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New treatment approaches in Raynaud's phenomenon

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CONTENTS

Abstract

This article presents a brief overview of novel approaches to the treatment of Raynaud's phenomenon, a transient, reversible vasospasm due to reduced blood flow to the fingers or toes, for which currently approved therapies are poorly effective. Further understanding of the pathophysiology of Raynaud's phenomenon is key for the development of targeted therapies, which may result in effective treatments for this condition. Here we will focus on experimental therapies that have been investigated in clinical trials.

Introduction

Raynaud's phenomenon is characterized by a transient, reversible vasospasm in the digits of the hands or feet, and which occasionally can affect the nose or ears. It is usually triggered by exposure to cold or stress, followed by a color change of the affected body part, turning first white due to ischemia, then cyanotic and finally red due to reperfusion. Raynaud's phenomenon can be primary (idiopathic, also called Raynaud's disease) or secondary to a variety of conditions, most commonly systemic sclerosis (also known as scleroderma) or mixed connective tissue disease. Raynaud's phenomenon has also been ascribed to autoimmune diseases such as systemic lupus erythematosus, Sjögren's syndrome or rheumatoid arthritis, among others (1).

Primary Raynaud's phenomenon is more common in women than men and is characterized by the presence of vasospasm alone which is not associated with any serious disorder. It may cause superficial ulceration of digital tips, but gangrene rarely occurs. In contrast, secondary Raynaud's phenomenon may result in significant morbidity, presenting with digital ulcers and life-threatening consequences (2). Digital ulcers in secondary Raynaud's are usually very painful, limit hand function and can lead to soft tissue infections or, in severe cases, to gangrene requiring digital amputation. Examination of nailfold capillaries is used to confirm Raynaud's phenomenon associated with systemic sclerosis.

To date, there is no effective treatment for primary Raynaud's disease. Self-help measures such as controlling stress, avoiding exposure to cold sources or warming up digits during a vasospastic episode are recommended. Drugs are of limited use for the primary form, while vasodilators, primarily calcium channel blockers, are often prescribed for secondary Raynaud's phenomenon.

Pathophysiology of Raynaud's phenomenon

The molecular mechanisms behind Raynaud's phenomenon are not yet well understood and will probably be different for the primary and secondary forms of the disease. Independent of etiology, manifestations of Raynaud's phenomenon encompass vasospasm of digital arteries and arterioles revealing impaired vasomotor control. Regulation of vascular tone depends upon the interaction among endothelium, smooth muscle and the autonomic nervous system that innervates blood vessels. Defective control of vascular tone may be associated with causes intrinsic to the vessel wall, such as abnormalities of structural or functional origin, or extrinsic due to impaired neural regulation or intravascular circulating factors, such as platelet activation or fibrinolysis (3).

Endothelial cells secrete vasoconstrictor (endothelin-1 [ET-1]) or vasodilator (nitric oxide [NO], prostacyclin) substances that participate in the regulation of vascular tone. Thus, endothelial dysfunction caused by different conditions may result in imbalanced in the secretion of vasoactive mediators, shifting the equilibrium towards excessive vasoconstriction, leading to vasospasm. For instance, the elevated levels of the vasoconstrictor ET-1 found in patients with systemic sclerosis suggest that endothelium-dependent factors may be important in

Raynaud's phenomenon (4). Abnormal regulation of vasodilators such as NO has also been reported. A recent study showed reduced nitrotyrosine levels in patients with primary Raynaud's phenomenon compared to patients with systemic sclerosis or healthy controls, suggesting potentially upregulated degradation of nitrated proteins. Nitrated protein residues are indicative of the formation of reactive oxygen species (ROS). Given the milder nature of primary Raynaud's symptoms, lower nitrotyrosine levels were suggested to be protective (5). Also, increased NO levels have been observed in patients with Raynaud's phenomenon and limited systemic sclerosis. However, patients with diffuse systemic sclerosis (more severe) presented with normal NO levels, but increased nitrated protein expression and circulating asymmetric dimethylarginine, an endogenous inhibitor of endothelial nitric oxide synthase (NOS) (6). These mixed findings reflect the complex role of NO metabolism in the pathophysiology of Raynaud's phenomenon.

A poor understanding of the causes underlying Raynaud's phenomenon accounts for the fact that therapies have been, in general, of limited success. Traditionally, calcium channel blockers (nifedipine) are among the most commonly used drugs to treat Raynaud's phenomenon, although according to recent reports their actual efficacy in both primary and secondary forms is moderate (7, 8). The prostacyclin analogue iloprost is a potent vasodilator that has been used to treat digital ischemia in patients with Raynaud's phenomenon and has also demonstrated efficacy in reducing the frequency and duration of vasospastic attacks (3).

Treatments under investigation for Raynaud's phenomenon

Therapeutic approaches to treat Raynaud's phenomenon are aimed at either reducing exaggerated vasoconstriction or increasing deficient vasodilatation. This section will discuss investigational drugs that have been studied for primary Raynaud's phenomenon or disease secondary to systemic sclerosis or autoimmune diseases. A summary of relevant clinical studies is displayed in Table I.

Endothelin receptor antagonists

Among vasoconstrictor substances potentially contributing to Raynaud's phenomenon, ET-1 has attracted

Table I: Clinical studies of experimental therapies for Raynaud's phenomenon (from Prous Science Integrity®).

Drug	Design	Treatments	n	Raynaud's phenomenon form	Conclusions	Ref.
Bosentan	Multicenter, randomized, double-blind	Bosentan, 62.5 mg p.o. b.i.d. x 4 wks → 125 mg p.o. b.i.d. x 12 wks Placebo	122	Secondary	Bosentan was generally well tolerated and showed efficacy in preventing the development of new digital ulcers in patients with scleroderma. Bosentan did not promote ulcer healing but was associated with improvement in hand function	9
	Multicenter, randomized, double-blind	Bosentan, 62.5 mg p.o. b.i.d. x 4 wks → 125 mg p.o. b.i.d. x 20-32 wks Placebo	188	Secondary	Bosentan decreased the occurrence of new digital tip ulcers and was associated with reduced pain and improvement in hand function in patients with systemic sclerosis. However, bosentan was ineffective for Raynaud's phenomenon or in facilitating healing of active digital tip ulcers	10
	Open	Bosentan p.o.	11	Secondary	Bosentan demonstrated sustained efficacy and safety in the prevention and treatment of severe Raynaud's phenomenon, cutaneous fibrosis and ischemic digital ulcers in patients with systemic sclerosis	11
Sildenafil	Randomized, double-blind, crossover	Sildenafil, 50 mg b.i.d. x 4 wks Placebo	18	Secondary	Sildenafil was well tolerated and effective in patients with Raynaud's phenomenon resistant to vasodilator therapy	12
	Comparative, randomized, double-blind, crossover	Sildenafil, 50 mg p.o. Vitamin E, 100 mg p.o.	15	Not specified	Sildenafil significantly increased basal forearm blood flow and reduced blood pressure, whereas vitamin E had no effect in patients with Raynaud's phenomenon	13

Continuation

Table I (cont.): Clinical studies of experimental therapies for Raynaud's phenomenon (from Prous Science Integrity®).

Drug	Design	Treatments	n	Raynaud's phenomenon form	Conclusions	Ref.
Sildenafil	Retrospective	Sildenafil, 12.5-100 mg p.o. o.d.	10	Secondary	Significant reductions in both pain scores and frequency of Raynaud's phenomenon attacks were observed in up to 80% of patients with Raynaud's phenomenon secondary to scleroderma treated with sildenafil; 75% of the patients with digital ulcers achieved complete resolution of the lesions. No significant adverse events were reported during the study	14
	Randomized, double-blind, crossover	Sildenafil, 50 mg p.o. b.i.d. x 2 wks Placebo x 2 wks	20	Primary	Sildenafil had no significant effect on signs and symptoms of primary Raynaud's phenomenon, did not reduce the number of Raynaud's attacks per day and had no significant impact on microcirculation and health assessment questionnaire disability scores	15
Tadalafil	Open	Tadalafil, 5-20 mg p.o. 1x/48 h	15	Secondary	Tadalafil was effective for the treatment of Raynaud's phenomenon secondary to inflammatory diseases	16
	Comparative	Tadalafil, 20 mg p.o. 2-3x/wk x 4 wks Pentoxifylline, 600 mg p.o. b.i.d. x 4 wks	14	Secondary	Tadalafil was associated with an increase in peripheral blood flow and reduced the frequency and severity of disease in patients with Raynaud's phenomenon associated with autoimmune diseases	17
Vardenafil	Open	Vardenafil, 10 mg b.i.d. x 2 wks	40	Primary (n=7) Secondary (n=33)	Vardenafil was associated with significant improvements in peripheral blood flow and clinical symptoms in subjects with Raynaud's disease	19
Cilostazol	Randomized, double-blind	Cilostazol, 100 mg/d b.i.d. x 6 wks Placebo	40	Primary (n=19) Secondary (n=21)	Cilostazol treatment was associated with increases in vessel diameter, but no improvement in conduit or microvascular indices was observed. Cilostazol also resulted in a positive change in the slope of brachial responsiveness to cold pressor testing, but only in patients with primary Raynaud's phenomenon	20
Ginkgo biloba	Randomized, double-blind	*Ginkgo biloba* extract, 120 mg p.o. t.i.d. x 10 wks Placebo	19	Primary	*Ginkgo biloba* proved effective in reducing the frequency of attacks in patients with Raynaud's disease	21
	Randomized, double-blind	*Ginkgo biloba* extract Placebo	45	Primary	This phase II study will assess the efficacy and safety of *Ginkgo biloba* in patients with primary Raynaud's phenomenon with regard to vasospastic attacks	22
OPC-28326	Randomized, double-blind, crossover	OPC-28326, 10 mg p.o. OPC-28326, 40 mg p.o. Placebo	13	Secondary	OPC-28326 at doses of 10 and 40 mg was well tolerated and the higher dose was associated with a shorter time to skin temperature recovery, suggesting that selective α_{2c}-adreneoceptor blockade improved digital skin perfusion during recovery from cooling in patients with Raynaud's phenomenon secondary to scleroderma	23

Continuation

Table I (cont.): Clinical studies of experimental therapies for Raynaud's phenomenon (from Prous Science Integrity®).

Drug	Design	Treatments	n	Raynaud's phenomenon form	Conclusions	Ref.
OPC-28326	Multicenter, randomized, double-blind dose-finding	OPC-28326, 2.5 mg p.o. b.i.d. x 2 wks OPC-28326, 10 mg p.o. b.i.d. x 2 wks OPC-28326, 40 mg p.o. b.i.d. x 2 wks Placebo	209	Primary (n=125) Secondary (n=84)	OPC-28326 dose-dependently reduced the incidence of attacks in patients with secondary Raynaud's phenomenon associated with scleroderma, but not in patients with primary Raynaud's phenomenon. OPC-28326 had no significant effect on the severity, duration or clinical impact of the attacks in either subgroup of patients	24
N-Acetylcysteine	Open, multicenter	Acetylcysteine, 150 mg/kg i.v. infusion over 2 h → 15 mg/kg/h i.v. infusion over 5 d	22	Secondary	*N*-Acetylcysteine was safe and showed activity in the treatment of Raynaud's phenomenon secondary to scleroderma	26
	Open	Acetylcysteine, 15 mg/kg/h i.v. infusion over 5 h 1x/2 wks	26	Secondary	*N*-Acetylcysteine acted as an effective vasodilator for the treatment of Raynaud's phenomenon secondary to scleroderma and induced significant changes in plasma adrenomedullin levels	27
Warfarin	Open	Warfarin	14	Secondary	Warfarin was safe and effective in patients with severe Raynaud's phenomenon and ischemic skin ulcers due to coagulation abnormalities or secondary to systemic sclerosis	28
Atorvastatin	Open	Atorvastatin, 10 mg p.o. o.d. x 12 wks	14	Secondary	Atorvastatin increased circulating endothelial precursors in patients with systemic sclerosis and may be effective for Raynaud's phenomenon	29
Nitroglycerin	Randomized, double-blind, crossover	Nitroglycerin [gel] top. Placebo	36	Primary/ secondary	Preliminary results of a phase IIIa study of nitroglycerin in a topical gel formulation in patients with moderate to severe Raynaud's phenomenon demonstrated enhanced blood flow within 5 min of application to the fingers after exposure to cold temperatures	31
	Multicenter, randomized, double-blind	Nitroglycerin [gel] top. Placebo	200	Primary/ secondary	A phase III study will assess the safety and efficacy of nitroglycerin in a topical gel formulation for the treatment and prevention of Raynaud's phenomenon	32
	Open	Nitroglycerin [tape], 5 mg top. over 1 h Control (n=6)	25	Secondary	A tape formulation of nitroglycerin significantly raised finger temperature in patients with systemic sclerosis, especially in those with low finger temperature (< 32.4ºC) before the application of the nitroglycerin tape	33
St. John's wort	Randomized, double-blind	St. John's wort x 6 wks Placebo	76	Primary (n=38) Secondary (n=38)	A phase III study will determine the efficacy of St. John's Wort as add-on therapy in Raynaud's phenomenon	34

attention since it appears to be increased in the serum of systemic sclerosis patients, suggesting a role in the pathogenesis of the disease (4). ET-1 is the most potent physiological vasoconstrictor known, acting through ET_A and ET_B receptor stimulation. It has also been demonstrated to increase smooth muscle cell proliferation and stimulate fibroblast matrix biosynthesis. Thus, evidence supports the hypothesis of a potential benefit in Raynaud's phenomenon for drugs antagonizing ET-1 effects.

Actelion's orally active dual ET_A and ET_B receptor antagonist bosentan (Tracleer®) was examined in the RAPIDS-1 (RAndomized Placebo-controlled Investigation of Digital ulcers in Scleroderma) study, which recruited 122 patients. In this trial, bosentan proved to be effective in preventing the onset of new digital ulcers in patients with systemic sclerosis, being especially effective in those patients who reported ulcers at baseline and in those with diffuse systemic sclerosis, which is the worst form of the disease. Improved hand functionality was also observed

(9). Results from a large multicenter, randomized, placebo-controlled clinical trial evaluating bosentan in 188 patients with systemic sclerosis and at least one recent active digital ulcer revealed reduced development of new ulcers together with improved pain and hand function, with no apparent effects on the healing of active ulcers (10). In contrast, existing ischemic digital ulcers were resolved in all cases in a small open-label study in 11 patients with systemic sclerosis. The number, frequency and time to healing of new ulcers also decreased with bosentan therapy, as well as the frequency and intensity of Raynaud's phenomenon, which improved in all patients (11).

Phosphodiesterase type 5 inhibitors

The vasodilating effects of NO are mediated by the cyclic nucleotide cyclic guanosine monophosphate (cGMP). Phosphodiesterase type 5 (PDE5) inhibitors prevent cGMP degradation, thereby increasing its accumulation in vascular smooth muscle cells, a therapeutic strategy that has proved successful in the treatment of erectile dysfunction and pulmonary hypertension. The efficacy of PDE5 inhibitors in Raynaud's phenomenon has been investigated in several clinical trials that reported overall improvement in vasospastic symptoms and a favorable safety profile. In particular, sildenafil exhibited efficacy in a double-blind, placebo-controlled, crossover study conducted in 18 patients with secondary Raynaud's phenomenon who showed resistance to previous vasodilator therapy (12). Administration of 50 mg sildenafil twice daily for 4 weeks produced a reduction in the frequency and duration of Raynaud's attacks compared to placebo. Two patients suffering from primary Raynaud's showed similar improvement. In all patients who had digital ulcers at baseline, ulcer healing was observed after sildenafil treatment, with total ulcer remission in 2 cases. Interestingly, improvement in Raynaud's symptoms correlated with a more than 4-fold increase in mean capillary flow velocity in sildenafil-treated patients. Another randomized, double-blind, crossover study in 15 patients with Raynaud's phenomenon (unspecified whether primary or secondary) reported a 75% increase in forearm blood flow after sildenafil treatment (13). The study compared sildenafil to the antioxidant α-tocopherol, which demonstrated no effects on blood flow parameters. Results from a small retrospective study of patients with Raynaud's phenomenon secondary to scleroderma who failed conventional vasodilator treatment and were offered sildenafil were also encouraging; 80% of patients experienced a reduction in pain and frequency of Raynaud's phenomenon attacks, and digital ulcer healing was seen in 75% of patients who had digital ulcers at baseline (14). However, sildenafil failed to improve primary Raynaud's symptoms in another randomized, double-blind, crossover study (15).

Other PDE5 inhibitors, such as tadalafil, also reduced Raynaud's symptoms according to a small open-label pilot study in patients with scleroderma and lupus (16). Another study of oral administration of tadalafil 20 mg 2 or 3 times per week during 4 weeks showed a significant reduction in vasospastic attack frequency and duration and increased peripheral blood flow at the end of the treatment period compared to pentoxifylline 600 mg b.i.d. (17). Interestingly, improvement was also seen after long-term treatment with tadalafil, indicating that acute vasodilatation may be only partially responsible for its effects. Also, tadalafil appeared to be a good alternative in a patient suffering from Raynaud's phenomenon secondary to chemotherapy for oral squamous cell carcinoma that did not respond to increasing doses of sildenafil (18). In this isolated case report, equipotent doses of tadalafil improved Raynaud's symptoms and increased capillary blood flow. Improved efficacy was attributed to the longer half-life of tadalafil (17.5 h *vs.* 3.8 h for sildenafil).

Finally, vardenafil was tested in an open-label pilot study carried out in 40 patients presenting with primary (18%) or secondary (82%) Raynaud's phenomenon (19). The duration, number and severity of Raynaud's attacks were reduced by 60%, 50% and 53%, respectively, in vardenafil-treated patients. Improved clinical symptoms correlated with increased digital blood flow in 70% of the patients.

Thus, PDE5 inhibitors appear to be potential therapeutic alternatives to more traditional agents due to their enhanced efficacy and good safety profile.

Phosphodiesterase type 3 inhibitors

It has been shown that PDE3 and PDE4 are the major cAMP-hydrolyzing enzymes. Cilostazol is a PDE3 inhibitor commercially available for peripheral vascular disease, intermittent claudication and stroke. The therapeutic potential of cilostazol in Raynaud's phenomenon was evaluated in a randomized, double-blind, placebo-controlled clinical trial in 19 and 21 patients with primary and secondary Raynaud's, respectively (20). The findings of this study were of moderate relevance and included a significant increase in diameter and flow-mediated dilatation of the brachial artery after 6 weeks of treatment with cilostazol 100 mg b.i.d. However, microvascular circulation and the frequency of vasospastic attacks remained unaffected by treatment.

Other phosphodiesterase inhibitors

Ginkgo biloba extract, which possesses PDE4- and PDE5-inhibitory activity, has also shown benefit in clinical trials for intermittent claudication. A randomized, double-blind, placebo-controlled clinical trial evaluated the efficacy of a standardized *G. biloba* extract (Seredrin®) in 19 patients with primary Raynaud's phenomenon (21). At the end of the 10-week treatment, patients receiving 360 mg of *G. biloba* extract daily reported a reduction in the number of weekly vasospastic attacks of 58% compared to 27% in the placebo arm. There was also a trend for a reduced duration and severity of attacks in the *G. biloba* group. *G. biloba*'s mechanism of action in Raynaud's phenomenon is not well understood and the authors attributed

the benefits to its antioxidant and antithrombotic effects. However, no differences in platelet aggregation could be observed between the active and the control group. A further randomized, double-blind, placebo-controlled efficacy and tolerability study of the *G. biloba* extract EGb-761® in patients with primary Raynaud's phenomenon was scheduled to be completed by July 2006 (22).

α_2-Adrenoceptor antagonists

Antagonizing the vasoconstrictive effects of the sympathetic nervous system is a strategy that has been pursued in the past with prazosin, an α_1-adrenoceptor blocker. However, its use was abandoned due to limited benefit in ameliorating Raynaud's symptoms and the occurrence of side effects. α_2-Adrenergic blockade was suggested to have an effect on Raynaud's phenomenon, since α_2-adrenoceptors are clustered in the fingers (2). Otsuka evaluated two oral doses (10 and 40 mg) of the α_2-adrenoceptor antagonist OPC-28326 in a randomized, double-blind, placebo-controlled, crossover study in patients with Raynaud's phenomenon secondary to scleroderma. Following administration of 40 mg OPC-28326, the time to rewarm the finger after a cold challenge was shorter in Raynaud's patients than in the placebo group, indicating improved digital perfusion (23). In a larger study conducted in 209 patients, OPC-28326 decreased the frequency of Raynaud's attacks in patients suffering from secondary, but not primary, Raynaud's phenomenon, compared to placebo. Other parameters, such as the severity or duration of Raynaud's attacks, were not modified by treatment (24).

N-Acetylcysteine

Oxidative stress has been postulated to contribute to endothelial dysfunction in Raynaud's phenomenon due to peroxidation of cell membrane lipids. In patients with primary and secondary Raynaud's phenomenon, markers of oxidative stress have been found and LDL proteins from scleroderma patients demonstrated increased susceptibility to oxidation (4). Furthermore, exposure to cold has been reported to increase ROS levels, which partly mediate cold-induced vasoconstriction in mouse skin arteries (25). The antioxidant and glutathione precursor *N*-acetylcysteine has been proposed as a potential treatment for Raynaud's phenomenon and its efficacy was tested in several preliminary studies. In an open-label clinical study performed in 22 patients with Raynaud's phenomenon secondary to systemic sclerosis, 5-day infusion of *N*-acetylcysteine reduced the frequency and severity of attacks compared to baseline values. Also, the number of digital ulcers decreased and the recovery time after a cold challenge was reduced at follow-up visits. Additionally, *N*-acetylcysteine was well tolerated and did not cause serious adverse effects (26). A posterior open-label study in 26 patients with secondary Raynaud's phenomenon gave similar results regarding the frequency and severity of vasospastic attacks. Digital perfusion also improved after treatment. Plasma adrenomedullin levels, which were increased in systemic sclerosis patients at baseline, were reduced after *N*-acetylcysteine treatment, which could be interpreted as a measure of treatment efficacy. In fact, adrenomedullin is a potent vasodilator that has been hypothesized to be increased in systemic sclerosis as a response to increased ET-1 secretion (27).

Warfarin

Digital ulcers in systemic sclerosis are thought to be related to tissue ischemia from several processes, including vasospasm secondary to Raynaud's phenomenon, intimal fibrosis proliferation and thrombosis of digital arteries. Therefore, anticoagulation has been proposed as a potential treatment option and low-molecular-weight heparin provided some benefit in cases of severe Raynaud's phenomenon (1). A small open-label study evaluating the efficacy of long-term warfarin was conducted in a mixed group of 14 patients suffering from primary and secondary Raynaud's phenomenon and presenting with ischemic digital ulcers. In patients with both primary and secondary disease, 4-month treatment with warfarin reduced the intensity of the attacks and the onset of new ulcers (28).

HMG-CoA reductase inhibitors

The rationale for the use of HMG-CoA reductase inhibitors for ameliorating the symptoms of Raynaud's phenomenon was recently reported by Japanese researchers who tested the efficacy of atorvastatin in an open-label pilot study in patients with systemic sclerosis (29). This research team recently proposed a new hypothesis whereby vascular abnormalities in systemic sclerosis may be due to impaired vasculogenesis, since this is also required for blood vessel repair. In fact, they found lower levels of circulating endothelial precursors (CEP) in systemic sclerosis patients than in healthy controls and also a lower proportion of CEP differentiating into endothelial cells (30). HMG-CoA reductase inhibitors, such as atorvastatin, have been shown to increase CEP number in patients with coronary artery disease, and therefore potential benefit in systemic sclerosis was proposed. Results from this pilot study showed an increase in CEP number by atorvastatin (10 mg b.i.d. for 12 weeks), along with improved symptoms, with a significant reduction in the Raynaud's Condition Score, which tended to deteriorate after atorvastatin discontinuation. Also, levels of angiogenic factors and endothelial activation/injury markers, which are usually upregulated in patients with systemic sclerosis, decreased after atorvastatin treatment. Further evaluation of statins in larger placebo-controlled clinical trials appears warranted.

Nitroglycerin

Systemic sclerosis features impaired vasodilatation since damaged endothelium compromises NO produc-

tion. This endothelium-dependent vasodilatation plays an important role in disease pathogenesis. Since nitroglycerin is an NO donor with an endothelium-dependent vasodilating effect, it was proposed as a treatment option to ameliorate the symptoms of systemic sclerosis, including Raynaud's phenomenon. Topical forms of nitroglycerin are preferred to avoid associated side effects, including headache and hypotension. MediQuest Therapeutics evaluated the safety and efficacy of a topical organogel containing nitroglycerin (MQX-503) in a randomized, double-blind, placebo-controlled phase III clinical trial (31). Thirty-six patients were included in this study to determine the response to two doses of the topical nitroglycerin formulation. Patients presented with moderate to severe Raynaud's phenomenon, primary or secondary to scleroderma or other autoimmune diseases, and were exposed to a controlled cold challenge. Within 5 min of local nitroglycerin application in the fingers, enhanced blood flow was observed. After completion of this trial, MediQuest scheduled a larger study in 200 patients. This randomized, double-blind, placebo-controlled phase III study will examine the efficacy of this topical nitroglycerin formulation in reducing the number of vasospasm attacks, improving Raynaud's assessment score and decreasing associated symptoms, as well as safety. Secondary outcomes include a reduction in the onset of digital ulcers in patients with scleroderma (32).

A nitroglycerin tape formulation (Millisrol®) was also evaluated by Japanese researchers in a pilot study of 25 patients with systemic sclerosis (33). Finger temperature, determined by thermography, was increased in 60% of scleroderma patients after nitroglycerin tape application, while the temperature in the placebo tape group remained unaffected. This finding suggested improved peripheral circulation after topical nitroglycerin treatment, which should be further investigated in controlled clinical studies.

St. John's wort

Anecdotal observations of selective serotonin reuptake inhibitors (SSRIs) showing improvement in the symptoms of Raynaud's phenomenon suggested the potential use of St. John's wort (*Hypericum perforatum*), which is believed to have a mechanism of action similar to SSRIs. A randomized, placebo-controlled trial is scheduled to commence in September 2006 and is expected to recruit 76 patients with both primary and secondary Raynaud's phenomenon (34). St. John's wort will be tested as a supplement to other available treatments. Primary outcome measures will comprise the frequency, severity and duration of vasospastic attacks.

Online links

Subscribers to Prous Science Integrity® have access to an online animation (Endothelin-1 Receptor Signaling Pathways (Animation + Audio)) illustrating ET-1 receptor signaling pathways.

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