no systemic absorption. In a multi-center, randomized, placebo-controlled trial of 37 subjects (70% with secondary RP), the MXQ-503 treated group recovered back to baseline blood flow after cold stress test faster than those in the placebo arm. However, no clinically meaningful differences were seen in pain, numbness, and tingling VAS scores thus the production of MXQ-503 was suspended. A recent meta-analysis of topical nitrate therapy in primary and secondary RP showed a moderate to large treatment effect in primary and secondary RP as compared to placebo, combining trials with either clinical or blood flow outcomes (SMD = 0.70, 95% CI 0.35–1.05, $P < .0001$) [16]. Headaches were more frequent in the topical nitrate treated group versus placebo, though headaches were less common in the newer formulations (e.g. MXQ-503).

A small study of 10 subjects with secondary RP evaluated topical 10% nifedipine and 5% sildenafil with regard to the endpoints of Doppler flow and vessel diameter 1 hour after application in comparison to baseline [17]. Doppler flow was significantly improved in the sildenafil group but not the nifedipine group. However, there were no significant changes in vessel diameter in either treatment arm. The frequency of administration of these topical agents for treatment of RP and their impact on RP disease course and symptoms are still unknown.

We will use topical nitrates in a situation of non-critical digital ischemia not responding to first line calcium channel blocker therapy and instruct patients to apply twice daily. Patients may become refractory to the nitrates and thus other oral agents are more practical and preferred for long-term therapy. Topical nitrates should not be used in combination with any phosphodiesterase 5 inhibitors (PDE5i), due to profound hypotension that can occur.

Pharmacologic Treatment: Systemic Therapy

Calcium Channel Blockers (CCBs)

Calcium channel blockade is the cornerstone of the pharmacologic management of RP. The non-cardioselective dihydropyridine extended release calcium channel blockers (CCBs) nifedipine and amlodipine are the most commonly used medications in the United States for treatment of RP. CCBs cause vascular smooth muscle relaxation resulting in a decrease in vascular resistance and increase in peripheral blood flow. In the early 1980's, two randomized placebo-controlled cross-over trials demonstrated a decrease in the frequency and severity of attacks by VAS or diary, thus ushering in the use of CCBs as the first-line pharmacologic treatment option [18,19].

Recently, a Cochrane review of CCBs for the treatment of primary or secondary RP found that people who took CCBs experienced, on average, 6 fewer attacks per week than those who took placebo [20]. The absolute risk difference in the severity of attacks and pain, measured by the VAS, favored the treatment group at 6% and 15%, respectively, a statistically significance response. Subgroup analyses revealed that higher doses were superior to lower doses in reducing the frequency, duration and severity of attacks. In fact, only higher doses of CCBs were found to significantly reduce the duration of Raynaud's attacks in comparison to placebo (weighted mean difference = -4.60 , 95%CI -6.76 to -2.45); low-dose CCBs compared with placebo did not produce this effect (weighted mean difference = 2.24 , 95% CI -0.24 to 4.73).

The European League Against Rheumatism (EULAR) recommends CCBs for the first line treatment of RP [strength of recommendation: A] [21]. We adhere to these recommendations in our own practice. We will use amlodipine titrating up to a dose of 10–15mg once daily or nifedipine extended release titrating up to a dose of 120mg once daily, while monitoring for common side effects including hypotension, edema, headaches, and/or flushing.

Phosphodiesterase 5 Inhibitors (PDE5i)

Nitric oxide is a potent vasodilator, acting via cyclic guanosine monophosphate (cGMP) in smooth muscle cells to reduce calcium and cause vasodilatation [22]. Phosphodiesterase 5

inhibitors (PDE5i) prevent the degradation of cGMP, thereby promoting vasodilatation through the accumulation of cGMP in vascular smooth muscle cells. Four oral PDE5i are available in the United States, including sildenafil, tadalafil, vardenafil and avanafil. The latter has not been studied in the treatment of RP. Side effects of PDE5i include hypotension, flushing, edema, hearing loss and visual disturbances.

I. Sildenafil—The first double-blind randomized placebo-controlled cross-over trial of PDE5i, sildenafil, for the treatment of RP was published in 2005 [23]. In 18 patients with treatment resistant primary or secondary RP (94% previously trying a CCB), sildenafil 50mg was given twice daily for 4 weeks. In comparison to placebo, there was a significant reduction in the number of RP attacks, the cumulative duration of RP attacks, and daily mean RCS over the 4-week period. The velocity of capillary blood flow (a measure of increased digital perfusion) under a controlled temperature was also significantly improved with sildenafil, when compared to baseline and placebo. The effect of sildenafil on healing of digital ulcerations was examined by Bruekner and colleagues in 19 patients with treatment refractory digital ulcers and fissuring [24]. After 6 months of sildenafil titrated to a maximally tolerated dose not exceeding 150mg daily, a significant reduction in digital ulcers from baseline was observed (49 vs. 17, $p<0.001$). Another study found that finger blood flow by LDI improved from baseline after 8 weeks of therapy with sildenafil 50mg twice daily when compared to placebo ($p=0.046$) [25]. Duration of RP attacks was also significantly improved in the sildenafil treatment groups, but frequency of attacks and RCS was similar between the groups at 8 weeks. In a multicenter, randomized, double-blind, placebo-controlled, parallel-group study of a modified release sildenafil formulation with once daily dosing, there were no significant differences from baseline in sildenafil modified release and placebo groups with regard to frequency of attacks, pain, duration, and RCS, though there were trends in improvement in RCS and duration of attacks in the sildenafil modified release group [26].

Sildenafil was also studied to determine its effect on digital ulcer healing in scleroderma in the SEDUCE trial [27]. In this multicenter randomized placebo-controlled trial of sildenafil 20mg three times daily, there was no difference between sildenafil and placebo at 12 weeks in the primary endpoint of time to healing of digital ulcers. There was a statistically significant difference in the number of ulcers present at 8 and 12 weeks in the sildenafil arm compared with placebo, favoring sildenafil. The study was underpowered; thus, limited conclusions can be made.

II. Tadalafil—Tadalafil is a PDE5i with a prolonged half-life of 15 to 35 hours [28]. In a randomized placebo-controlled crossover trial of 20mg of daily tadalafil in RP secondary to scleroderma, there were no significant differences in RCS, frequency or duration of RP attacks in treatment versus placebo arms [29]. A high placebo response was believed to be a confounding factor in this trial. Another study reported improvements in RCS, frequency, and duration in RP attacks when tadalafil 20mg was given as add on therapy in treatment resistant RP, as compared to baseline and placebo [30]. There was also a significant improvement in healing of pre-existing digital ulcers, and a reduction in new digital ulcers, when tadalafil treated patients were compared to placebo controls. Flow mediated dilatation,

a marker of endothelial function, improved in the tadalafil treated group when compared to placebo group and to baseline.

III. Vardenafil—PDE5i vardenafil has been shown to significantly reduce RCS, frequency, and duration of attacks when compared to placebo controls in one randomized, double-blind, placebo-controlled crossover study [31].

A systematic review and meta-analysis of PDE5i for the treatment of secondary RP found statistically significant improvements in RCS ($P=0.002$), frequency of RP attacks ($P<0.0001$), and daily duration of RP attacks favoring PDE5i ($P<0.0001$). We use PDE5i in patients who are not responding to CCBs, as defined by either 1) poor quality of life due to RP symptoms, or 2) recurring critical digital ischemia. We first try to maximize the CCB. If tolerated, in these resistant cases, we combine a PDE5i with the CCB watching the blood pressure and monitoring for any signs of edema.

Prostanoids

Prostacyclins cause vasodilation, have anti-platelet properties, and have protective effects on the endothelium of blood vessels [32,33]. In RP, particularly in secondary RP in which an underlying vasculopathy is present, prostacyclin pharmacotherapy may help replace endogenous prostacyclins that are lost as part of the vascular injury from the disease process. Commercially available prostacyclins that have been studied for the treatment of RP with or without digital ulcers include intravenous epoprostenol, intravenous or oral iloprost and oral treprostinil. Oral selexipag, a prostacyclin receptor agonist, has also been studied [34].

Common side effects of prostanoids include headache and flushing, particularly during intravenous administration. These side effects can be controlled with reduction in the infusion rate. One retrospective study evaluating the frequency of ischemic cardiovascular events in scleroderma patients receiving intravenous prostanoids (either iloprost or alprostadil) found that a significantly higher number of patients undergoing prostanoid treatment experienced an ischemic cardiovascular event ($n=7/50$, 14%) compared to controls ($n=1/42$, 2.4%; $p=0.041$ for comparison)[35]. Events were significantly more frequent in the subgroup of patients with baseline high cardiovascular risk, suggesting that cardiovascular risk should be assessed prior to the administration of prostanoids in scleroderma patients with RP with careful consideration of the risks and benefits of therapy in patients at higher risk for ischemic cardiovascular events.

I. Epoprostenol—The use of intravenous epoprostenol for the treatment of RP increased in the 1980s with several case series and small cohort studies showing varied improvements in cold tolerance, pain, duration of attacks, or skin temperature [36]. A double-blind placebo-controlled trial of 14 patients showed an improvement in the frequency and duration of attacks at one and six weeks post-infusion as compared to baseline, in those treated with epoprostenol [37]. Weekly infusions of 7.5 ng/kg/min were administered over 5 hours for three weeks in this study. One week after the third infusion, finger temperature was noted to be 1.6 degrees Celsius higher than the control group; baseline finger temperatures were the same in both groups. Initially observed improvement in finger temperature was noted to have declined at measurements taken 6 weeks post infusion, suggesting that another infusion

may be needed as soon as 6 weeks. Another double-blind placebo-controlled trial of 12 patients, with a cross-over design, showed improvements in finger skin temperature (with an increase in 2.6 degrees Celsius from baseline) during epoprostenol infusion as compared to placebo, but these effects did not persist at 1 week follow-up [38]. Likewise, a significant increase in LDF was also seen during infusion in the epoprostenol group, as compared to placebo. The impact of the incremental increases in skin temperature on frequency, duration, and severity of attacks is unclear from this trial, as patient reported outcomes were not assessed.

In our practice, we use epoprostenol in patients with severe refractory Raynaud's phenomenon with digital ischemia. We also consider epoprostenol infusion in patients with severe RP with inadequate symptom response to oral/topical vasodilator therapy. We start at a dose of 0.5ng/kg/min and titrate up to 2ng/kg/min, with a total administration time of 6 hours. We repeat infusions daily for 3–5 days. Retreatment is defined by the clinical situation but benefit usually lasts 10–12 weeks.

II. Iloprost—Intravenous iloprost has been demonstrated in a meta-analysis to be effective in reducing the frequency and severity of RP secondary to scleroderma, however, the intravenous iloprost formulation is not available in the United States [39]. Doses vary in clinical studies and range from 0.5–3ng/kg/min for 3–5 consecutive days. EULAR recommends the use of intravenous iloprost for the treatment of severe RP in scleroderma after failure of oral therapy to reduce the frequency and severity of RP attacks [21].

Oral iloprost for the treatment of RP has also been studied. One multicenter double-blind placebo-controlled parallel group study with oral iloprost 50mcg given twice daily for six weeks did not show any differences in duration or frequency of attacks, or in severity as assessed by the RCS [40]. However, a higher-than-expected placebo response was seen in this trial resulting in a larger-than-expected improvement in placebo and ultimately a lack of differences between groups. Another double-blind randomized placebo-controlled trial of oral iloprost at twice daily 50 mcg or 100mcg doses found that at 6 weeks, the duration of attacks and severity of attacks (by the RCS) decreased but the frequency of attacks did not [41].

III. Treprostinil—Treprostinil is a prostacyclin that is available for intravenous, subcutaneous, inhaled, or oral routes of delivery and is approved in the United States for treatment of pulmonary arterial hypertension.

An open label study of 20 subjects treated with twice daily treprostinil showed improvements blood flow by LDI; skin temperatures also correlated with plasma drug concentration levels [42]. In a multicenter randomized, placebo-controlled, parallel group study of oral treprostinil in 148 subjects with scleroderma and at least one digital ulcer, treprostinil twice daily (up to a maximally tolerated dose of 16 mg twice daily) did not result in a significant reduction in net ulcer burden at 12 weeks but did result in improvements in the Scleroderma Health Assessment Questionnaire-Disability Index (SHAQ-DI) components related to hand function as well as patient impression of RP symptoms [43]. A retrospective study of the digital ulcer burden upon withdrawal of treprostinil after an open label

extension of the aforementioned randomized controlled trial revealed a statistically significant increase in digital ulcer burden [44]. Subgroup analyses revealed that there appeared to be a group of patients with a stable ulcer burden over time, regardless of treatment, and another group who had a decrease in ulcer burden on treatment with a striking increase in ulcer burden off of treatment. Data suggested that subjects who were negative for anti-centromere antibody may have more benefit from oral treprostinil for reducing digital ulcer burden than those positive for anti-centromere antibody.

We consider using oral treprostinil in patients with severe refractory RP with digital ischemia who are unable to obtain intravenous infusions of epoprostenol. We start at a dose of 0.25mg twice daily, and titrate up to a maximally tolerated dose. In the open label extension study, the average total daily dose of treprostinil was 5.7mg [44].

IV. Selexipag—Selexipag is an oral selective IP prostacyclin-receptor agonist which was shown in a phase 3 trial to decrease the risk of the composite end point of death or complication related to pulmonary artery hypertension, as compared to placebo [45]. Recently, the efficacy and safety of selexipag in adults with RP secondary to scleroderma was evaluated in a randomized placebo-controlled trial [34]. No significant differences in frequency of RP attacks, RP attack duration, or RCS score was observed.

Overall, the evidence supports the use of intravenous prostacyclins, but not oral prostacyclins/prostacyclin agonists, for the treatment of RP. In our practice, we use intravenous prostacyclins in patients with critical digital ischemia (Figure 1). We also use intravenous prostacyclins in patients with refractory RP symptoms after maximally titrated CCBs or combination oral vasodilator therapy.

Endothelin Receptor Antagonists (ERA)

Vascular endothelial injury results in increased expression of endothelin-1 (ET-1). In addition to its vasoconstricting properties, ET-1 has also been shown to stimulate fibroblast and smooth muscle proliferation, which are key features of the underlying vasculopathy seen in scleroderma [22]. ET-1 accomplishes cell signaling through two receptors, ET_A and ET_B [46,47]. ET_A and ET_B are expressed on vascular smooth muscle cells; activation of these receptors by ET-1 mediates vasoconstriction. However, ET_B receptors are also expressed on endothelial cells, and mediate vasodilation through production of nitric oxide and prostacyclin. There are three ERAs—bosentan, ambrisentan, and macitentan—that have been studied for the treatment of RP. The most frequent side effects include liver enzyme elevation and edema [48].

I. Bosentan—Bosentan is a dual ERA. In observational studies, bosentan has been shown to decrease frequency, duration, and severity of RP attacks [49–52]. However, in a small randomized double-blind placebo controlled trial of bosentan titrated to a dose of 125mg twice daily, bosentan did not decrease the frequency, duration, pain, or severity of RP attacks [53]. Others have also not shown any improvements from baseline in the RCS, despite improvements in laser Doppler blood flow [54].

The use of bosentan for the prevention of digital ulcers in RP associated with scleroderma has also been evaluated in the RAPIDS (Randomized Placebo-controlled study on Prevention of Ischemic Digital ulcers in Scleroderma) 1 & 2 studies. In RAPIDS-1, 122 patients with scleroderma were randomized to receive either placebo or bosentan, which was titrated to a dose of 125mg twice daily by the end of week 4 [55]. Among patients in the bosentan group, there was a reduced number of new ulcers, with a mean of 1.4 new ulcers per patient in the treatment group, compared with 2.7 ulcers per patient among those receiving placebo ($P = 0.0083$). As the bosentan treated group had a significantly lower number of digital ulcers at baseline, perhaps reflecting less severe vascular involvement, a separate subgroup analysis was performed for patients who had digital ulcers at baseline in both groups. In this subgroup analysis, bosentan-treated individuals had an average of 1.8 new ulcers per patient during the course of the study compared with 3.6 ulcers per patient in the placebo group, a reduction of 50% ($P = 0.0075$). RAPIDS-2 was designed to evaluate time to healing of digital ulcers present at baseline, and to confirm the reduction in new ulcers found in RAPIDS-1 [56]. In this placebo-controlled trial, patients receiving bosentan had a 30% reduction in the occurrence of new digital ulcers compared with placebo ($P = 0.035$). There were no differences in the time to healing of the cardinal ulcer between the two groups.

In our practice, we use bosentan for the prevention of digital ulcers only in patients with scleroderma after failure of oral vasodilator therapy or as an alternative to IV prostacyclin. In resistant case we use combination therapy with both vasodilator agents and bosentan.

II. Ambrisentan—Ambrisentan selectively blocks the vasoconstrictive effect of ET_A receptor stimulation, while allowing the vasodilatory ET_B receptor to be unopposed. In a prospective, open label, observational study of 16 patients, Ambrisentan significantly decreased digital ulcer burden and mean maximum diameter of lesions as compared to baseline [57]. Ambrisentan did not, however, seem to prevent new ulcer formation in this study. In a randomized, double-blind, placebo-controlled study of the effect of ambrisentan on blood flow measured by LDI, there was no improvement by the end of the 12 week study in mean microvascular blood flow compared to placebo, indicating no demonstrable vasodilatory effect of ambrisentan [58]. Interestingly, there was a significant improvement in the S-HAQ score and the RCS despite no objective improvements in blood flow by LDI.

III. Macitentan—Macitentan is an ERA that has slower receptor dissociation kinetics than bosentan and ambrisentan, and is thought to block fluctuating ET-1 induced signaling more effectively [59]. In two international, randomized, double-blind placebo-controlled trials (DUAL-1 and DUAL-2), a total of 554 patients with scleroderma and at least one visible, active ischemic digital ulcer were randomized to received either 3mg or 10mg of macitentan or placebo [60]. The primary endpoint was the cumulative number of new digital ulcers from baseline at the end of 16 weeks of therapy. There was no difference between each treatment group versus placebo groups. There were also no improvements in secondary endpoints, which included the Health Assessment Questionnaire-Disability Index [HAQ-DI], Hand Disability in Systemic Sclerosis-Digital Ulcers [HDISS-DU] scores, Scleroderma Health Assessment Questionnaire visual analog scores [SHAQ-VAS] for overall global

assessment of disease and for activity limitations due to digital ulcers and to RP, and digital ulcer burden. These results do not support the use of macitentan for treatment or prevention of digital ulcers in scleroderma.

Combination Therapy

Bosentan has now been studied in combination with IV iloprost. In an open label prospective study of twenty-six patients with severe secondary RP who had received cyclic IV iloprost for 2 years, 13 patients were additionally given bosentan 125mg twice daily due to the appearance of ischemic digital ulcerations. Patients were followed for three years, and those treated with IV iloprost and oral bosentan were found to have increased peripheral blood flow by LDF and increased capillary density when compared to baseline and to the iloprost only group [61]. Patient reported outcomes were not obtained to determine the clinical relevance of the increased peripheral blood flow. We will add bosentan in patients with scleroderma with recurrent digital ulcers already on IV prostacyclin therapy, given benefits in preventing new digital ulcers that have been previously been shown with bosentan therapy [56].

Procedures and Surgeries

Botulinum Toxin (BTX) Hand Injections

In an open label study of BTX injections given to the non-dominant hands of 20 patients with scleroderma, 80% of patients reported an overall improvement in their symptoms by VAS at 8 weeks in the injected hand, though results did not reach statistical significance [62]. However, objectively, 90% showed an improvement in pinch grip and 65% an improvement in power grip. A randomized double-blind placebo-controlled trial of BTX injections in 40 patients with scleroderma actually showed a decrease in blood flow in BTX injected hands compared with placebo injected hands at one month with no changes seen between groups at 4 months [63]. Despite a decrease in blood flow in the BTX treated hand, there were modest but non-statistically significant improvements in clinical measures, which included the RCS, pain VAS, McCabe Cold Sensitivity Score, and Quick Disabilities Arm Shoulder Hand (DASH) scale. In a planned subgroup analysis, negative trends in LDI acquired blood flow were driven by patients with diffuse cutaneous scleroderma or a longer disease duration, suggesting that there may be subgroups of patients that are less likely to benefit from treatment than others. Further clinical trials, which include other RP populations and/or use different BTX doses, need to be performed to define the subgroup (s) most likely to benefit from this procedure.

Sympathectomy

Long-term retrospective follow-up of 35 patients with primary or secondary RP who underwent thoracoscopic sympathectomy targeting the thoracic sympathetic chain revealed that while 77% of patients had an excellent or satisfactory response to surgery, 60% had experienced recurrence of symptoms at a median follow-up time of 5 months (range 2 – 18 months) [64]. Adverse effects of the procedure in this series included compensatory sweating, dry hands, and in rare cases, Horner's syndrome. Another series of 25 patients with primary RP who underwent video thoracoscopic sympathectomy targeting the thoracic

sympathetic chain reported similar basal LDF and maximal refilling times after 1-minute occlusion when comparing to normal controls [65]. Patient severity scores diminished to 0 post-operatively, and only 28% increased to pre-operative values at 5-year follow-up. Recently, a small series of 9 patients with primary RP reported 100% satisfaction with surgical results at 1 month, however, at one year 89% reported no remaining effects of the sympathectomy [66]. A more distal digital periarterial sympathectomy can also be performed, in which a section of adventitia containing the sympathetic nerves over the vasculature of the affected digits is removed. This has been performed in cases of digital ischemic ulcers, with improvement in ulcers or complete healing seen in 28 of 42 digits in those with an underlying autoimmune disease at mean follow-up of 90 months [67]. Interestingly, over a third of patients express regret at having undergone a surgery to treat RP, even in the setting of digital ischemia [64,66]. An axillary block with liposomal bupivacaine is a less invasive option that has been shown to increase radial and ulnar diameter and improve QuickDASH (disability arm shoulder hand) scores at 30 days in patients with RP with digital ischemia [68].

We reserve referral for digital sympathectomy for patients with critical digital ischemia who have failed medical management with oral vasodilators and intravenous prostacyclins. Patients should be counseled on the adverse side effects and likelihood of recurrence of symptoms. We prefer digital sympathectomy as our initial approach; however, others may perform a thoracic sympathectomy or axillary block first. Choice of procedure will often depend upon the available expertise at each individual institution.

Our Approach to Pharmacologic Management

We first assess the severity of RP by asking each patient the level of pain they experience with attacks, the frequency of attacks, and the duration of attacks. We counsel all patients regarding the importance of maintaining a warm core and peripheral body temperature and avoiding emotional stress, as this is a fundamental aspect of the successful management of RP in every patient [5]. In patients who experience moderate to severe RP in whom conservative management has failed, or in patients with evidence of digital pitting (an indicator of digital ischemia) or ulcerations, we initiate treatment with a CCB. We have found that even low doses (2.5mg of amlodipine daily) can improve symptoms in patients with borderline low blood pressures. If patients continue to experience moderate to severe RP symptoms, we will add an additional oral vasodilator, typically a PDE5i such as sildenafil, after maximizing the dose of CCBs. In patients with persistent digital ischemia or symptoms, we will start intravenous prostacyclin therapy. If patients continue to experience digital ischemia on a CCB, PDE5i, and an intravenous prostacyclin, we will consider BTX injection or a digital sympathectomy. In situations of critical digital ischemia we rapidly institute CCB and concurrently start intravenous prostacyclins. We will quickly progress to digital sympathectomy pending on clinical response in medical therapy, in an effort to prevent digital loss. We firmly believe that each patient requires a tailored approach, which depends on serial examinations and timely institution of therapies that balances the risks with the benefits.

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•• Of major importance

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Figure 1. Our treatment approach for Raynaud's phenomenon with or without digital ischemia

Figure 1. Our management approach. We start with calcium channel blockers, and add a phosphodiesterase 5 inhibitor for refractory RP symptoms or digital ulcers. If patients continue to have an inadequate response, we will add intravenous prostacyclins and ultimately consider sympathectomy. In situations of critical digital ischemia in which there is imminent threat of digit loss, we will proceed straight to the addition of intravenous prostacyclins onto therapy with calcium channel blockers and will consider digital sympathectomy. In cases of chronic, recurrent, digit ulcers despite prostacyclins therapy, we will add bosentan. *Botulinum toxin injection may also be considered.

Table 2. Outcomes of randomized controlled trials over the last 10 years evaluating effects of treatment versus placebo on digital ulcers

	Author & Year	No. 1°/2°	Dose	Clinical Outcomes*					
				DU Pain VAS	DU Burden	DU Healing Time	New DU	Patient Global VAS	Physician Global VAS
Sildenafil	Hachulla et al. 2016 [27]	0/84	20mg TID x 12 wks.	NS	↓*	NS			
Tadalafil	Shenoy et al. 2010 [30]	0/24	20mg QOD x 6 wks				↓**	↓**	
Treprostinil	Seibold et al. 2011 [43]	0/148	titration up to 16mg BID x 20wks		NS				↓*
Bosentan	Matucci-Cerinic et al. 2011 [56]	0/188	62.5mg BID x 4 wks. then 125mg BID x 20 wks.		NS	NS	↓*		
Macitentan									
DUAL-1		0/289	3mg or 10mg daily x 16 wks.	NS§	NS§		NS§	NS§	NS§
DUAL-2	Khanna et al. 2016 [60]	0/265		NS§	NS§		NS§	NS§	NS§

NS = non-significant difference between treatment and placebo;

* denotes p 0.05;

** denotes p 0.005;

blank means not done

§ indicates comparisons between 3mg vs. placebo and 10mg vs. placebo

⚡ For clinical outcomes, a decrease indicates a positive effect of the treatment