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REVIEW

New lines in therapy of Raynaud's phenomenon

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Abstract Current knowledge about the pathogenesis of Raynaud's phenomenon (RP) results in novel approaches for therapy. Vasospasm without endothelial damage is thought to be the main cause for primary RP. The pathogenesis of secondary forms of RP is supposed to be initiated primary by endothelial damage. The aim of the review is to present main groups of medications as well as non-pharmacological regimen, that are used for the treatment of RP. The necessity of immediate assessment and treatment in severe forms of the disease with digital ulcers is highlighted. The mild forms of primary RP can be controlled by non-pharmacologic approaches. If the effect is insufficient, medications of first choice are calcium channel blockers. In the severe forms of the disorder, intravenous infusion of prostacyclin as well as endothelin-1 receptor antagonists and specific inhibitors of phosphodiesterase-5 are the treatment of choice. Treatment in the future may include selective blockers of alpha-2c adrenergic receptors, inhibitors of protein tyrosine kinase and Rho-kinase, as well as calcitonin gene-related peptide.

Keywords Raynaud's phenomenon · Treatment · Prostacyclin · Endothelin-1 receptor antagonists

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Introduction

Raynaud's phenomenon (RP) is characterized by reversible digital vasospasm provoked by cold and emotional stress. The aim of the treatment in patients with RP is to improve digital blood flow and to prevent digital ischemia. Current knowledge about the pathogenesis of primary and secondary forms of RP explains different severity of symptoms and stimulates new lines in therapy. Vasospasm without endothelial damage is thought to be the main cause for primary RP. Patients with primary RP usually have a long-standing history with symptoms starting in puberty. The symptoms are usually mild to moderate without complications and digital ulcers. In contrary, in patients, in whom RP is a feature of rheumatic diseases, particularly systemic sclerosis (SSc) and mixed connective tissue disease, the onset of the symptoms is later (usually after 25 years of age) and often presents with digital ulcers [1–3]. In SSc and secondary RP, there is frequently endothelial damage with overexpression of adhesion molecules (E-selectin, P-selectin, VCAM-1, ICAM-1) [4, 5], associated with a decreased production of vasodilators—prostacyclin and nitric oxide (NO) and increased levels of vasoconstrictors e.g., endothelin-1 (ET-1). There are also structural changes of the vessels such as intimal fibrosis and abnormal angiogenesis [6, 7]. The choice of appropriate medication for the treatment of RP depends on the severity of ischemia. The presence of rheumatic disease requires also a specific treatment. The aim of the review is to present main groups of medications as well as non-pharmacologic regimen, that are used for the treatment of RP. A large number of medications are used for treatment of RP, but no gold standard or universal guidelines for the treatment of RP exist.

Non-pharmacologic treatments

The mild forms of primary RP are controlled by non-pharmacologic measures, e.g. changes of lifestyle. Patient education in avoiding exposure to cold and emotional stress, warm clothes, cessation of smoking and using protective devices in working with vibration is very important. Treatment with beta blockers, interferon as well as avoiding substances such as caffeine are important to these patients. It has been speculated that special diet with fish oil supplement which consist of omega-3 fatty acids may be beneficial in RP patients, but has not been proven in controlled clinical trials [1, 8–10].

Drug treatment

The main goal of medical treatment in patients with RP is to induce vasodilation.

Calcium-channel blockers

Calcium-channel blockers (CCBs) have been the treatment of choice for patients with RP for many years. They are vasodilators with direct effect on vascular smooth muscles and in addition inhibit platelet activation. The treatment starts with low dose followed by an upward titration according to therapeutic effect, the level of blood pressure and the toleration of the patient. Treatment with CCBs in patients with RP reduces severity and frequency of vasospastic episodes. Thompson and Pope [11] perform a meta-analysis of 18 randomized, placebo-controlled, and double-blinded trials, which evaluated the efficacy of CCBs in patients with primary RP. An average decrease of 2.8–5.0 attacks over a 1-week period and a 33% reduction in severity could be found. These findings are similar to those of a meta-analysis by the same authors addressing the therapeutic effect of CCBs in RP secondary to SSc—a decrease of four attacks per 1 week and a 35% reduction in severity [12].

Dihydropiridine class of CCBs

Nifedipine is the best studied and the most often used drug from this group. It is used at a dose of 30 mg daily and may be increased to 60 mg daily in refractory cases. Other dihydropiridines are also used in patients with RP—felodipine, amlodipine, nicardipine and isradipine [8, 13]. Felodipine shows a high vasoselectivity. Its dose is 2.5–10 mg b. i. d. The selectivity of these CCBs for vasculature/heart is 7:1 for diltiazem, 14:1 for nifedipine and 100:1 for felodipine [14]. In our study, addressing the therapeutic effect of CCBs in RP, we observed healing of digital ulcers in SSc patients treated with felodipine. The advantages of the drug are its usage as tablet form and a low price [15]. There are data from the literature that dihydropiridines improve also endothelial function by their antioxidant properties in that they reduce the catabolism of NO [16, 17]. Side effects from CCBs are common—flushing, hypotension, dizziness, headache, tachycardia, ankle edema, constipation etc. In these cases slow-release forms are better tolerated [1, 9, 10, 15].

Benzothiazepine class of CCBs

Diltiazem (30–120 mg t. i. d.) shows also a good therapeutic effect in RP.

Diphenylalkylamine class of CCBs such as verapamil have not proven to inherit a therapeutic effect in RP patients [13].

ACE inhibitors

ACE inhibitors are potent vasodilators, but their therapeutic effect in patients with RP is not well studied [1, 8, 13]. However, current knowledge about the effect of this group of drugs on endothelial function increases the interest in their usage especially in SSc patients with secondary RP. ACE inhibitors inhibit angiotensin II formation and bradykinin degradation. One of the functions of bradykinin is to release NO from endothelium. Quinapril is thought to be more potent than the other medication from this group [1, 18, 19].

Angiotensin II receptor antagonists

These medications are successfully used in arterial hypertension. They are not well studied in patients with RP. Dziadzio et al. [20] conducted a comparative study of the therapeutic effect of losartan (50 mg daily) and retard nifedipine (20 mg b. i. d.) in 25 patients with primary RP and 27 patients with SSc and secondary RP. They found that losartan reduces severity and frequency of vasospastic episodes as its effect in patients with primary forms of the disease is better. They concluded that the therapeutic effect of losartan is greater than that of nifedipine. In this study, after a 12 weeks course of treatment a significant decrease of VCAM-1 serum levels could be found. Thus, it was suggested that losartan improves also endothelial function [20].

Of note, CCBs, ACE inhibitors and angiotensin II receptor antagonists are contraindicated in pregnancy and in women of child-bearing age, who do not use effective contraception. In addition, they are not recommended in children [9].

Prostacyclin and derivates of prostaglandins

Intravenous infusion with prostacyclin is a treatment of choice in patients with severe secondary RP with digital ulcers.

Epoprostenol is a prostacyclin with very short half-life (6 min), the drug is unstable at pH values below 10.5. So it cannot be given orally and requires intravenous application. The start dose is 1–2 ng/kg per min, which is increased upward to 20–40 ng/kg per min. Serious complications, particularly intravenous-line related infections have been reported. The therapeutic effect of epoprostenol in RP and pulmonary arterial hypertension (PAH) secondary to SSc is proven in randomized, controlled trials e.g., a large study that includes 111 SSc patients in 17 pulmonary hypertension referral centers. Epoprostenol reduced the severity of RP and frequency of digital ulcers. The medication improved also the exercise capacity [21].

Treprostinil is an epoprostenol analogue with a half-life of 3 h and is stable at room temperature. It is given as a continuous subcutaneous infusion at the dose of 10–20 ng/kg per min; the drug can also be given intravenously. Intravenous and subcutaneous treprostinil produces similar hemodynamic effects compared to those of epoprostenol in patients with PAH [22].

Iloprost is a chemically stable prostacyclin analogue with longer half-life—20–25 min and similar biological properties. It causes vasodilation, inhibition of platelet aggregation, inhibition of leukocyte chemotaxis and adhesion to the endothelium. Iloprost downregulates expression of adhesion molecules on endothelial cells and phagocytes; it enhances fibrinolytic activity [23]. In most studies, it is found that iloprost given as venous infusion for 6–8 h, at the dose of 0.5–3 ng/kg per min in patients with severe RP secondary to SSc reduces frequency and severity of vasospastic episodes, relieves the pain and heals digital ulcers. The mean duration of a therapeutic course is 5–10 days. These effects may be maintained by a 1 day infusion at intervals of several weeks according to the therapeutic effect [24–26]. Scorza et al. [26] also found significant skin softening in SSc patients treated with iloprost which suppose that this drug may inherit also disease-modifying activity. Della Bella [24] found that iloprost inhibits lymphocyte adhesion to endothelial cells, significantly inhibits IL-1β-induced endothelial expression of ICAM-1, but no significant effect was observed with regard to the expression of VCAM-1. After 5–7 days infusion of iloprost in SSc patients with secondary RP, Mittag and Beckheinrich [25] found reduced serum levels of sICAM-1, sVCAM-1, sE-selectin, ET-1 and vascular endothelial growth factor. These authors suggested that iloprost, in addition to its vasodilative effect may modulate inflammatory processes in SSc. Side effects during infusion of iloprost are well known: headache, nausea, vomiting, diarrhea, myalgia, arthralgia, chill, fever, arrythmia, hypotension, erythema and pain at the infusion site. In addition, iloprost may provoke chest pain especially in patients with coronary heart disease. Of note, prostaglandins for inhalation exist, which are used in PAH [2, 23, 24, 27].

Oral iloprost is also used in RP patients. The results of this therapy are contradictory. A multicenter, placebo-controlled, dose-comparative study with 103 SSc patients with secondary RP treated with oral iloprost 50 or 100 μg b. i. d. resulted in reduced duration and severity of RP. The 50 μg iloprost dose was better tolerated [28]. According to another double-blind, multicenter, placebo-controlled study oral iloprost leads to improvement in RP patients and its effect is stronger than placebo, but did not reach statistical significance [29].

Beraprost is the first oral prostacyclin analogue with vasodilative and antiplatelet action and a half-life of approximately 1 h. The peak plasma level is reached within 2 h after oral administration. In the ALPHABET study, which included 130 patients with PAH, beraprost was used at an initial dose of 20 μg four times daily. Thereafter, the dose was increased by 20 μg to four times a day each week. The maximum allowed dose in the study was 120 μg q. i. d. and the mean dose 80 μg q. i. d. The increase in dose was limited by side effects like flushing, diarrhea and headache. Beraprost is effective in primary and secondary PAH. It improves blood flow and increases skin temperature in RP patients [30, 31].

Alprostadil (PgE1) causes vasodilation of arterioles and precapillary sphincters, inhibits platelet activation and synthesis of thromboxanes. It is used at the dose of 0.1–0.4 μg/kg per min, given as a venous infusion for 6–24 h, on 2–5 consecutive days. After administration of alprostadil, increased skin temperature registered by thermography could be found [10, 32].

Phosphodiesterase inhibitors

Nitric oxide is a potent vasodilator and an inhibitor of platelet activation and vascular smooth muscle proliferation. Synthesis of NO is regulated by the family of NO synthases and its effect is mediated via cyclic guanosine monophosphate (cGMP). The intracellular concentration of cGMP is regulated by phosphodiesterases, which rapidly degrade cGMP in vivo [33].

Pentoxiphylline is widely used drug from this group, which dose is 400 mg t. i. d. It has not proven to be effective in severe forms of RP [10, 13].

Sildenafil is a specific inhibitor of the phosphodiesterase-5 isoform. It causes vasodilation for less than 60 min after intake. Sildenafil, at a dose of 50 mg three or four

times per day, leads to improved blood flow in patients with severe secondary RP [32, 34, 35].

The new specific inhibitor of phosphodiesterase-5—tadalafil, which has a longer half-life—17.5 versus 3.8 h for sildenafil, may be an alternative for those patients with RP, who did not improve with sildenafil [36].

Cilostazol (100 mg b. i. d. orally) is a phosphodiesterase-3 inhibitor, which is studied in a randomized, double-blind, placebo-controlled trial for the treatment of RP. These data show an increase of mean brachial artery diameter, but no significant changes of the microvascular flow or clinical symptoms were observed [37].

Endothelin receptor antagonists (ERA)

ET is a peptide, which plays a key role in pathogenesis of RP and PAH secondary to connective tissue diseases. It has a number of deleterious effects and leads to vasoconstriction, fibrosis, inflammation and vascular hypertrophy. ET-1 is the main isoform in humans. There are two classes of receptors for this mediator—ET_A and ET_B. ET_A receptors are mainly expressed on vascular smooth muscle cells and cardiac myocytes, while ET_B are found primarily on endothelial cells and to a lesser extent on vascular smooth muscle cells and fibroblasts. Activation of ET_A receptors (ET_B on vascular smooth muscle cells) leads to vasoconstriction and proliferation of smooth muscle cells. ET_B receptors have clearance function and may facilitate vasodilation via release of smooth muscle relaxants such as NO and prostacyclin [6, 7, 33, 38, 39].

Bosentan is a non-selective ERA and is the first drug from this group, which is approved for treatment of PAH associated with systemic rheumatic diseases in US, Canada, Switzerland and European union. It is used at the dose of 62.5–250 mg per day. Bosentan improves exercise capacity in patients with PAH (BREATHE-1 study). Therapy with bosentan in severe secondary RP leads to healing of digital ulcers. It is proven in double-blind, placebo-controlled trial in SSc patients for a period of 16 weeks (RAPIDS-1 study). Observed side effects are headache and elevation of liver enzymes [39–41].

Sitaxsentan is a new, oral, once-daily used, highly selective ERA, that has a long duration of action and high specificity for ET_A receptors (ET_A:ET_B—6,500:1). It is used at the dose of 50–100 mg per day. Selective ET_A receptor antagonism leads to blocking vasoconstrictor effect of ET-1 and maintaining the vasodilator and clearance function of ET_B receptors. The effectiveness of sitaxsentan in patients with PAH is proven in randomized, multicenter, placebo-controlled studies—STRIDE-1, 2, 3, 4, 6. The observed side effects are similar to those during therapy with bosentan—elevation of hepatic transaminases [42].

Ambrisentan is a potent and selective inhibitor of ET_A receptors (ET_A:ET_B—4,000:1). The half-life of the medication is 9–15 h which allows once-daily dosing (2.5–10 mg per day). Ambrisentan differs as compared to bosentan and sitaxsentan in its chemical structure. It is a propanoic acid class molecule rather than a sulfonamide class agent. Effectiveness of ambrisentan is evaluated in two phase-3 randomized, double-blind, placebo-controlled studies (ARIES-1, 2) in patients with PAH. Ambrisentan improves exercise capacity with a dose dependent effect. It has an improved safety profile compared with sulfonamide class ERA, which may cause liver abnormalities and require monthly liver function testing. In contrast, ambrisentan has demonstrated a lower incidence of hepatotoxicity. Bosentan induces the cytochrome P-450 isoenzymes (CYP2C9 and CYP3A4) and may decrease the systemic exposure of other drugs that share this metabolic pathway. Sitaxsentan inhibits the activity of CYP2C9 and in this way increases the systemic exposure to drugs metabolized by this cytochrome P-450 isoenzyme (warfarin, sildenafil, oral contraceptives, statins, cyclosporine A). The main metabolytic pathway of ambrisentan is hepatic glucoronidation and to a lesser extent hydroxylation. It has little effect on the activity of cytochrome P-450. There are studies which prove that co-administration of ambrisentan and warfarin does not require correction the dose of the oral anticoagulant. Drug–drug interactions in co-administration of ambrisentan and sildenafil have also not been observed [33, 43, 44].

Drugs that are donors of NO

Nitric oxide is a vasodilator produced by endothelial cells, which use aminoacid L-arginine as a precursor.

Topical nitrates

Topical administration of nitroglycerin cream and glyceril trinitrate patches serve as donors for NO. It can induce local vasodilation in an endothelial-independent mechanism. It results in reducing severity and frequency of vasospastic episodes in patients with primary and secondary RP. Every 24-h period glyceril trinitrate patches have to be removed to avoid nitrate tolerance. The main side effect during their application is headache [1, 45, 46].

L-arginine

Rembold and Ayers [47] report their observations of therapeutic effect of L-arginine (2.0–6.0 g per day), which reversed digital necrosis in four patients with RP and led to improvement of symptoms.

Tucker [48] applied a gel, which is a donor of NO, in 20 patients with RP and observed an improvement of blood flow.

Adrenergic receptor blockers

Prazosin

Prazosin is a specific α1 adrenergic blocker, which causes vasodilation. It is used at the dose of 1–2 mg t. i. d. It is found to be more effective than placebo in primary RP. Side effects such as orthostatic hypotension and tachycardia are rare when medication is used in doses lower than 3 mg daily [13, 49, 50].

Selective α2-c adrenergic receptor blockers

Postreceptor α1 and α2 receptors mediate vasoconstriction of arteries of the extremities in humans. In vascular smooth muscle cells of distal microvasculature, the predominant type of receptors are the α2 adrenergic receptors, which consist of three subtypes α2—a, b and c [51]. In animal models, a cold-induced expression of α2-c adrenergic receptors can be found, which are not active at room temperature [52]. Wise et al. [53] performed a study with the oral selective α2-c adrenergic receptor blocker OPC-28326 at a dose of 40 mg per day in 13 SSc patients with secondary RP and compared the effect with placebo. They observed an improved blood flow and a shorter time for skin temperature recovery after cold provocation test, but it was not statistically significant.

There is evidence that increased contractile response to α2-c agonists is associated with increased protein tyrosine kinase (PTK) activity and tyrosine phosphorylation. Using immunofluorescence and an antiphosphotyrosine antibody it could be shown, that there is greater intracellular tyrosine phosphorylation in response to cooling (31°C) in arterioles from patients with primary and secondary RP than in control subjects. Changes are reversed by genistein which is a PTK inhibitor. The potential use of PTK inhibitors is interesting and requires further investigations [54, 55].

Rho-kinase inhibition

Bailey et al. [56] found that cooling induces activation of Rho/Rho-kinase signaling pathway, and this causes translocation of the α2-c adrenoreceptors from the Golgi complex to the plasmatic membrane as well as an increased sensitivity to Ca^{++} contractile proteins. Rho is a member of the Ras family of small GTP-binding proteins. Rho plays a key role in regulating actin/myosin-dependent contractility in vascular smooth muscle. Its effector molecule Rho-kinase inhibits myosin light chain phosphatase, increases phosphorylation of myosin light chain and causes contraction of vascular smooth muscle, in the absence of an increase in intracellular calcium concentration [56]. Fasudil, which is a specific Rho-kinase inhibitor, is effective in suppressing coronary artery spasm in patients with myocardial ischemia [57, 58]. Tanaka et al. [59] used effectively fasudil to treat cerebral vasospasms after subarachnoid hemorrhage. Moreover, the small GTP-binding protein Rho may be stimulated by ET-1 [60]. Thus, Rho-kinases may be an attractive therapeutic target in patients with RP.

Other possibilities for drug treatment of RP

Antioxidants

In SSc and secondary RP, there is significant oxidative stress. Free oxygen radicals are produced during ischemia and reperfusion. Oxidation of membrane lipids and low-density lipoproteins are among the underlying mechanisms. Therefore, it could be hypothesized that antioxidants may be beneficial [4, 61]. Probucol is a powerful synthetic antioxidant, which has been developed originally as a drug to lower cholesterol. Its administration in RP patients reduces severity and frequency of vasospastic episodes and decreases oxidation of low-density lipoproteins [62]. However, Mavrikakis et al. [63] did not observe a benefit after administration of the antioxidant ascorbic acid in RP. Thus, antioxidants are thought to be beneficial if they are applied in the early phase of SSc, before presence of severe structural damage, but this hypothesis still needs to be proven [1].

Ginkgo biloba

Therapeutic effect of *Ginkgo biloba* has been studied in patients with primary RP in double-blind, placebo-controlled trial. Reduction of frequency of vasospastic attacks in 56% of patients treated with *Ginkgo biloba* versus 27% of the group receiving placebo could be found [64].

L-carnitine

It has been reported that administration of L-carnitine in patients with RP leads to an improved blood flow, measured by capillaroscopy, but no detailed evaluation has been done [2, 65].

Calcitonin gene-related peptide

Calcitonin gene-related peptide (CGRP) is a neuropeptide and a potent vasodilator produced by peripheral sensory nerves. In RP, especially in the secondary form in SSc, a

deficiency of CGRP could be found [66]. Bunker et al. studied the therapeutic effect of CGRP. They observed an effect in ten patients with RP divided into two groups—receiving CGRP and saline, respectively. CGRP was given as an intravenous infusion (0–6 g/min for 3 h, on 5 consecutive days) They observed a significant increase of skin temperature and an improvement in blood flow, measured by laser Doppler. In four cases, healing of digital ulcers could be observed. Side effects were flushing, diarrhea, headache, hypotension [67].

Serotonin receptor antagonists and serotonin reuptake inhibitor

Ketanserin is a serotonin receptor antagonist. It has been used for the treatment of RP for a long time. Improvement, especially in SSc and secondary RP, could be observed [8, 10]. However, according to other data, its effect is not different from that of placebo [13].

Coleiro et al. [68] report about their observations on therapeutic effect of fluoxetine in 26 patients with primary and in 27 with secondary RP. The effect of fluoxetine used at a dose of 20 mg daily, was compared with those of nifedipine (40 mg daily). They observed a reduction in severity and frequency of vasospastic attacks. The strongest response was observed in females and in primary RP. Fluoxetine is a selective serotonin reuptake inhibitor, which is used in clinical practice for the treatment of depression. It decreases the serotonin, which acts as a selective vasoconstrictor. The serotonin plasma level in patients is usually low, but can increase when platelets, as storage compartment, aggregate. Fluoxetine depletes platelet serotonin by 95%. The drug has low incidence of hemodynamic side effects, which are often associated with the administration of other vasodilators such as CCBs [68].

L-thyroxin

In patients with RP and hypothyroidism therapy with L-thyroxin leads to reducing of vasospastic episodes, but large clinical trials have not been performed [69].

Estrogens

The predominance of primary RP in females and the increased severity of symptoms between menarche and menopause suggest that hormonal factors may play an important role in pathophysiology of the disorder. In addition, a positive association between RP and estrogen use is found in postmenopausal women. This effect is not observed in women receiving combined hormone replacement therapy. The role of estrogen may be explained by potentiation of α-adrenergic mediated constriction. Estrogen may also influence blood viscosity and fibrinogen level [70]. Vice versa, the arterial vasodilation is linked to the ability of 17β estradiol to increase NO synthase expression and can induce calcium-dependent NO production [71]. Estrogen administration results also in an increase of flow-mediated dilation of the brachial artery [72].

Antithrombotic drugs

There are data from the literature addressing alteration of platelet functions, coagulation, fibrinolysis etc. in patients with secondary RP. As a result of endothelial damage and decreased production of prostacyclin, activation and aggregation of platelets is enhanced. It is known that plasma levels of a number of platelet's derived mediators are increased in SSc patients, e.g. platelet factor-4, β-thromboglobulin, thromboxane A2, transforming growth factor, platelet growth factor etc. [73]. Thereafter, endothelial damage leads to thrombosis in arterioles. Ames et al. [74] found a defect release of tissue plasminogen activator (t-PA) and increased levels of its inhibitor. Fibrinogen and D-dimer are also found to be elevated in SSc patients. As mentioned above, CCBs and prostacyclins are vasodilators with antiplatelet effects [11, 23]. In addition, it appears reasonable to treat patients with low-dose aspirin in severe forms of RP with digital ulcers [1, 3, 8]. Denton et al. [75] performed a study addressing the therapeutic effect of low-molecular-weight heparin (LMWH) given subcutaneously in 16 patients with severe RP. They found an improved mean finger blood flow recovery time. After treatment serum levels of ICAM-1, VCAM-1 and E-selectin are found to be lower as compared to pre-treatment values. Authors concluded that therapy with LMWH is well tolerated, and potentially beneficial, in patients with severe RP and requires further investigations [75]. Fritzler and Hart [76] found that therapy with recombinant t-PA, used for treatment of acute myocardial infarction, leads to improvement of RP and cutaneous sclerosis. Defibrotide is a drug that increases fibrinolysis and inherits antithrombotic, antiatherosclerotic and antiischemic effects. These properties are probably a consequence of its ability to increase prostacyclin and prostaglandin E2 levels selectively. It also increases t-PA function and decreases the activity of its inhibitor. It is administered intravenously and intramuscularly. In patients with RP, defibrotide restored deficient fibrinolysis, but its true clinical potential needs further assessment [77]. However, the prolonged treatment with anticoagulants is under debate [78].

Other methods of treatment

Laser therapy in low doses and acupuncture have shown good effect in patients with primary and secondary RP.

Hirschl et al. investigated in a placebo-controlled, double-blind intervention, that low-level laser therapy reduces frequency and severity of vasospastic attacks significantly. The mechanism of action of low-dose laser therapy remains unclear as well as the degree of improvement [8, 79]. al-Awami et al. [80] observed a beneficial effect of laser therapy in 47 patients with primary and secondary RP.

Surgery may be indicated in severe RP with digital ulcers in the case of resistance to drug treatment. Debridement of necrotic tissue is the most commonly performed surgical procedure. Some patients, especially those that are developed osteomyelitis, require amputation.

In cases of severe ischemia for local vasodilation and reducing pain is used digital nerve blockade with local anesthetics such as lidocain, bupivacain.

Cervical sympathectomy is a method for treatment of severe ischemic attacks and the current way to achieve a sufficient effect is by thoracoscopy. However, the procedure is risky and the results are usually not sustained, therefore it is not recommended in therapeutic approach of RP patients.

Other surgical techniques for treatment of severe RP are adventitial stripping and digital artery sympathectomy [1, 13, 81].

Treatment of severe RP with digital ulcers

Patients with severe RP and digital ulcers usually need consideration of the underlying disease—the most often is SSc. Patient with severe RP and digital ulcers usually require hospitalization because of the risk of infection or necrosis with subsequent autoamputation. The treatment of choice is intravenous infusion of prostacyclin. In recent years other drugs—ERA such as bosentan, specific inhibitors of phosphodiesterase-5 (sildenafil, tadalafil) have shown to be effective in severe forms of RP as they influence different pathogenetic mechanisms of the disorder. In addition, advantage is that they can be applied orally [1, 23–27, 32, 34–36, 39–41]. Antibiotic treatment is necessary if ulcers are infected. In these cases, immediate surgical consultation is required [1].

Conclusion

Mild forms of primary RP can be controlled with non-pharmacologic measures—lifestyle changes. If these procedures fail to control RP, CCBs are the treatment of first choice. Patients with severe forms of secondary RP and digital ulcers require hospitalization. Most frequently, intravenous infusion of prostacyclin as well as ERA and specific inhibitors of phosphodiesterase-5 are the treatment of choice in these patients as they influence key pathogenetic mechanisms of the disorder. Low-dose aspirin and LMWH have shown good therapeutic effect in these cases. Selective blockers of alpha-2c adrenergic receptors, inhibitors of protein tyrosine kinase and Rho-kinase, CGRP are potential lines of therapy in the future.

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