



Insight into the Current Pharmacological Treatment and Clinical Trials for Systemic Sclerosis-Secondary Raynaud's Phenomenon vs. Primary Raynaud's Disease

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Abstract

The initial management of Raynaud's phenomenon includes the same panel of initial pharmacological agents according to the current guidelines for treating the condition, regardless of primary Raynaud's disease or secondary Raynaud's phenomenon, also recognized as Raynaud's syndrome. The current pharmacological therapies show different efficacy in treating primary Raynaud's disease compared to secondary Raynaud's phenomenon. These pharmacological therapies reduce ischemia and increase blood flow via various mechanisms, including inhibiting calcium influx, providing exogenous vasodilating nitric oxide, elongate cGMP life, or increasing cAMP. The article explains the mechanism of reportedly more significant benefits of nitric oxide-related drugs in treating secondary Raynaud's phenomenon. Due to complicated and unknown mechanisms underlying secondary Raynaud's phenomenon, more small-scale clinical trials with other vasodilators have been conducted, for example, soluble guanylyl cyclase activator or sympathetic vasoconstriction inhibitors. The article also discusses two classes of drugs that seemed promising initially, however, failed in an early stage of clinical trial in terms of efficacy. In patients with refractory or progressive Raynaud's phenomenon, an innovative regenerative therapy with autologous fat tissue or fat tissue-derived stromal vascular fraction is under clinical investigation. The article aims to inspire to discover new drug targets and develop novel therapy, which differentially treats the condition for better management when the exact pathophysiology is not well understood.

Keywords: Raynaud's Phenomenon; Raynaud's Disease; Systemic Sclerosis; Vasospasm; Vasoconstriction; Cutaneous; Vascular Abnormalities

Abbreviations: PRP: Primary Raynaud's Phenomenon; SRP: Secondary Raynaud's phenomenon; SSc: System Sclerosis; IRI: Ischemia-Reperfusion Injury; NO: Nitric Oxide; CCBs: Calcium Channel Blockers; PDE5: Phosphodiesterase

5; eNOS: Endothelial Nitric Oxide Synthase; sGC: Soluble Guanylyl Cyclase; Btx: Botulinum Toxin; SVF: Stromal Vascular Fraction.

Introduction

Raynaud's phenomenon (RP), characterized by exaggerated cutaneous vasoconstriction in extremities commonly triggered by exposure to environmental cold temperature or emotional stress, presents initial digital pallor, cyanosis, and redness [1]. With the restoration of blood flow, the skin will return normal hue. Recurrent cycles of excessive vasoconstriction-induced ischemia and reperfusion, depending on the duration and severity of ischemia, will repeatedly induce ischemia-reperfusion-injury (IRI) to the affected sites such as extremities, nose, and earlobes [2-4]. Recurring IRI can lead to a wide range of consequences, from superficial ulceration to necrosis of deep tissue with gangrene that may require amputation. RP is classified into primary RP (PRP) and secondary RP (SRP), named Raynaud's disease and Raynaud's phenomenon or Raynaud's syndrome, respectively. SRP is notably linked to systemic sclerosis (SSc), arterial occlusion, neurological disorders, etc. [5]. Among various etiologies, RP secondary to SSc has received the most attention. Clinical trials of available pharmacological agents have been conducted to pursue potential applications to improve circulation and reduce IRI-induced complications in SSc-related SRP. This review mainly covers the different efficacies of pharmacological therapies or clinical trials for PRP and SSc-related SRP. The literature search is mainly conducted in Pubmed using keywords of "Raynaud's phenomenon, management, treatment". Article type of "clinical trial", "meta-analysis", "randomized controlled trial", or "systemic review" and publication date of "10 years" were selected.

Discussion

According to guidelines, L-type calcium channel blockers (CCBs), phosphodiesterase 5 (PDE5) inhibitors, topical nitrate, angiotensin II receptor blocker, and serotonin reuptake inhibitors are the most common pharmacological measures for both primary and secondary RP in initial management [6]. CCBs, specifically dihydropyridine class with relatively higher peripheral selectivity, generally reduce the attack frequency, duration, severity, pain, and disability in RP patients compared to the placebo; CCBs are more effective in PRP than SRP [7]. Patients who cannot tolerate or have contraindicated the first-line treatment with CCBs may have the alternates, including PDE5 inhibitor, topical nitrate, or L-arginine, depending on the side effect profile and potential additional clinical benefits against other concurrent conditions [8,9]. Vasorelaxant nitric oxide (NO) donor nitrate and NO precursor L-arginine improve blood flow by activating the NO/cGMP/PKG signaling cascade. At the same time, the PDE5 inhibitor enhances vasorelaxation by highly selectively delaying the degradation of cGMP by PDE5. Combination of the PDE5 inhibitors with nitrates

or L-arginine should be prevented to avoid the excessive decrease in peripheral vascular resistance and subsequent hypotension. A systemic review of nitrates efficacy in treating RP demonstrates that this class of medicine is effective, despite variable preparations and doses; furthermore, subgroup analysis shows that SRP patients received greater therapeutic benefits than those with PRP [9]. Similarly, L-arginine is effective for treating SRP but not PRP [10]. SRP patients present peripheral microvascular endothelial dysfunction and damage via exhibiting lower flow-mediated endothelium-dependent vasodilation, predominately capillaroscopic late pattern, and microangiopathy evolution score [11-13]. Significantly greater responsiveness to exogenous NO in SRP receiving nitrates or L-arginine is highly likely attributed to the low levels of endothelium-derived NO due to damaged endothelium and subsequently reduced basal cGMP, consistently suggested by mechanistic studies using pre-clinical models of endothelial nitric oxide synthase (eNOS) knockout mice, removal of the endothelium, or application of eNOS inhibitors [14,15]. While there are more studies on the therapeutic benefits of PDE5 inhibitors for SRP patients, mainly SSc-associated SRP, than with PRP, subgroup analysis is not yet available for comparison [13,16,17]. PDE5 inhibitor is proved to be a valid alternative for SSc-associated RP resistant to vasodilator therapies and benefits patients with concomitant pulmonary arterial hypertension [18].

Due to the complex pathophysiology and pathologies underlying the secondary Raynaud's phenomenon, especially systemic sclerosis, patients with secondary Raynaud's phenomenon are prone to refractory or progressive ischemia leading to severe ulceration or gangrene and may require amputation. Prostaglandins, another vasodilator by increasing cAMP approved to treat pulmonary arterial hypertension (PAH), are intravenously administered to treat acute or prolonged ischemia which fails in responding to the vasodilators used in PRP; however, no systemic evaluation has yet to be conducted in relevant clinical trials [7,19]. Digital or local nerve blocker, lidocaine or bupivacaine, is also suggested for patients with severe ischemia to resolve ischemia temporarily and rapidly relieve pain [19].

Another vasodilator approved to treat PAH, soluble guanylyl cyclase (sGC) activator riociguat, is trialed to treat SSc RP. A pilot study demonstrates that riociguat increases digital blood flow at room temperature and following cold exposure, measured 2 hours post-administration [20]. A 1-year follow-up trial showed Raynaud's condition score is improved in more than half of the patients with early diffuse cutaneous SSc [21]. Good tolerance of riociguat is reported in both trials. Further trials of riociguat in the treatment of SSc RP are expected.

Botulinum toxin (Btx) A increased blood flow in pre-clinical

animal models by inhibiting sympathetic vasoconstriction. Assessment of therapeutic efficacy of btx A in the treatment of SPR in SSc patients presents inclusive results. Treatment with Btx A improved Reynolds score, dermatoscopic parameters, and nailfold capillary pattern staging in a small-scale randomized self-control trial [22]. Another clinical trial reported the improvement of blood flow in the 1-month follow-up did not repeat at the 4-month follow-up; the secondary clinical outcomes measured by QuickDASH, McCabe score, pain VAS, and Raynaud's Condition Score were approximately positive, however lacking clinical effect [23]. Injection of Btx B to SSc-associated RP is additionally examined in a small-size trail. Similarly, the improvement in pain or numbness visual analogue scale scores and Raynaud's score at the 1-month follow-up did not last to the 4-month follow-up; the improvement in skin temperature recovery and the number of digital ulcers sustained for one month [24]. The clinical trial of btx A or btx B was conducted in small sizes of SSc patients and complexed with different conditions of SSc. Therefore, multiple large-scale and disease condition-controlled clinical trials are warranted to assess the efficacy of btx A or B.

Other drugs, including Rho-kinase inhibitors and $\alpha 2C$ -adrenoceptor antagonists, were proposed for RP treatment and underwent small-scale trials; however, they failed to show therapeutic advantages. The $\alpha 2C$ -adrenergic receptor is suggested to play a role in RP, by enhancing cutaneous vasoconstriction induced by a cold environment [25,26]. This finding is corroborated by studies that show the specific subtype of receptor significantly increases vasoconstriction in response to cooling by translocating the $\alpha 2C$ -adrenergic receptor from the cytoplasm to the cell membrane [27-30]. The same receptor subtype also accounts for vibration-induced vascular smooth muscle contraction [31]. Rho-kinase participates in the translocation of $\alpha 2C$ -adrenoceptors following cooling [32,33]. However, clinical trials of highly selective $\alpha 2C$ -adrenergic receptor antagonist ORM-12741 and Rho-kinase inhibitor fasudil did not improve blood flow recovery following cooling in SRP with SSc [34,35]. It should be noted that these findings of $\alpha 2C$ -adrenoceptors and Rho-kinase in enhanced vasoconstriction are established in pre-clinical in vitro, ex vivo, and in vivo models without any profound underlying pathologies subject to cooling or vibration. Hence, participation of $\alpha 2C$ -adrenergic receptor and Rho-kinase in hypersensitivity and hyperactivity of cutaneous vessels in response to a drop in temperature or vibration may be appropriate for the scenario of PRP. Since PRP presents intrusive vasospasm while no prominent abnormality in the vascular bed, it would be reasonable to repeat these trials in patients with PRP instead of SRP to evaluate the therapeutic efficacy of the two classes of medicine, $\alpha 2C$ -adrenoceptor antagonists and Rho-kinase inhibitors. In contrast, SSc-related RP presents vasospasm in macro- and

micro-vasculature frequently refractory to vasorelaxant treatment. Severe and long-standing ischemia is further exacerbated by progressive obliterative microangiopathy of SSc, leading to the varied extent of vascular abnormalities typically manifesting as micro-hemorrhage, dilated capillary loops, avascularity, and neoangiogenesis [36]. The mechanisms underlying the observed vascular remodeling within SSc are poorly understood. The treatment options available for SSc-associated RP mainly target relieving vasospasm and restoring blood flow; however, they fail to combat the cause or minimize the pathological changes to the vascular bed.

Despite the pharmacological options mentioned above, patients suffering from refractory or progressive RP may undergo a highly specialized digital or periarterial sympathectomy, which should be performed before irreversible deep tissue damages. Unfortunately, the success of the microsurgical procedure is not guaranteed [19]. Regenerative therapy with autologous fat injection is first attempted, demonstrating a significant improvement manifested as reduced pain, fewer cold attacks, improved skin and soft-tissue texture, decrease in ulcerations, and patient-reported improved function, without major complications [37]. Phase I trial of injection of adipose-derived stromal vascular fraction (SVF) validates safety, tolerability, and potential efficacy, presenting a substantial improvement in Raynaud's condition score, hand disability, pain, and finger edema [38]. The long-term between 22- and 30-month follow-up reported sustained improvement [39]. The clinical benefits of SVF are still waiting for validation by two ongoing clinical trials in France and the USA.

Conclusion

Treatment for SRP should be tailored to maximize therapeutic potential because the current pharmacological options do not address the vascular abnormality in SRP. Since the complicated pathophysiology underneath SRP is still waiting for elucidation, mechanistic studies of vascular dysfunction and remodeling in SSc remain demanded. Moreover, there is an increased need to discover new drug targets to intervene pathological progression of the vasculature. To effectively treat refractory Raynaud's phenomenon and reduce its complications, new drugs should precisely address its underlying cause and progression.

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