Complex Raynaud's phenomenon: evolving concepts of management

Raynaud's phenomenon (RP) can occur as benign, usually primary, RP. By contrast, complex RP is mainly secondary and can be caused by severe, chronic diseases such as systemic sclerosis. This article mainly reviews treatment opportunities for secondary RP, but also refers to primary RP wherever evidence is at hand. The main focus is on drugs recommended by expert panels or research consortia, such as the European League Against Rheumatism Scleroderma Trials and Research (EUSTAR) group. In addition, this review intends to provide a comprehensive overview of the different therapeutic approaches that have been tested in RP to date, some with more impact versus others with less impact. Thereby, conclusions about the pathogenesis of RP can be drawn, which can guide future clinical trials and research.

KEYWORDS: botulinum toxin calcium channel blockers clinical trials digital ulcers endothelin-1 receptor antagonists management phosphodiesterase inhibitors prostanoids Raynaud's phenomenon systemic sclerosis

In 1862, Maurice Raynaud described a common condition termed 'local asphyxia of the extremities' [1-3]. Raynaud's phenomenon (RP) is characterized by digital ischemic vasospasms usually evoked by either exposure to low temperatures or emotional stress. Typically episodic and transient in nature, RP is easily distinguished from continuous acrocyanosis. Vasoconstriction of digital arteries, arterioles and cutaneous arteriovenous shunts consecutively leads to ischemic paleness of the fingers that can, but does not need to be, followed by cyanosis [1,4]. Attacks generally terminate, as described by most of the patients, with a painful reperfusion of vessels and capillaries, representing reactive hyperemia. White, blue and red colored fingers and toes are commonly referred to as 'tricolor phenomenon', but manifestation is not limited to the extremities as nose, ears and even the tongue, nipples and the penis can be affected [5-11].

Primary RP (PRP, old term: Raynaud's disease) without an identifiable, underlying cause is differentiated from secondary RP (SRP, old term: Raynaud's syndrome). Box 1 summarizes risk and associated factors of SRP.

For the clinician, especially the rheumatologist, the differentiation between PRP and SRP is of utmost importance as SRP, particularly RP related to systemic sclerosis (SSc), may lead to ulceration, infection, gangrene, or even autoamputation of fingers or toes. TABLE 1 provides a simplified comparison that guides the decisionmaking process of PRP versus SRP.

One of the key studies, which focused on the sequence from PRP to SSc-related RP, investigated 586 patients with RP, which were followed up for 3.197 person-years and a median follow-up period of 4 years [1]. In this study, 210 patients with PRP did not develop definite SSc during their follow-up, whereas autoantibodies and microvascular damage were independent predictive factors for the progression to SSc in patients with unclassified RP at baseline [1].

The comprehensible preliminary criteria of PRP are [5-11]:

- Typical vasospastic attacks precipitated by cold or emotional stress;
- Symmetric attacks involving both hands;
- Absence of tissue necrosis or gangrene;
- No history or physical findings suggestive of a secondary cause;
- Normal nailfold capillaries;
- Normal erythrocyte sedimentation rate;
- Negative serologic findings, particularly negative test for antinuclear antibodies.

RP should be diagnosed by assessing a detailed patient history (e.g., digital ulcers, photosensitivity, medication, occupational and family history) and further investigations, such as laboratory investigations and nailfold capillaroscopy [2,12]. In most cases, attacks rarely occur during a medical visit, therefore color charts or photographs of patients may be helpful to clarify whether the phenomenon is indicative for RP [2,8,13]. The basic laboratory profile should include at least a blood

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Box 1. Risk-associated and causative factors of Raynaud's phenomenon.

General

- Exposure to low temperatures
- Female gender
- Low BMI
- Low blood pressure
- Family history of Raynaud's phenomenon
- Older age

Autoimmune diseases

- Systemic sclerosis (e.g., spectrum)
- Mixed connective tissue disease
- Systemic lupus erythematosus
- Sjörgren's syndrome
- Dermatomyositis or polymyositis
- Undifferentiated connective tissue disease
- Rheumatoid arthritis
- Vasculitis (e.g., Takayasu arteritis, giant cell arteritis and thrombangiitis obliterans)
- Primary biliary cirrhosis

Vasospastic disorders

- Migraine or vascular headaches
- Prinzmetal angina

Neurologic disorders

- Neuritis
- Syringomyelia
- Spinal disc herniation

Malignant disease

- Ovarian carcinoma
- Angiocentric carcinoma
- Malignancies

Hematological disorders

- Thrombocytosis
- Cryoglobulinemia
- Cold agglutinine syndrome
- Polyneuropathy, organomegaly, endocrinopathy/edema, M-protein, skin abnormalities syndrome
- Cryofibrinogenemia

Infections

- Parvovirus B19
- *Helicobacter pylori* infection

Other conditions

- Trauma (e.g., use of vibrating tools and crutch pressure)
- Frost bite
- Thoracic outlet syndrome (e.g, scalenus anterior syndrome, cervical rib syndrome and costoclavicular syndrome)
- Diabetes mellitus
- Algodystrophic syndrome
- Carpal tunnel syndrome
- Peripheral arterial embolism
- Eripheral arterial embolism
- Hypothyroidism

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Box 1. Risk-associated and causative factors of Raynaud's phenomenon (cont.).
Medication, drugs & toxins
β blocker, clonidine
IFN-α or IFN-β
 Oral anticonception
Nose drops (e.g., oxymetazolin) or other sympathomimetic drugs
Chemotherapeutic agents (e.g., bleomycin, cisplatin, vinblastine and polyvinyl chloride)
Drugs (e.g., amphetamine, nicotine, cocaine and alcohol)
Heavy metals
 Alkaloids (e.g., ergots)
Trichloroethylene
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count, erythrocyte sedimentation rate, C-reactive protein and analyses of antinuclear antibodies, including its subsets [12]. A pathologic nailfold capillaroscopy has a good predictive value to differentiate between PRP and SRP [1]; FIGURE 1 shows normal and abnormal capillaroscopic findings [14]. If a patient fulfills the criteria of PRP and does not develop any signs or symptoms suggestive of SRP, or has abnormal laboratory results, a secondary cause of RP is highly unlikely [7].

Pathophysiology-targeted treatment approach

The physiological und pathophysiological mechanisms of microcirculation are complex and incompletely understood, but the impaired microcirculation still provides several potential new targets for therapeutic intervention (Figure 2).

In general, microcirculation can be considered as a constant interplay of vasodilation and vasoconstriction that is balanced in a healthy subject. However, in patients with RP, microcirculation is out of balance. To rebalance microcirculation, vasodilation or inhibition of vasoconstriction can be targeted, but individual responses may differ and over-reactions of the circulation commonly occur. Therefore, the respective drug-induced side effects need to be explained to the patients to facilitate the necessary compliance. There are various pathways and molecules that contribute to this process and consequently to endothelial damage, reduced blood flow or a procoagulant tendency [12]. To date, several algorithms of the treatment strategies for RP are discussed, which is reflected by continuous publications on that topic [12,15-17]. However, the algorithms generally refer to SRP rather than to PRP and suggest either an increase of treatment intensity, as symptoms progress over time [12], or they already discriminate between mild or more severe RP at the beginning [17]. Besides general, drug-independent measurements or the removal of an underlying

cause, medication for RP may include calcium channel blockers (CCB), angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors (ACEis), al-adrenergic antagonists (a1-blockers), selective serotonin reuptake inhibitors (SSRIs), phosphodiesterase type 5 inhibitors (PDE5is), formulations of topical nitroglycerin, intravenous (iv.) prostanoid therapy and endothelin-1 receptor antagonists (ERAs). This may be accompanied by anticoagulant therapy, analgesia, antibiotic therapy or surgical interventions, such as debridement, selective sympathectomy or local injections of botulinum toxin A [12,17]. FIGURE 3 provides a scheme of the currently suggested treatment algorithm for RP, which refers mainly to SSc-related RP. Of note, the majority of studies refer to SSc-related RP, not to PRP or other underlying conditions for RP. This inherits a strong bias of mainly two dimensions. First, the approaches used for SSc cannot in any case be translated to the whole spectrum of RP-associated syndromes and second, SSc is a multisystem disease with a wide range of comorbidities, for example, coexisting large vessel disease interferes strongly with the presence of difficult RP [18,19].

Accordingly, this review is divided into two major sections. First, treatment for RP with strong recommendations based on meta-analyses or randomized, controlled trials. This includes CCBs, iv. prostanoid therapy, ERAs and PDE5is. Second, alternative approaches with less evidence to provide a background for potential future therapies for RP or other therapies that have failed that therefore give deeper insight into RP pathophysiology.

Therapies with strong recommendations

Calcium channel blockers

In 2009, the European League Against Rheumatism (EULAR) and the EULAR Scleroderma Trials and Research (EUSTAR) group published

Table 1. Primary versus secondary Raynaud's phenomenon.		
Characteristics	Primary RP	Secondary RP
Associated disease	No	Yes
Age at onset	Younger (<30 years)	Older (>30 years)
Nailfold capillaries	Normal	Pathologic
Antinuclear autoantibodies	Usually negative	Frequent
Endothelial cell activation	Yes	Yes
Endothelial damage	No	Frequent
Structural occlusion	No	Yes
Large vessel disease	No	Common
Digital gangrene	Rare	Common
$\alpha 2$ adrenergic activity	High	High
RP: Raynaud's phenomenon. Adapted with permission from Elsevier [2].	

the first recommendations for the treatment of SSc. They include one section on SSc-related digital vasculopathy, defined by RP and digital ulcers. It was shown that dihydropyridine-type CCB, usually oral nifedipine, should be considered as first-line therapy [16]. In addition, CCBs are not only considered beneficial for SSc-related RP, but also for PRP [12]. Two meta-analyses demonstrate that CCBs have significant positive effects on the severity and the frequency of RP and provide evidence for these hypotheses [20,21].

With respect to PRP, the meta-analysis included 18 randomized, double-blinded and placebo-controlled studies, mostly crossover trials without an order effect analysis, from the year 1983 to 2000 with a total of 344 patients. After removal of two studies due to heterogeneity, the overall weighted mean difference (WMD) in the reduction of RP attacks was highly significant, favoring the treatment arm (-2.80; 95% CI: -3.90 to -1.70; p < 0.00001) [20]. However, the treatment effect was also positive with respect to symptom severity on a 10 cm visual analog scale (-1.39; 95% CI: -2.2 to -0.58; p = 0.0007), reflecting a 33% reduction in the severity of attacks [20].

In terms of SSc-related RP, the meta-analysis included only eight small randomized, placebocontrolled and double-blind studies with a total of 109 patients published between 1983 and 1999 [21]. Again, seven of the trials used a crossover design, but did not take an order effect into account. All of them studied nifedipine versus a placebo, except one that compared nifedipine with losartan, and another that crossed-over nifedipine with iv. iloprost [22,23]. Similarly, nifedipine reduced the frequency of ischemic attacks with a WMD of -8.31 (95% CI: -15.71 to -0.91; p = 0.03) and also improved the severity with a WMD of -0.69 (95% CI: -1.21 to -0.17; p = 0.01), which translates into a mean reduction of approximately eight attacks in 2 weeks and an improvement of severity of more than 35% [21]. Interestingly, the comparative study of nifedipine with iv. iloprost (n = 23) further documented the frequency and course of digital ulcers over a 16-week period and found a significant reduction compared with baseline in both groups, but not between groups [22]. Since the study was underpowered, the results have to be interpreted with care.

Both meta-analyses concluded that larger trials are needed with a parallel design, higher doses and longer durations, as the general tendency may favor CCB treatment for RP. However, several issues, mainly the rather moderate treatment effect is still a matter of discussion [20,21]. Therefore, many patients require higher doses to achieve the necessary effects. It is recommended to commence vasodilative drugs at low doses with a gradual increase of the dose if tolerated. Side effects such as headache, hypotension, tachycardia or edema are common, but mainly in the first 2 weeks of treatment as the circulation adjusts, which should be explained to the patients beforehand to increase compliance. Furthermore, sustained release and not short-acting preparations should be preferred [12]. Moreover, patients with SSc should be monitored for gastroesophageal reflux as CCBs may decrease the tonus of the lower esophageal sphincter [24]. The main function of CCBs is to block the flow of calcium ions to the cell by voltage-gated channels (mainly the L-type channel), thus leading to a relaxation of vascular smooth muscle cells and vasodilation. Though the L-type channels are not only expressed by vascular smooth muscle cells, but also in nonvascular tissues like cardiac, bronchial, gastrointestinal, genitourinary, uterine tissue or noncontractile tissues, such as pancreas, pituitary, adrenal, and salivary glands as well as on leukocytes and platelets, a respective effect is likely [25]. This led to the hypotheses that CCBs may interfere with growth and proliferation of vascular smooth muscle cells and fibroblasts [26,27]; T-cell function [28,29]; and platelet function [30,31], although the latter is discussed controversially because of the variety of chemical structures. One study reports that amlodipine is associated with an enhanced P-selectin expression [31], whereas a different study showed a dose-dependent inhibition of both collagenand ADP-induced platelet aggregation [30]. Until recently, only the vasodilative effect of CCBs was an accepted mechanism of action - further

functions that may be beneficial for RP remain an issue for future investigations.

Prostacyclin analogs

If CCBs do not sufficiently improve the frequency and severity of RP attacks, several second-line treatment options are available. However, the second-line treatment of RP is still controversial [12,15,17] and dependent on the licensing status in the respective country [12]. In this situation, angiotensin II receptor antagonists, ACEis, α 1-blockers, SSRIs or PDE5is are the usual suggested treatment options. As there are currently no studies that have examined the rationale of switching RP therapies, we will follow a different approach and discuss the current A-level recommendations for SSc-related vasculopathy in accordance with the EULAR/ EUSTAR guidelines [16]. Evidence is sufficient for CCBs, prostacyclin analogs, PDE5is (for treatment of RP) and ERAs (for prevention of digital ulcers but not treatment of RP).

The EULAR/EUSTAR recommendations state that prostacyclin analogs are not only capable of reducing the frequency and severity of SSc-RP attacks, but are also efficacious in healing digital ulcers [16]. The main evidence for this recommendation results from a meta-analysis regarding iloprost and cisaprost for RP in SSc, and two randomized controlled studies with a total of 166 patients [32]. In the largest study of iv. iloprost for SSc-related RP (n = 131), the mean weekly number of RP attacks was reduced by 39%, the severity score improved by approximately 35%, and significantly more patients showed digital ulcer healing (at least 50%) [33]. Interestingly, the placebo response was also high - that is, a reduction of RP frequency by 22% (p = 0.005), a phenomenon that has also been observed in other clinical trials [20,33,34]. Currently, only two small studies compared iloprost with alprostadil in the treatment of RP, but are of low value [35,36]. Similar to CCBs, the main treatment effect of the prostacyclin analogs is explained by their ability to induce vasodilation, but it is believed that iloprost may also downregulate adhesion molecules on endothelial cells [37], modulate CD4⁺ T cell function [38] and interfere with platelet activation [39]. Those modes of action may be the reason why the effects of prostacyclin analogs are not limited to vasculopathy, but lead to an improvement in skin score and diffusion capacity [40]. Unfortunately, only 44% of the study population suffered from the diffuse subset of SSc and the route of administration differed compared with other studies. Hence, this

study is difficult to integrate, especially as a subset analysis for the diffuse subset of SSc has not been performed, but skin involvement and impaired lung function is more severe in this group [41]. It is important to mention that all studies examining the effect of RP treatment in a placebocontrolled design show a high placebo response, so it is sometimes difficult to identify significant results [32]. The majority of studies used the same route of administration with an infusion dose of 0.5-2 ng/kg/min over 6 h on 5 consecutive days [33,42,43], alternatively only on 3 consecutive days [44-46], or designed a long-term intervention with initial daily infusions and repeated administrations every 6 or 8 weeks thereafter [22,40]. When high-dose iloprost (2 ng/kg/min) was compared with low-dose (0.5 ng/kg/min), both were equally effective [47]. In terms of effect duration, studies suggest that the therapy effect can last for 2 months or even longer [47,48]. Oral application of iloprost showed some efficacy in two smaller multicenter trials [49,50], but was not better than placebo in another larger multicenter trial with a total of 308 patients [51]. Although these preliminary results were disappointing, there is an ongoing effort to develop an oral prostanoid therapy



Figure 1. The normal capillaroscopic pattern is defined by a capillary density of >9 capillaries per mm and normal hairspin-shaped capillaries. Capillaries can sometimes appear torqued, which can be more pronounced in some patients, but is of no pathologic background. By contrast, scleroderma-like patterns show increased capillary damage that expands from early (few hemorrhages, few enlarged or irregular-shaped loops) to active (frequent hemorrhages and giant capillaries, significant capillary loss) to late (severe capillary damage with insufficient and aberrant angiogenesis) [14]. For color images please see online www.futuremedicine.com/doi/suppl/10.2217/ ijr.13.65.



Figure 2. Some of the key elements and mechanisms in the pathogenesis of Raynaud's phenomenon. Adapted from [4], with permission from Oxford University Press.

for RP. Treprostinil was tested in a case of severe digital ulcer disease associated with SSc as subcutaneous infusion therapy and significantly accelerated the healing [52]. Most recently, the first results of treprostinil as an oral sustained release tablet have been published and provide evidence for successful absorption. Moreover, cutaneous perfusion and temperature increased during this Phase I pharmacokinetic study [53]. Although side effects were common throughout all studies with prostacyclin analogs [32], in most cases this therapy was not discontinued [47]. Common side effects usually include headache, flush and nausea, but more importantly, rapidly occurring hypotension that can lead to steal syndrome as blood flow decreases, especially in atherosclerotic arteries.

Therefore, the current evidence agrees on the efficacy of prostacyclin analogs (principally indicated only for severe RP) in reducing the frequency and severity of RP and effectively, in healing digital ulcers. Despite a clear approval for treating RP with iv. prostanoids, infusion therapy is well established in everyday clinical practice, whereas the choice for the route of administration (iv., subcutaneous or oral) and repetition of application (need of fixed intervals or repetitive infusions as required) is mostly individual and should be studied more extensively in the future.

Endothelin receptor antagonists

An example for the balance of microcirculation is given by the interplay of endothelin (ET) and nitric oxide (NO). ET was first described at the end of the 1980s as a novel potent vasoconstrictor [54]. Its potency is believed to be 100-times stronger than norepinephrine and, to date, three different isoforms, namely ET-1, -2 and -3 have been described. The most important isoform is ET-1 and vascular endothelial cells mainly secrete ET-1. A variety of factors have been associated with either increased or decreased levels of ET-1. Endothelial dysfunction is a hallmark of SSc, which is characterized by high levels of cytokines, growth factors, or vasoconstrictory peptides such as IL-1, TGF- β , VEGF, adrenaline, angiotensin II or vasopressin in different stages of the disease [55]. All of these are potential regulators of ET-1 and may account for the increased levels of ET-1 found in SSc [56]. On the other hand, factors such as prostacyclin, atrial natriuretic peptide, EGF or NO are capable of blocking ET-1 synthesis [55]. With respect to the interplay of ET-1 and NO, the key mechanism of ET-1 is vasoconstriction and it is mainly generated by the interaction with ET-1 receptor type A (ET_A) and to some extent by ET-1 receptor type B on the surface of vascular smooth muscle cells. The binding of ET-1 at ET-1 receptor type B on endothelial cells (autocrine regulation), however, leads to the release of NO that – in return – antagonizes the ET-1 effect on vascular smooth muscle cells and leads to relaxation and vasodilation by an increase of cyclic GMP. The initial hypothesis to use ET-1 blockade was



Figure 3. Schematic diagram of the treatment for Raynaud's phenomenon as suggested by Herrick [12]. The flow chart differs between **(A)** uncomplicated Raynaud's phenomenon and **(B)** Raynaud's phenomenon that has progressed to digital ulceration and/or critical ischemia.

⁺Avoidance of exposure to cold, wearing gloves and cease smoking.

ACE: Angiotensin-converting enzyme; AR: Angiotensin receptor; CCB: Calcium channel blocker; ERA: Endothelin-1 receptor antagonist; PDE: Phosphodiesterase; SSc: Systemic sclerosis; SSRI: Selective serotonin reuptake inhibitor. Adapted from [15], with permission from Wolters Kluwer Health [15].

to reduce the cardiovascular risk and burden, but the ERAs failed in arterial hypertension or congestive heart failure studies. On the contrary, trials in pulmonary arterial hypertension demonstrated beneficial results and led to the approval of three ERAs; bosentan [57], sitaxentan [58] and ambrisentan [59], with more being currently investigated [60,61]. However, adverse reactions of ERAs, considered to be class effects, have to be taken into account. They include interalia headache, edema, flushing and elevated liver enzymes, which can be associated with liver failure and therefore should be monitored closely. Liver toxicity in single patients was thus the main reason why sitaxentan was removed from the market. Patients with SSc suffer frequently from pulmonary arterial hypertension as a comorbidity (21%) [41]. Patients, who were treated with bosentan, due to pulmonary arterial hypertension, showed a significant improvement of digital ulcer disease [62-64] and one report also concluded that bosentan is successful in the treatment of severe RP [63]. This was the basis for two large randomized clinical trials with bosentan in patients with digital ulcers due to SSc, the RAPIDS-1 and -2 trials [65,66]. The primary end point of both Phase III studies was the efficacy of bosentan to reduce the development of new digital ulcers during a treatment period of 16 or 24 weeks. Both trials reached their primary end point and bosentan was approved for the prevention of digital ulcers in SSc. Unfortunatelely, the trials did not address specifically the course of RP. However, Korn et al. reported in their discussion that bosentan fails to show improvement in Raynaud's symptoms and concluded that bosentan may exert other effects besides mediating dilation [65]. In this context, one study showed that ET-1 not only triggers vasoconstriction, but also promotes fibroblast activation in terms of increased collagen I and III synthesis, which depended on both receptors. They further demonstrated a decreased expression of matrix-metalloproteinase zymographic activity exclusively by the ET_A [67]. Moreover, autoantibodies against ET_A have been described recently and showed intrinsic receptor activity that mediated increased $TGF-\beta$ gene expression by the extracellular signal-regulated kinases-1 and -2 [68]. This effect could be prevented by a selective ET_A blockade [68]. The effects of ERA therapy can therefore be extended to induce potentially long-term vascular modification. This is in line with recent reports that describe a positive effect on capillary density and angiogenesis [69,70]. By contrast, short-term intervention of

12 weeks did not show any significant changes in vasodilator responses (Doppler fluxmetry combined with iontophoresis), capillary permeability (fluorescence videomicroscopy) and capillary density (nailfold capillaroscopy), after bosentan treatment of patients with limited SSc [71].

The main difference between the RAPIDS-1 and -2 studies was the follow-up of a so-called 'cardinal ulcer' [65,66]. The important outcome was that bosentan did not improve the healing rate of ulcers compared with the placebo. This is the reason for the clear statement in the EULAR/EUSTAR recommendations that bosentan only has a confirmed efficacy for the prevention of new digital ulcers, an effect which was even more prominent in patients with multiple digital ulcers [16]. Bosentan has therefore only received approval for the prevention of digital ulcers, not for complex RP. After a period of 4 weeks, in which bosentan is prescribed twice daily in doses of 62.5 mg, the dosage should be increased to 125 mg twice daily if tolerated. Other ERAs have not yet been approved except for pulmonary arterial hypertension and reports about their efficacy in terms of perfusion, RP frequency, and digital ulcers are limited. Sitaxentan has been withdrawn from the market, whereas just a few studies deal with efficacy of ambrisentan in SSc vasculopathy. A recent case study observed the course of six patients with SSc and digital ulcers who presented with lack of efficacy or side effects of bosentan [72]. In four patients, the ulcers healed completely, whereas two suffered from one remaining at the end of the study. RP attacks, Raynaud Condition Score (RCS) and visual analog scale for pain decreased significantly during the observational period of 24 weeks [72]. The applied dose was 5 mg daily. Unfortunately, no placebo arm was included. Macitentan is another ERA currently running in Phase III trials for the treatment of digital ulcers in SSc patients, but also in patients with pulmonary arterial hypertension (NCT01474109 [201], NCT01474122 [202]), and there are strong indications that this compound would be superior in all RP and digital ulcer situations compared with bosentan [61]. It will also be of great interest to see whether ERAs could be regarded as 'disease-modifying' drugs in the treatment of SSc in the future [73,74].

PDE5 inhibitors

In 1998, a new class of drugs was introduced due to the approval of sildenafil, a selective PDE5i for the treatment of erectile dysfunction. Later, in 2005, the US FDA also approved sildenafil for the treatment of pulmonary arterial hypertension. By that time, the first case studies had reported beneficial effects of sildenafil in the treatment of RP [75,76]. To date, three different PDE5is are available for the aforementioned indications, namely sildenafil, tadalafil, and vardenafil. All have been found to work in RP [34], but long-term studies are needed to confirm the promising results. PDE5i degrades cyclic GMP to GMP, but PDE5i protects cyclic GMP from degradation by imitating its molecular structure. Therefore, relaxation of vascular smooth muscle cells is maintained and vasodilation assured. The main differences between the three PDE5is are the longer half-life, less affinity for PDE6 (retina, lower frequency of transient impaired vision) and PDE3 (heart muscle, lower frequency of cardiac side effects) and a high oral bioavailability of tadalafil compared with vardenafil and sildenafil [77].

Two double-blind placebo-controlled studies evaluated the efficacy of sildenafil in patients with PRP and SRP during a period of 2 and 4 weeks using 2 × 50 mg/day [75,78]. A crossover setting was performed with an intermediate washout period of 1 week. In patients with PRP, no significant differences between sildenafil and placebo were observed [78], whereas patients with SRP (mainly SSc, but also mixed connective tissue disease) showed a significant reduction of the frequency and duration of RP attacks, an increase of the capillary blood flow assessed by laser-Doppler imaging and a reduction in size and number of digital ulcers [75]. A third placebo-controlled study in 57 patients with RP, secondary to limited SSc, observed a different formulation of sildenafil (modifiedrelease sildenafil 200 mg once daily [79]). The mean percentage of attacks was significantly reduced by sildenafil compared with placebo. However, secondary end points, such as reducing the severity (RCS) and duration of attacks (number of attacks per week), were not achieved. Interestingly, the mean values and changes in biomarkers from baseline were similar between groups. Additionally, in a further uncontrolled pilot study, an effect of sildenafil on the severity of SRP and also the healing of digital ulcers in 16 patients with SSc was reported (with three patients discontinuing therapy during the first month) [80]. By increasing the dose of sildenafil to the maximal tolerated level, the number of digital ulcers decreased from a mean of 3.1 to 1.1 per patient on an average of 5.2 months. All secondary outcomes (visual analog scale for RP, pain and activity) showed a significant improvement

with sildenafil therapy. In a recent second prospective, open-label uncontrolled pilot study, the effect of sildenafil on the severity of SRP was also observed [81]. Generally, relief of ischemic pain and increased digital perfusion occurred soon after therapy initiation within 12–48 h [82,83].

For tadalafil, several studies observed an effect on RP and partly on digital ulcer disease in small cohorts of nine to 39 patients [84-88]. The results differed throughout the studies. For example, one randomized crossover study from 2010 demonstrated that 20 mg of tadalafil every other day as an additive medication to pre-existing vasodilators, significantly improved the mean frequency and the mean duration of attacks as well as the RCS [84]. Furthermore, all 25 digital lesions healed during follow-up in the tadalafil group compared with only three out of 13 in the placebo group; 13 new lesions occurred with placebo but only one with tadalafil [84]. Another study observed whether tadalafil increased the digital blood flow by Doppler at rest, during heat or cold exposure [87]. Tadalafil was taken only once at a dosage of 10 mg and results were compared with placebo; no significant improvement of perfusion was observed [87]. Additionally, another randomized, double-blind, placebocontrolled crossover study of 39 women with SRP (due to SSc), which compared tadalafil 20 mg/day versus placebo for 4 weeks, reported lack of efficacy for tadalafil. Moreover, the observed treatment effects were comparable to those of iloprost [80]. The conclusion drawn from these different results was that tadalafil might have a potency to alleviate the burden of difficult RP, but the mechanism of action is not purely based on vasodilation and it might take time to be fully effective.

Data on vardenafil as treatment option for RP are limited and both studies that are currently available have been performed in a monocentric approach only [89,90]. Both trials included PRP and SRP patients with a preponderance of SSc-related RP. The intervention consisted of vardenafil 10 mg twice daily, but the more recent trial was conducted as a double blind, placebocontrolled crossover study, rather than a pilot intervention study. Taken together, the results indicate that vardenafil was able to reduce the number, duration and severity of attacks, but again (as also observed for tadalafil) the effect cannot fully be ascribed to an improved digital blood flow [90].

Besides SSc-related RP and digital ulcer disease, PDE5i showed promising effects in other underlying conditions, such as mixed connective

tissue disease, systemic lupus erythematosus, antiphospholipid antibody syndrome and malignancies [75,91,92]. In some patients, PDE5i proved to be very effective, but a higher grade of evidence was not at hand until a systematic review and meta-analysis of randomized trials were recently published [34]. Six randomized controlled trials that included most of the aforementioned studies were analyzed. PDE5i demonstrated a significant effect on the reduction of RCS (-0.46; p = 0.002), the daily frequency of ischemic attacks (-0.49; p < 0.0001), and the daily duration of RP attacks by -14.62 min. (p < 0.0001) in patients with SRP (n = 350). Therefore, PDE5i showed a similar potential to ameliorate RP compared with CCBs. However, the study durations were only 4-8 weeks and the underlying causes of SRP (diffuse SSc, limited SSc or mixed connective tissue disease) were not differentiated. The authors therefore concluded that there is still a major need for larger clinical trials. A head-to-head study that compares iloprost with PDE5i would also be of great interest in this respect.

Alternative treatment approaches

Angiotensin II receptor antagonists In a 12-week, randomized, parallel-group (losartan vs nifedipin) trial, in patients with primary and SSc-related RP, a reduction in the severity and frequency of RP episodes was documented [23]. The clinical effect in this study was, however, more prominent in patients with PRP and overall, side effects were less frequent compared with nifedipin. Although a benefit was clearly demonstrated, experts would prefer, especially for SSc-related RP, PDE5i as second-line treatment after failure of CCBs [12,17,93]. Of note, angiotensin II receptor antagonists were chosen in a survey as third-line therapy only for mild disease (< five attacks/week [17]). Unfortunately, no further clinical trials have been performed in recent years, but in light of recent data that showed the functional involvement of autoantibodies against angiotensin II type 1 receptors, this treatment approach appears rational [68] and more data in this field is needed.

Angiotensin-converting enzyme inhibitors

Apart from a few smaller anecdotal reports from the 1980s, which examined the effects of enalapril and captopril on RP symptoms with conflicting results, only one randomized, double-blind, placebo-controlled study evaluated the benefit of quinapril in patients with limited cutaneous SSc [94]. Unfortunately, the up to 3-year longterm administration of 80 mg/day of quinapril had no demonstrable effect in terms of digital ulcer occurrence and frequency, as well as on the severity of RP episodes. In addition, the tolerability was limited as about 20% of the patients reported side effects such as dry cough. Owing to the findings of the ACEi study in RP, no further studies have been performed with ACEi in this condition [17].

α1-blockers

Vascular smooth muscle cells express the $\alpha 1$ receptor and binding of catecholamines leads to vasoconstriction. Therefore, it appears rational to investigate whether an antagonist such as prazosin would alleviate the burden of SSc-related RP. One Cochrane meta-analysis included two studies with a total of 40 SSc patients [95]. The observed effect was only modest compared with placebo, whereas side effects occurred frequently [95]. To date, and maybe due to the limited effect, no further studies with prazosin or similar antagonists were performed.

Antiplatelet agents

Acetylsalicylic acid and dipyridamole have been studied in PRP and SRP, and low-molecular weight heparin only in SSc-related RP. Whereas for the latter a potential effect on the severity of RP was described, neither acetylsalicylic acid nor dipyridamole exerted beneficial effects in patients with RP [96,97]. Nevertheless, a recent review concludes that platelets are most likely to substantially contribute to the pathogenesis of SSc [98]. Taking this strong theoretical rationale into account, additional studies are required to determine the potential of antiplatelet therapy, especially in critical digital ischemia and digital ulcer disease associated with SSc [17]. At the moment, it seems plausible to use antiplatelet therapy as an add-on, if necessary.

Rheologic agents

Pentoxifylline and, in part, *Ginkgo biloba* extracts to improve red blood cell deformability (known as a hemorheologic effect) and therefore decrease blood cell viscosity. Pentoxifylline is also believed to reduce the potential of platelet aggregation, to act as a competitive nonselective PDE inhibitor and may moderate inflammation. *Gingko biloba* extracts have been tested in the treatment of PRP with moderate to no effect [99,100], whereas pentoxifylline showed some effect in terms of paraesthesia and cyanosis, but none in terms of duration and frequency of RP [101]. Other studies concluded that pentoxifylline has moderate effects [102–104], but an overall recommendation cannot currently be given. Interestingly, one study compared pentoxifylline with ketanserin, wherein the latter group reduced subjective symptoms and reduced duration of attacks were observed; an improvement in the cold provocative test was also reported [101]. This highlighted the question: what role does serotonin play in RP pathogenesis?

Serotonin signaling

Ketanserin acts as a serotonin antagonist by selectively interfering with the serotonin receptor 5-HT_{2A}, although its main target is the α 1-blocker. Confirmation of this principle is partly achieved by a different 5-HT_{2A} receptor antagonist, namely sarpogrelate hydrochloride [105]. In an observational trial of 11 SSc patients, sarpogrelate was able to reduce disease burden, assessed by quality-of-life questionnaires and by a healing tendency of digital ulcers, but a control group was not included [105]. Another small study focused on SRP rather than digital ulcer disease, and found sarpogrelate to improve frequency and duration, as well as symptoms during cold exposure and pain [106].

Fluoxetine, a SSRI, has been studied in a comparative, crossover trial with nifedipine for a total of 14 weeks, including a 2-week washout period [107]. The authors found a significant reduction of the duration and frequency of RP in the fluoxetine group only and the effect was more prominent for patients with PRP [107]. Although the results for fluoxetine seem promising, the finding that nifedipine does not influence RP at all is remarkable. Therefore, the results should be interpreted with care. This is underlined by some reports that describe RP as a consequence of fluoxetine therapy, and severe RP as a side effect of SSRI therapy has previously been observed [108–112].

Topical nitrates

To apply nitroglycerin topically would be an elegant treatment as NO can be supplemented directly where it is needed and side effects are greatly diminished compared with systemic administration. MQX-503, a novel formulation of topical nitroglycerin, has been tested in a multicenter, randomized, placebo-controlled study over a complete observational period of 6 weeks [113]. In total, 219 patients with either PRP or SRP applied 0.9% MQX-503 gel or placebo immediately before, or within, the first 5 min of an RP episode [113]. The RCS decreased

significantly, whereas the duration and frequency of the episodes were not affected. However, as MQX-503 was well tolerated and provided an acute intervention possibility, approval and availability should be pursued.

Antioxidants

Different courses of N-acetylcysteine have been tested in two open-label pilot studies [114,115]. Although the administration in the first study was a single 5-day period iv. infusion, starting with a loading dose of 150 mg/kg/h in the first 2 h, continuing with 15 mg/kg/h thereafter for an additional 5 h, the effects in SSc-related RP were clearly demonstrated by a reduction of the frequency and severity of RP attacks [114]. Furthermore, digital ulcers were less in number during the whole follow-up period of 11 weeks. The second study observed the administration of 15 mg/kg/h for 5 consecutive days every second week between October and May for 2 years, reporting interesting results [115]. Again, the severity and frequency were significantly reduced compared with baseline levels. In addition, the global hand function was increased. The same working group then performed a second observational, prospective trial over 3 consecutive years with N-acetylcysteine every 2 weeks, irrespective of the time of year, in a cohort of 50 scleroderma patients [85]. Digital ulcers per patient per year, and the visual analog scale for digital ulcers, decreased significantly as the RP severity and frequency decreased. Side effects were minor throughout all studies, but they all lacked a necessary control group. A rationale for administering antioxidant as a form of therapy for RP is given by the fact that reactive oxygen species are high in the condition and, as a consequence, levels of antioxidants, such as ascorbic acid, are decreased [116].

Rho-kinase inhibitor

Reactive oxygen species can induce constriction of arterioles is mediated by Rho-kinase and as a result of this pathophysiologic finding, translocation of the α 2c-adrenoreceptor is taking place [117-120]. It was thus attractive to evaluate the efficacy of the Rho-kinase inhibitor in SSc-related RP. Fasudil, a RhoA/Rho-kinase inhibitor, was studied in 17 patients [121]. The oral tablet was administered 2 h prior to cold challenge. Skin temperature, time to recover, digital blood flow by laser-Doppler imaging and further end points were measured. Neither the 40- or 80-mg dose could significantly influence the response to cold challenge in this patient cohort. Although this therapeutic principle seems promising, the study design needs to be questioned, as it is not possible to estimate the efficacy of Rho-kinase inhibition by the results of this study.

Statins

Two studies have evaluated the effect of statins on RP so far [122,123]. The more extensive study of Abou-Raya et al. included 84 patients with SSc-associated RP and tested placebo-controlled 40 mg atorvastatin in a 2:1 randomized fashion for 4 months [122]. The total number of digital ulcers decreased (26%) as the frequency of new ulcers did (36%). Furthermore, reductions in the health assessment score, the scale for pain and the physician's global were noted. A Japanese study observed the effects of atorvastatin long-term application over 24 months in eight patients with SSc-related RP [123]. They reported no side effects, but significant reductions in the RCS and the visual analog scale were observed. Furthermore, biological effects could be demonstrated as angiogenic factors such as VEGF and bFGF, factors of vascular injury or activation, such as VCAM-1 and E-selectin, and the number of endothelial progenitor cells decreased [123]. However, no control group was in the followup and all patients were on vasoactive therapy, including beraprost. As statins are considered to exert pleiotropic effects and as patients with scleroderma show an increased atherosclerotic risk [18,19], it is most likely that statins could be beneficial, but data are too limited to support a respective recommendation at present.

Complementary & alternative medicine

In 2009, Malenfant et al. conducted an extended literature research to perform a metaanalysis regarding the efficacy of complementary and alternative medicine in the treatment of RP [10]. They reported approximately 20 randomized controlled studies subdivided into trials regarding acupuncture (n = 2), antioxidants (n = 2), biofeedback (n = 5), essential fatty acids (n = 3), Gingko biloba (n = 1), L-arginine (n = 2), laser (n = 3), glucosaminoglycans (n = 1) and therapeutic gloves (n = 1). Therapeutic gloves were the favored treatment, whereas laser resulted in only one less RP over 2 weeks. No differences could be found in the other subcategories or else the data quality was too limited to draw conclusions. They concluded the report by stating that there is a need for well-designed trials of complementary and alternative medicine [10].

Botulinum toxin A

The efficacy and potential of botulinum toxin in the treatment of RP has recently been summarized in a review article [124]. The review reports from five clinical trials that have been conducted in the last decade [125-129]. Three studies were retrospective analyses and two prospectively followed the patient cohort; none of them included a control group. A reduction of pain severity was observed throughout all studies and all described an effect on digital ulcers, but terms were different as a differentiation between healing and improvement was not made. Botulinum toxin is known for its effect on the neuromuscular endplate, as it inhibits the release of acetylcholine vesicles at the motor endplate, leading to the inhibition of smooth muscle cell vasoconstriction [124,130]. Further mechanisms of action are the blockades of the transmission of norepinephrine vesicles and the recruitment of specific α 2c-adrenoreceptors. The latter is known to be of significant importance in the regulation of the digital vessel tone, particularly in response to cold stimuli. Large centers that care specifically for patients with SSc-related RP and other forms of critical ischemia are currently gaining experience in the use of botulinum toxin [131]. However, so far, the need for well-designed studies is great and those studies will have to demonstrate the efficacy of a standard technique. As suggested by Iorio et al. this includes injections for all digits along the level of the superficial palmar arch, using a standard dose of botulinum toxin [124]. Control or placebo groups are a must in this setting and should be part of any upcoming clinical trial. Furthermore, injection-related side effects, especially pain, might be a major limitation for patients with SSc, compared with other conditions.

Thoracic sympathectomy

Currently, there is only evidence from one randomized, controlled trial that studied thoracic sympathectomy at the level of T2 and T3 with percutaneous radiofrequency versus T2 thermolesion with local application of 0.5ml of 6% phenol for the treatment of acral ischemia in RP [132]. In both groups, pain assessed by the visual analog scale decreased, whereas peripheral temperature and quality of life increased after the procedure. No significant differences between the groups were observed. As both groups performed well during the observational period of 3 months, the shorter duration of the single-shot therapy at T2 should be preferred. More reports on thoracic sympathectomy and the different procedures have recently been collected and summarized [133]. As a potential side effect, reduced blood flow in the contralateral extremity has been described [134]. In addition, stellate block does not have an effect on ulnar artery occlusions [135]. The long-term benefit of this procedures seems, if at all, more favorable for patients with SRP [133], but from a rheumatologist's point of view, thoracic sympathectomy should be regarded as the absolute last therapeutic option.

Conclusion

For the treatment of RP, one has to clearly differentiate between PRP and SRP. Therefore, detailed patient histories and technical examinations, especially capillary microscopy and laboratory results (in particular antinuclear antibody and ENA Screening), should guide the decision for a patient-oriented treatment. If a decision cannot be made at the first visit, regular (yearly) followups should be recommended [1.7]. PRP frequently follows a benign course, therefore nonpharmacological approaches should be preferred. If patients suffer from high disease burden, CCBs can be effective, but are often only of moderate effect. Thus far, further pharmacological or alternative interventions have not been studied or validated.

In patients with SRP, the underlying cause of the disease has yet to be identified in order to provide a definite diagnosis. Therefore, a

necessary prognosis for the affected patient is reassured but physicians must also be aware of potential organ involvement, which should guide therapeutic decisions on an evidencebased level. Besides nondrug measures (such as preventing exposure to low temperatures, smoking cessation or the use of therapeutic gloves), CCBs are considered first-line therapy. However, many different treatment approaches have been tested during the last years. Current evidence is, however, limited in answering the question of how to progress if CCBs fail. Several treatment algorithms have been suggested, including mainly PDE5is, iv. prostanoids and ERAs. Currently, prostanoids are preferred to accelerate the healing of digital ulcers, but PDE5i may have a positive potential in this situation as well. However, larger, well-designed controlled trials are needed to confirm this potential.

The rate of development of new digital ulcers can be decreased using the ERA bosentan, and patients with severe, recurrent RP may be susceptible to PDE5i. Moreover, the results of trials using the new generation vasodilators such as macitentan, selexipag and others will hopefully add valid data for treatment recommendations for SRP. To conclude, there is still a clear need for high-quality studies questioning the relevance of antiplatelet therapy, statins, botulinum toxin, topical nitrates and other interesting therapies that may improve the vasculopathy in SRP.

Executive summary

Differentiation between primary & secondary Raynaud's phenomenon

Besides a detailed patient history and physical examination, capillaroscopy and testing for antinuclear antibodies should support the decision as to whether to follow-up the patient on a tight basis because of complex secondary Raynaud's syndrome, or diagnose a more benign primary Raynaud's phenomenon (RP).

Therapies with a high strength of recommendation

- Calcium channel blockers have shown a significant, but moderate, effect in meta-analyses for both primary and secondary RP.
- Nifedipine has been the most studied here sustained release formulations should be preferred and the drug should be started at a low dose and then gradually increased if tolerated.
- Intravenous prostanoids have been shown to be effective not only in reducing the frequency and severity of RP, but also in accelerating the healing of digital ulcers, although no specific approval for intravenous prostanoids for RP is existing.
- The route of administration and the repetition intervals are still a matter of discussion and more studies are needed to answer this question appropriately.
- Endothelin-1 receptor antagonists have a clearly defined approval status for patients with multiple digital ulcers and have been shown to reduce the rate of new digital ulcers; but at present, no evidence for an effect on digital ulcer healing or RP is available.
- Phosphodiesterase type 5 inhibitors, as shown in a recent meta-analysis, result in a moderate but significant improvement of the severity, frequency and duration of RP.

Potential alternative strategies

- Angiotensin II receptor antagonists have shown moderate effects in systemic sclerosis-related RP, but should be considered for mild courses of disease only.
- Angiotensin-converting enzyme inhibitors have failed to show any effect in the treatment of RP.
- More studies are needed to determine a possible role for α1-adrenergic blockers, antiplatelet and rheologic agents, selective serotonin reuptake inhibitors, topical nitrates, antioxidants, Rho-kinase inhibitors and statins in the treatment of RP.

Future perspective

Studying the tightly controlled mechanisms of microcirculation is difficult, but should therefore be promoted more intensely. With respect to trial design, several weeks, placebo-controlled crossover studies observing the frequency and severity of RP are recommended, whereas at least 6 months are needed to investigate an effect on digital ulcer healing or prevention of new ulcers. The latter should be controlled by standard care including skilled nursing and wound care, as well as vasoactive drug interventions, most likely iloprost infusions. The teaching of patients and keeping a patient diary are also recommended.

Up to now, we have learned a lot about the altered microcirculation in RP by reviewing the different treatment approaches undertaken during the last years for treatment of this condition. Several concepts failed, for example, ACEi, blockade of al-adrenoreceptors, hemorheologic agents, Rho-kinase inhibition or complementary and alternative medicine, which might also be due to limited study designs (e.g., Rho-kinase inhibitor). Others by contrast have showed interesting, but still conflicting results, such as angiotensin-II receptor antagonists, antiplatelet therapy, SSRIs, topical nitrates, statins and antioxidants. For these, as well as for interventions with botulinum toxin or thoracic sympathectomy, more high-quality studies are needed. In

addition, the evidence for PDE5i and ERA is increasing. Both are considered to play an important role in diminishing endothelial damage. It will thus be of substantial interest whether they positively influence capillary recovery and vasculopathy. Preliminary data supporting capillary recovery is already at hand for ERA. The use of PDE5is will hopefully increase over the following years as sildenafil becomes generic and other PDE5is will follow. To achieve these goals, high-quality reports from large registries, such as the EUSTAR cohort [41] or the Desscipher project [203], and long-term efficacy studies, will be needed to create successful strategies including combination therapies to reduce the burden of disease for the affected patients in the future.

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