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Scleroderma (D Khanna, Section Editor)

Management of Raynaud's Phenomenon and Digital Ulcers

Fredrick M. Wigley, MD[1]
Ariane L. Herrick, MD, FRCP[2,*]

Address
[1]Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, USA
[*,2]Centre for Musculoskeletal Research, Institute of Inflammation and Repair, Salford Royal NHS Foundation Trust, The University of Manchester, Manchester Academic Health Science Centre, Manchester, M6 8HD, UK
Email: ariane.herrick@manchester.ac.uk

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Abstract

This review describes the principles of approach to, and management of, the patient with Raynaud's phenomenon (RP). The first step is to establish whether RP is primary or secondary to an underlying cause. If RP is secondary, then this has implications for management: the cause may be treatable, and the RP is likely to be more severe than primary RP. If RP is secondary to systemic sclerosis (the type of RP which has been most researched), then the patient will have structural as well as functional vascular changes which may progress to digital ulceration and critical ischemia. Triggering factors should be avoided, and therefore, patient education is an important part of management. The approach to drug treatment is described for patients with mild, moderate and severe RP (severe meaning complicated by the development of digital ulcers or critical ischemia). Surgical interventions are briefly described, bearing in mind that only a minority of patients require surgery. The final section of the review discusses novel (possible future) therapies.

Opinion statement

Raynaud's phenomenon (RP) is the clinical manifestation of disrupted regulation of the peripheral vasculature that is critical for tissue nutrition and body thermoregulation. While not all patients develop ulceration or critical ischemia, managing RP is most important to improve quality of life (QOL) and prevent secondary complications. Non-drug therapy should be used in every case including cold avoidance, elimination of

smoking, stopping aggravating drugs and providing support and education to reduce stress. Drug therapy is helpful to improve QOL and prevent secondary complications, but ideal studies are lacking to provide solid evidence for best options. We prefer calcium channel blockers alone for moderate cases and prostaglandins for severe RP. Combination therapy such as a calcium channel blocker and a phosphodiesterase type 5 (PDE5) inhibitor appears helpful in complex cases. While botulinum toxin (Botox) injections are becoming popular, studies are needed to provide evidence for this approach. Patients with systemic sclerosis (SSc; scleroderma) and secondary digital ulcers or those with critical ischemia require more intense therapy with both vasodilation therapy and agents that have the potential to prevent further vascular insult. This is an area in need of further study, but the use of intermittent prostacyclin, antiplatelet therapy, or use of an endothelin receptor antagonist are current options. Digital sympathectomy may provide benefit (but which may only be transient) for critical ischemia. Macrovascular disease can coexist with SSc-related microangiopathy, and comorbid conditions need to be addressed with surgical correction of occlusive disease if feasible. There is a need for new agents that directly target the disease process.

Introduction

When confronted with a patient with Raynaud's phenomenon (RP) (with or without systemic sclerosis [SSc], also termed 'scleroderma'), there are several principles to consider when designing therapy. These principles will help guide decisions on the exact non-drug and drug intervention that is needed. They can also give insight into how likely it is that the therapy will help improve the clinical situation. The basic goal is not to eliminate every Raynaud's event, but it is to improve quality of life (QOL) and to prevent critical ischemic events that can cause digital ulcers or digital loss. It is also probably true that improving digital blood may have some benefit for local tissue and bone health; good tissue oxygenation may reduce factors provoked by hypoxia that mediate tissue fibrosis, calcinosis and osteolysis. There is also the idea that RP is the manifestation of a systemic vascular disease. Therefore, good control of RP may have a generalised systemic benefit.

First, it is important to recognise that thermoregulatory vessels and the vessels providing nutritional blood flow have independent and distinct roles in the cutaneous circulation [1, 2]. The thermoregulatory are arteriovenous (A–V) shunts that are densely distributed on non-hair glabrous skin such as the palmar surface of the fingers and hands [3]. These vessels react to various ambient temperatures or the local temperature of objects touching the surface of the skin via regulation from the sympathetic adrenergic system [4]. Body core temperature is normally maintained by rapid shifts of blood in the skin via these thermoregulatory vessels and small arterioles that also supply nutritional flow to skin capillaries [5]. Warm temperatures cause increased flow by dilation of skin vessels via the release of neuropeptides from sensory nerves in the skin; a skin blush and a loss of heat from skin arterioles occur [6]. Conversely, cold induces a decrease in flow to the surface of the skin due to vasoconstriction of the A–V shunts via increase sympathetic tone, thus shunting blood centrally and conserving body heat. Clinically this appears as pallor (no flow) or cyanosis (reduced flow with venous dilatation) of the skin. Nutritional flow is maintained during cold exposure through skin arterioles and capillaries that are linked to the thermoregulatory A–V shunts, but protected from sympathetic vasoconstriction. Because the specialised thermoregulatory shunts react to cold but the nutritional vessels do not vasoconstrict during usual daily cold temperature challenges, nutritional flow is not compromised unless cold exposure is extreme. Patients with primary RP have an exaggerated response to cold but maintain enough nutritional flow, thus avoiding critical ischemic events.

Often, patients with primary RP will have dramatic skin colour changes (e.g. deep cyanosis), yet never get digital lesions. This is because nutritional flow is maintained and the cyanosis is in part due to venous dilatation. Patients with secondary RP (e.g. SSc) have structural disease in the microcirculation including the nutritional arterioles and capillaries. In some cases, significant peripheral

macrovascular disease also exists that compromises peripheral blood flow. This combination of structural disease and abnormal thermoregulation increases the risk of critical ischemia and significant morbidity. Thus, RP in patients with SSc is not caused solely by abnormal vasoreactivity and vasospasm but is associated with a fibro-proliferative vasculopathy. This means that the vascular lumen of the involved vessels is compromised altering normal resting blood flow. This "mechanical defect" can be demonstrated in a warm environment when a loss of reactive hyperemia is seen following tourniquet occlusion of forearm blood flow [7]. Endothelial dysfunction is also present that not only mediates vasospasm but also increases the risk of vascular occlusion via platelet activation and abnormal fibrinolysis [8]. Therefore, one must recognise that vasodilator therapy alone will have its limitations in treating SSc-related vascular disease and digital ischemia.

Another key principle is that the environment (physical and emotional) has a huge impact on the severity of RP. This is due to the fact that the thermoregulatory system in the skin is provoked by the adrenergic nervous system. Patients have fewer Raynaud's attacks and improved QOL after they understand why RP is happening and how to avoid the various triggers for a Raynaud's attack. The ambient temperature in the area of the patient's daily environment needs to be controlled in that shifting temperatures (moving into air-conditioning or sitting in a cool breeze) is a major trigger for RP. Interestingly, acclimatisation to a cold environmental situation can occur. This response is influenced by adjustment to the cold and emotional stress adjustment. A laboratory-based study, using the same cold challenge on serial visits, found that provoking RP became harder as the patient adjusted to the study environment [9]. Every patient with RP needs to learn and use non-drug strategy to reduce RP intensity (Fig. 1). When a patient has a critical ischemic event such as a new digital ulcer or demarcated finger, then they need to go to a controlled environment with an ideal warm ambient temperature and reduce hand and body activity.

Not all patients with SSc will have critical ischemic events. Digital ulcers occur in 15–50 % of patients with SSc, and deeper tissue injury causing digital loss occurs in a smaller subset of patients [10]. While all patients with SSc should be considered at risk, certain subsets of patients are at greater risk for severe ischemic events which can lead to digital amputation. The patients at greatest risk of digital loss are those with limited SSc and anticentromere antibodies [11]. However, recurrent ischemic digital ulcers are more likely to occur in patients with diffuse skin disease [10]. Patients with antitopoisomerase antibodies may have a younger age of onset of digital ulcers compared to those with anticentromere antibodies and a shorter time interval between onset of RP and the first digital ulcer [12]. Interestingly, patients will be consistent over time and seem to follow a pattern of either no ischemic ulcers or one of recurring lesions. A patient with no history of digital lesions but symptomatic RP can be treated with a conservative programme of non-drug strategy and a

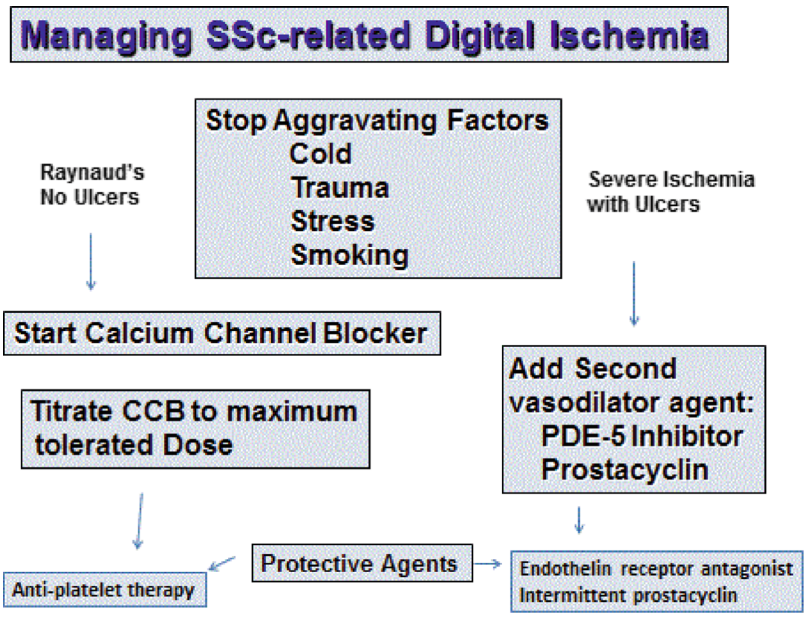

Fig. 1. Flow chart—managing SSc-related digital ischaemia.

modest dose of a vasodilator alone (Fig. 1). The goal in this case is to improve quality of life.

Comorbid conditions and factors compromising peripheral blood flow can influence the response to therapy for RP and increase the risk for digital ischemic lesions. Smoking, diabetes, hypertension and hyperlipidemia can increase the risk of larger vessel arterial sclerosis that can complicate digital blood flow, particularly in the lower extremity. Patients with SSc who are current smokers have an increased severity of Raynaud's [13, 14], and in our experience, the healing of digital ulcers is delayed in the setting of smoking. A metabolic disorder like hypothyroidism may cause cold hands or RP. A peripheral neuropathy such as a carpal tunnel syndrome can aggravate or associate with RP. The use of vasoconstrictors needs to be avoided. For example, dextroamphetamine/amphetamine used for attention deficit hyperactivity disorder (ADHD) can cause or aggravate RP [15]. An untreated anxiety disorder is likely to make RP worse, while the use of a selective serotonin reuptake inhibitor (SSRI) can reduce anxiety and improve RP [16]. Serotonin is known to be a vasoconstrictor when engaging its receptor. The use of beta blockers is unlikely to have a negative impact on RP and can be used if needed for underlying cardiovascular disease. Being aware and treating aggravating factors in every patient with RP is most important.

It is also important to recognise that not all digital lesions are secondary to critical ischemia and therefore may not respond to vasodilator therapy. For example, dry skin and painful fissures are often confused with ischemic ulcers. Traumatic lesions can occur, particularly in areas of severe skin fibrosis or secondary skin atrophy over joint contractures. Subcutaneous calcium can rupture through the skin and mimic a digital ischemic ulcer. These lesions are unlikely to recover with treatment of RP alone.

In summary, designing a treatment plan for a patient with RP should then take into account several factors that required careful assessment.

1. Determine the underlying cause of RP. Is it primary RP or secondary RP, and if secondary, is it correctable?
2. Determine the severity of the RP. Is there any impact on QOL? Is there a history of digital ulcers or ischemic events?
3. Educate the patient about RP and avoid the known triggers for their events. What degree of stress or emotional disturbance is aggravating RP?
4. Determine if there are comorbid conditions or factors that are correctable. What degree of macrovascular disease is present?
5. Recognise that patients with SSc have a complex peripheral vascular disease and both vasospasm and structure disease is present. Therefore, treatment should include a combination therapy that addresses RP and a strategy to prevent vessel damage and occlusion.

Drug and surgical treatment

Mild RP (RP which has not progressed to digital ulceration or critical ischemia)

Calcium channel blockers

Drug treatment is required when general (non-drug) measures are insufficient to control symptoms. Most clinicians agree that calcium channel blockers are first line. A recent Cochrane review of calcium channel blockers for primary RP [17••] concluded that the seven randomised trials which included 296 participants, provided moderate-quality evidence that calcium channel blockers were 'minimally effective', as measured by frequency of attacks (1.72 [95 % confidence intervals 0.60 to 2.84] fewer attacks per week on calcium channel blockers compared to placebo). A limitation of the review was the small sample sizes of the included studies [17••]. Earlier meta-analyses had also concluded that calcium channel blockers conferred benefit in primary RP [18] and also in SSc-associated RP [19]. Although small sample sizes limit conclusions, it is worth emphasising that the evidence base

for most other vasoactive therapies for RP is even weaker, reflecting the difficulties in mounting clinical trials of treatment in RP. These difficulties include the need to run trials over the winter months when RP is most troublesome, the heterogeneity of RP and the limitations of current outcome measures for RP. Other recent reviews of drug treatment for primary [20] and secondary RP [21] again highlight the need for more high-quality clinical trials. A disadvantage of calcium channel blockers is that many patients experience side effects, mainly vasodilatory including headaches, flushing and oedema. Therefore, patients may tolerate only low doses or have to discontinue treatment altogether. In our experience, sustained release preparations are better tolerated than short-acting ones, and an important principle is to begin at low dose and gradually increase. Options include sustained release nifedipine, commencing at a dose of 10 mg bd and gradually increasing if tolerated and indicated up 40 mg bd, or amlodipine 5 mg daily, increasing if tolerated and indicated to 10 mg daily.

Blocking the renin-angiotensin system

Angiotensin II receptor blockers are favoured by some clinicians. Although there is a good theoretical rationale for their use, the evidence base is weak (only one open-label randomised clinical trial [22]). Angiotensin converting enzyme (ACE) inhibitors are seldom used for RP: the minimal evidence base examining their use is conflicting, and the largest study which was of quinapril (210 patients with either limited cutaneous SSc or with SSc-specific autoantibodies) reported no benefit in terms of either RP attacks or digital ulcers [23].

Topical nitrates

Currently, these are seldom used. When administered (for example by patch) for their systemic effect, then they are associated with a high frequency of vasodilatory side effects [24]. Applying nitrates locally to the fingers in low dose (to obviate systemic side effects) is an attractive option, and a study of a novel topical formulation (MQX-503) demonstrated benefit in both primary and SSc-related RP [25]. However, at present, there is no commercially available preparation for application to the fingers.

Phosphodiesterase type 5 (PDE 5) inhibitors

Up to now, these have tended to be reserved for use in patients with severe RP, as discussed below. However, it seems likely that they will be used increasingly for milder RP and that PDE5 inhibitors will become 'second line' after calcium channel blockers, at least in SSc-related RP, as suggested by surveys which canvassed opinion from clinicians with an interest in SSc [26]. Initial studies gave conflicting results, but three recent controlled trials have all suggested that PDE5 inhibitors confer benefit [27, 28, 29••], and a very recent study suggested that udenafil 100 mg/day has comparable efficacy to amlodipine 10 mg/day in improving RP attacks [30]. A recent meta-analysis suggested that PDE5 inhibitors improve Raynaud's Condition Score and reduce frequency and duration of RP attacks in patients with

secondary RP [31]. Randomised controlled trials of PDE5 inhibitors have so far been of only a 6-week duration or less [32], and ideally longer term studies are required.

Selective serotonin reuptake inhibitors (SSRI)

Some clinicians prescribe these especially in patients who are prone to vasodilatory side effects and who are intolerant of other vasodilators. As with many other drugs used in RP, the evidence base is weak, with only one randomised trial which was open label [16].

Other drugs

There are many other vasoactive drugs (e.g. adrenergic receptor antagonists; pentoxifylline) that have been used for RP but are no longer popular either due to side effects or lack of efficacy.

Moderate RP

By 'moderate' we mean RP which severely impacts on lifestyle but which has not progressed to digital ulceration or critical ischaemia. Patients with moderate RP may have an inadequate response to single therapy treatment, for example with a calcium channel blocker or PDE5 inhibitor. For these patients, combination therapy should be tried, although it must be emphasised that there are no controlled clinical trials of combinations. Adding a PDE5 inhibitor (or an angiotensin II receptor blocker) to a calcium channel blocker may be tried although the propensity to side effects, especially vasodilatory, will be increased in patients on combinations.

Severe SSc-related RP with digital ischemic ulcers

Patients who have progressed to digital ulcers (Fig. 2a) require more aggressive therapy. A key point in management is early intervention: patients should be instructed to report ulcers early so that

a. Vasodilator therapy can be maximised (depending on severity, this may involve admission for intravenous vasodilator therapy),
b. Antibiotics may be prescribed if there is any question of secondary infection, which could progress to osteomyelitis if left untreated,
c. Adequate analgesia may be prescribed: digital ulcers can be extremely painful, for example keeping patients awake at night,
d. A surgical opinion may be sought if necessary.

As with treatment of mild and moderate RP, the evidence base for the treatment of SSc-related digital ulceration is relatively weak, with most studies of a small sample size. A meta-analysis has recently been conducted by Tingey et al. [33••]. The European League Against Rheumatism (EULAR) treatment recommendations also outline the evidence base for SSc-related digital vasculopathy [34].

Oral vasodilator therapy

Maximising oral vasodilator therapy may be all that is necessary for minor ulcers, as long as it is emphasised to the patient that s/he must report

immediately if symptoms progress. In patients with severe ulcers requiring admission to hospital, oral vasodilator therapy should be reviewed (and maximised) at the time of discharge from hospital.

Intravenous prostanoid therapy

This is a current 'gold standard' therapy for patients with severe RP which has progressed to digital ulceration. Intravenous (IV) iloprost is most commonly prescribed. A Cochrane review [35] concluded that IV iloprost was effective in digital ulcer healing and ulcer prevention and also in reducing frequency and severity of RP attacks. IV iloprost is used in some centres in patients with severe RP even in the absence of digital ulceration. The availability of IV prostanoid therapy and the exact protocol used vary very substantially between countries. The authors both use the protocol found to be effective in a randomised controlled trial of 131 patients [36]: 5 days of 0.5 to 2.0 ng/kg per minute for 6 h. IV iloprost can be used both in the emergency situation (when a patient presents with a new painful ulcer, with or without critical ischemia) and in the non-urgent setting of a patient with severe RP and less acute ulceration which is proving refractory to other therapies.

Endothelin receptor antagonists

The dual endothelin-1 receptor antagonist bosentan is licenced for the prevention of digital ulcers in patients with SSc and recurrent digital ulcers. Two randomised, double-blind placebo-controlled clinical trials [37, 38] both showed that bosentan reduced the number of new ulcers in patients with SSc and that this effect is most marked in those with multiple ulcers. The more recent RAPIDS-2 study [38] included 188 patients who had at least one digital ulcer at baseline: the treatment period was 24 weeks. A number of observational studies have also been published including a recent one from France [39] which highlighted how patients who smoke tend to have the most severe digital ulcer disease. In the RAPIDS-2 study [38], the number of new digital ulcers was not reduced in current smokers.Studies of other endothelin receptor antagonists (ERA) are limited. A recent trial of macitentan was discontinued, and data is not yet available.

Botulinum toxin

Injections of botulinun toxin are being increasingly used in the treatment of severe RP: a number of small series report good response in patients with severe digital ischemia, including in patients with SSc [40, 41]. The mechanism of action is unclear, and a randomised controlled trial is required. Rajendram and Hayward [42] suggest that injecting the botulinum toxin under ultrasound guidance may improve toxin delivery and reduce the risk of complications.

Surgery

There have been no randomised trials of any form of surgery for refractory digital ulceration in patients with SSc-related digital ulcers [43]. The aim of

surgery is to prevent or minimise tissue damage, preserve hand function and improve quality of life. A number of different procedures have been advocated [43], but the one most commonly performed is probably surgical debridement of necrotic tissue, although this will vary between centres. In recent years, there has been increasing interest in digital (palmar) sympathectomy [44, 45], a highly specialist procedure which should be considered in patients with severe digital ulcers and/or critical ischemia.

Severe SSc-related RP with critical digital ischemia

A minority of patients is unresponsive to the treatments outlined above and progress to critical digital ischemia (Fig. 2b): a study of 1168 patients with SSc [10] followed at a single centre over 18 months reported development of critical digital ischemia in 1.6 % (gangrene in 1.4 %). The rarity of critical ischemia makes clinical trials virtually impossible, and there is therefore no good evidence base to guide treatment. Although there have been no randomised controlled trials of treatment of critical ischemia in patients with SSc, key aspects of management are believed to be as follows:

1. Patient education, asking patients to report early if a finger or toe becomes permanently discoloured (before tissue injury is irreversible).
2. Ensuring that there is no contributory cause requiring specific intervention, for example proximal large vessel disease or vasculitis.
3. Maximising oral vasodilator therapy or intravenous prostanoid therapy.
4. Digital sympathectomy. This should be considered for critical ischemia as for refractory digital ulcers.
5. Reconstruction of larger vessel disease. For reasons unknown, the ulnar artery is commonly involved in SSc. The clinician should therefore have a low threshold for arranging arterial Dopplers in patients with finger ulcers or critical ischemia. If the ulnar or other large artery is involved, then this may be amenable to reconstruction.

'Other therapies' to prevent RP or progression of digital vasculopathy

Ideally, what is required is a treatment which will prevent progression of digital vasculopathy, reducing RP attacks and preventing progression to ulcers and digital ischemia. However, there is no good evidence base for prevention. Treatments which theoretically may prevent disease progression, and which deserve further research, include the following:

1. Antiplatelet therapy. Platelet activation is well recognised in SSc and may contribute to digital vascular disease. For this reason, many clinicians prescribe aspirin, clopidogrel or dipyridamole.
2. Statins. These may confer benefit in digital vasculopathy for a number of reasons, and one randomised trial of 84 patients with SSc suggested benefit from atorvastatin 40 mg/day [46]. However, further studies are required.
3. Endothelin receptor antagonists. As above, these are licenced for the prevention of recurrent SSc-related digital ulcers.

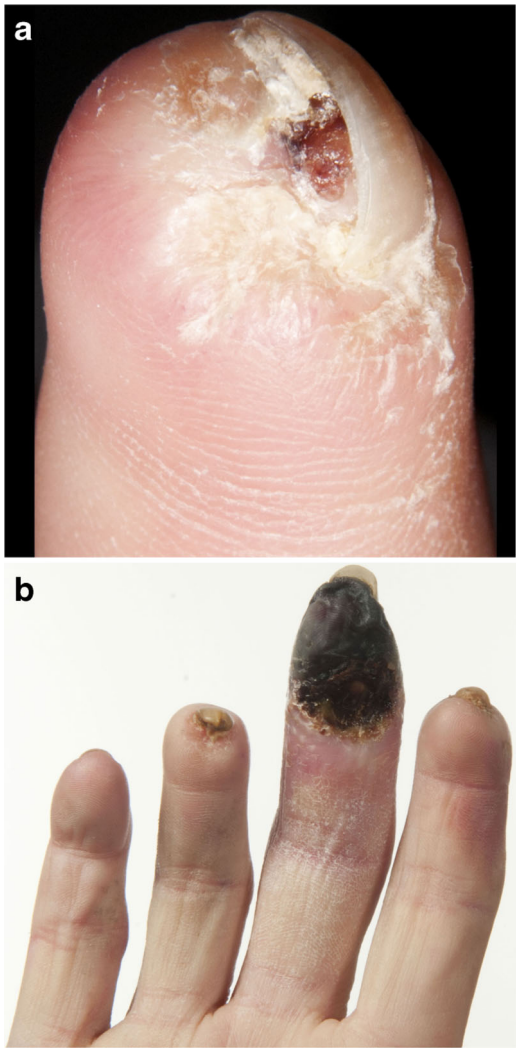

Fig. 2. a Digital ulceration and **b** critical ischemia in patients with SSc. Copyright with Salford Royal NHS Foundation Trust.

4. Immunosuppression. This is not advocated for SSc-related digital vasculopathy which is primarily non-inflammatory. It is possible that this approach could change in the future, as more becomes known about the early stages of the disease.
5. Antioxidants. Oxidant stress may drive SSc-related digital vasculopathy [47], leading some investigators to advocate antioxidant therapy, for example *N*-acetylcysteine [48]. Again, clinical trials are required.

Novel (Possible Future) Therapies

Understanding of the pathophysiology of RP has increased in recent years, underpinning the number of new avenues of therapy currently being researched.

Nitric oxide (NO) is a major vasodilator released by the endothelium. An agent that enhances the release of NO or works in synergy with it has the

potential to be helpful in treating RP. Soluble guanylate cyclase (sGC) is a key enzyme of the NO signalling pathway. The enzyme catalyses synthesis of the second messenger cyclic guanosine monophosphate (cGMP); cGMP generates vasorelaxation and inhibition of proliferation of smooth muscle cells, leukocyte recruitment, and platelet aggregation [49]. Riociguat is the first-in-class of a new group of compounds, sGC stimulators. Riociguat directly stimulates sGC, thereby increasing levels of the signalling molecule cGMP. Riociguat enhances the activity of sGC in vitro by up to 73-fold and acts in synergy with NO to increase the sGC activity up to 122-fold [50]. Two key features of riociguat include the following: (1) it directly stimulates sGC independently of NO and (2) it sensitises sGC to low levels of NO. Riociguat is considered a novel and valuable extension of treatment options in pulmonary arterial hypertension (PAH) class 1, functional classes II and III, especially for combination therapy with ERA, and a first approved therapy for non-operable chronic thromboembolic pulmonary hypertension (CTEPH) and sustained CTEPH after pulmonary endarterectomy [51••]. It therefore has the potential to help peripheral vascular disease including the abnormal vasoactivity of RP and the proliferative vasculopathy of SSc. Studies are now being proposed to study riociguat in RP and SSc.

Engagement of alpha-adrenergic receptors (AR) on smooth muscle of vessels in the skin mediates vasoconstriction. Cutaneous smooth muscle cells express alpha2A-ARs and alpha2C-ARs, but only alpha2C-ARs are selectively involved in cold-induced vasoconstriction [52]. OPC-28326 is a selective alpha-adrenergic antagonist with preferential binding to the alpha2C-adrenergic receptor (alpha2C-AR) subtype and was studied in patients with RP in a laboratory-based double-blind, placebo-controlled, randomised study [53]. While digital skin perfusion was improved with the drug, it was not further studied in an ambulatory setting to define its clinical role in treating RP. In a similar fashion laboratory study, another high-potency alpha2C-adrenoceptor antagonist ORM-12741 was studied in patients with RP secondary to SSc [54••]. There was a paradoxical worsening of measures of digital blood flow after cold exposure, possibly secondary to augmentation of sympathetic transmission due to the drug's inhibitory effects on pre-junctional alpha2C-ARs causing an increase in the release of local norepinephrine. While in concept it is attractive to consider that blocking alpha2C-AR would improve RP, the systemic effects make this approach challenging. This suggests that inhibiting pathways downstream of the alpha2C-AR may be more effective (e.g. Rho-kinase inhibitors).

The RhoA/Rho-kinase pathway is important in cold-induced vasoconstriction, the function of vascular smooth muscle cells and vascular homeostasis. Fasudil, a Rho-kinase inhibitor was studied in a laboratory-based cold challenge study [55]. There were no significant differences with respect to skin temperature recovery time and the digital blood flow after acute dosing of a low or high dose of fasudil. It is important to note that statins also inhibit the RhoA/Rho-kinase pathway, and as discussed above, these agents have shown some benefit in preventing digital ulcers in SSc. More studies of RhoA/Rho-kinase inhibitors are warranted.

Platelets are thought to play a role in the pathogenesis of RP and the vascular disease of SSc. The rationale is that platelet products can induce inflammation, vasoconstriction and tissue remodelling with fibrosis [56]. As discussed above, it makes sense to use antiplatelet therapy in patients with RP and SSc, but there are too few studies to define ideal therapy. Inhibiting thromboxane (dazoxiben), inhibiting ADP signalling (clopidogrel, ticlodipine) or inhibiting

adenosine reuptake (dipyridamole) alone or in combination with aspirin have all been considered as approaches to therapy [56]. Largely negative trials of antiplatelet drug use in managing RP including ticlopidine [57] and thromboxane synthetase inhibitors [58–61] are reported. However, studies to date have not only been few in number but also small in size, and ideal dosing may not have been achieved. Likewise, studies using anticoagulation or antifibrinolytic therapy are not adequate to define options. A study of low molecular weight heparin suggested some benefit in severe RP [62]. Another study showed that 600 mg of aspirin potentiated the acetylcholine-evoked dilator responses in patients with RP [63]. The use of a low-dose aspirin is recommended in patients with complicated RP such as those with severe RP in SSc despite the lack of good data to support this. However, the risk and benefit of aspirin may be considered to be favourable for treating digital ulcers in SSc.

Several other novel therapies have been investigated that may provide new avenues of treatment for RP and/or digital ischemic lesions including low-dose light therapy [64], potassium channel inhibitors [65], oral or inhaled prostacyclin [66] or injectable cell-based therapy [67••].

Conclusions

The management of RP presents many challenges, especially in those patients with severe RP (for example those with SSc) who progress to digital ulceration or critical ischemia. The clinician should always look for an underlying cause, for example proximal vessel disease, requiring specific treatment. For those patients requiring drug treatment, there are many different options, although the evidence base for most treatments is weak. First-line treatment is with a calcium channel blocker. Combination therapies (for example a calcium channel blocker and phosphodiesterase inhibitor) may be helpful in complex cases. For patients who progress to digital ulceration or critical ischemia, other options include intravenous prostanoid therapy, an endothelin receptor antagonist, botulinum toxin injections and digital sympathectomy. A number of novel therapies are currently being researched: what are required are therapies which directly target the underlying disease process.

Compliance With Ethics Guidelines

Conflict of Interest

Fredrick M Wigley has received research support from Kinemed, Medimmune, Novartis, United Therapeutics, CSLBehring, Actelion Pharmaceutical and Eiger Biopharmaceuticals. He has also received consultancy fees from Novartis, United Therapeutics and Eiger Biopharmaceuticals.

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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