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Contemporary Management of Raynaud's Phenomenon

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Raynaud's phenomenon (RP) is defined as reversible pallor, and also rubor or cyanosis especially digits and it is very common on the general population. It can be an early sign of a connective tissue disease, especially scleroderma and may negatively impact patients' quality of life. Lifestyle modifications including smoking cessation, cold-avoidance, and avoidance of medications that could worsen RP should be considered as first-line therapies. For those who are resistant to conservative measures, dihydropyridine calcium channel blockers (CCBs) are the preferred first-line treatment. The majority of treatment trials in RP study nifedipine, but other drugs such as amlodipine and felodipine. Otherwise, there is evidence supporting the use of topical nitrates and oral phosphodiesterase type 5 (PDE5) inhibitors. Intravenous prostaglandins (prostacyclins, PGI2 such as iloprost and PGE1 which is alprostadil) can be used for refractory cases. There remains a paucity of data for the benefit of botulism toxin, fluoxetine, or bosentan for treating RP in these patients.

Introduction

Raynaud's phenomenon (RP) is a condition with vasospasm of blood vessels, particularly extremities (especially fingers and toes) where one or more digits have pallor and often rubor and cyanosis. It is common in the general population (approximately 5%).[1] RP can be unrelated to other diseases (primary or idiopathic) or associated with other diseases such as connective tissue diseases (CTDs) and is considered then as secondary RP.[1-4] RP is caused by small arteriolar vasospasms in digital arteries/arterioles, and is caused by local interactions between the endothelium, smooth muscle, and autonomic systems.[5]

One of the earliest presenting features of systemic sclerosis (SSc, scleroderma) is frequently RP, and RP may precede other disease manifestations in SSc by several years in the limited cutaneous SSc subset.[1,2] The pathophysiology of SSc associated RP is poorly understood as often the blood vessels obliterate over time. However, new and emerging treatment methodologies are being explored to help alleviate the symptoms of RP and the associated tissue damage, and these will be discussed in this review.

Lifestyle modifications

For most patients, lifestyle modifications can have a significant impact on moderating the severity of RP. These include smoking cessation, avoiding cold exposure, and using vibration-moderating impact tools for those with occupational exposure. Regarding smoking, both abstinence and cessation are associated with reduced RP symptoms. Patients who smoke heavily are more likely to require admission to the hospital for intravenous vasodilators, while those who have never smoked are 4-fold less likely to require surgical debridement of digital ulcers (a complication of severe RP associated ischemia).[6-8] Keeping warm is another key lifestyle modification for those with RP, where cold exposure is a known trigger and is significantly more prevalent in colder climates. There is also sessional variability; as RP is both more frequent and severe in the colder months.[9] One study identified that individuals who had frostbite had were 12 times more likely to develop RP.[10] In addition, hand-arm vibration is a known precipitator and exacerbator of RP, with those having occupational risk factors showing a 7-fold higher prevalence of RP.[11]

Medications can contribute to RP flares and can exacerbate poor peripheral perfusion in these patients. Beta blockers are known to exacerbate RP by increasing alpha-adrenergic tone.[12] One meta-analysis found that the pooled prevalence of RP in those on beta blockers was as high as 14%.[13] Central nervous system stimulants such as methylphenidate and atomoxetine are associated with RP attacks, cold sensitivity, and even digital autoamputation.[14] Calcitonin gene-related peptide (CGRP) antagonists, an emerging treatment for migraine headaches, have been shown to decrease reflex-vasodilatory responses, and can potentially worsen RP.[15] Some chemotherapies and receptor tyrosine kinases (RTKs) can trigger endothelial dysfunction and increase sympathetic activation, and precipitate RP. Vinblastine, particularly in combination with cisplatin and/or bleomycin, may cause RP.[16-18]

For patients who do not respond to the conservative measures mentioned above, pharmacological management is recommended. Interestingly, a meta-analysis of complementary and alternative medicine treatment in RP found that none were more effective compared to placebo.[19]

Calcium channel blockers

The European Alliance of Associations for Rheumatology (EULAR) guidelines recommend dihydropyridine CCBs as the first-line treatment for those who fail conservative management described above.[20,21] Nifedipine was used in the majority of RP data using CCBs. CCBs function in RP by preventing calcium uptake in vascular smooth muscle, which causes vasodilatation, helping to counteract the vasospasm observed in RP.[22] A large 2017 Cochrane review of 38 randomized controlled trials (RCTs) investigating CCBs in RP showed a reduction in the frequency of weekly attacks by 6 RP attacks compared to placebo.[23] In addition, CCBs reduced subjective attack severity. Improvement in RP with nifedipine seems dose dependent.[23] A smaller Cochrane review reported a less impressive, but still significant decrease in the frequency of RP attacks in those treated with CCBs compared to placebo.[24] Interestingly, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) did not show any benefit in reducing RP severity or the development of digital ulcers compared to placebo.[25,26]

Nitrates

For patients who can't tolerate CCB treatment, or who prefer a topical route, topical nitrates have been shown effective in treating RP. Topical nitrates function by releasing nitrous oxide within the vascular smooth muscle, activating cGMP-mediated vasodilation.[27] A 2018 meta-analysis of RCTs reported a small positive effect of topical nitrates compared to placebo.[28] The use of topical nitrates has been shown to improve blood flow to the tips of the fingers, improve finger systolic pressure, and reduce skin discolouration.[29] Topical nitrates should be used in low doses to avoid systemic adverse events such as hypotension and headaches.[30]

PDE5 inhibitors

PDE5 inhibitors are recommended for patients who are non-responsive to CCB treatment for RP or for severe/complicated RP.[20,21] A meta-analysis suggested a nearly 15 minute reduction in daily RP time with PDE5 treatment.[31] Another meta-analysis of 9 RCTs of PDE5i in severe RP (mostly secondary to SSc), reduced pain with treatment.[32] There is likely a dose range that can improve RP more. The side-effects sometimes limit treatment. For

instance, sildenafil is associated with headaches or facial flushing occur in 10% of patients, and 1 in 50 may experience visual impairment.[33] Patients may become hypotensive especially if used with nitrates.[34] Vardenafil and tadalafil have similar side-effect profiles to sildenafil, and should not be taken in combination with nitrates, alpha-adrenergic antagonists, or antiarrhythmics.[35-38] One RCT investigating sildenafil in RP found a significant improvement in digital ulcer healing with sildenafil compared to no treatment.[39]

Prostaglandin analogues

Intravenous prostaglandin analogues have been shown to induce peripheral dilation and improve outcomes in patients with RP who were resistant to treatment with conventional therapies. EULAR guidelines only recommend prostaglandin analogues after failure of oral therapies.[21] Iloprost has positive RCT data and daily treatment for 5 days of peripheral IV therapy yields improvement for several months on average reducing the frequency of attacks.[40] A RCT on alprostadil showed a 20% reduction in RP events in the first week compared to placebo, along with a reduction in overall severity but the results were not sustained beyond the short term.[41]

Fluoxetine

The most recent EULAR guidelines suggest limited evidence for the use of fluoxitene, recommending it if patients are not tolerant to the aforementioned therapies or if those therapies are contraindicated.[41] A small 2001 RCT of 26 patients showed that the mean frequency of RP attacks was 3 in the fluoxetine group compared to 1.5 in the control. There was also a mean reduction in severity by 20%.[42] However, in general fluoxetine is not used for RP due to weak evidence unless if RP is mild and the patient has another reason to require a selective serotonin reuptake inhibitor (SSRI) such as depression or anxiety.

Ketanserin

Ketanserin, a 5HT2A receptor antagonist with known vasodilatory properties, is thought to improve digital blood flow. It was studied in RP decades ago, and is not used in Canada. While the proportion of patients who improved was higher with ketanserin, it did not show a decrease in the severity of RP attacks, and its side-effect profile was significantly higher than that of the placebo.[43]

Botulinum toxin

Until recently, the use of botulinum toxin to treat RP was primarily based on small uncontrolled studies.[44,45] Botulinum toxin inhibits adrenergic responses and promotes vasodilation. Two small RCTs evaluated the use of botulinum toxin in RP. One trial with 16 patients reported improvements in composite scores, dermoscopic patterns, and nailfold capillary pattern scoring in the botulinum group compared to the control group.[46] A subsequent larger multicentre RCT did not show any differences in outcomes between the botulinum toxin and controls.[47] There remains a paucity of evidence for the use of botulinum toxin, and more research is needed in larger cohorts to make definitive treatment conclusions.

Endothelin receptor antagonists (Bosentan and Macitentan)

Bosentan, a dual endothelin receptor antagonist (ERA) used in the treatment of pulmonary arterial hypertension (PAH) and has been studied in RP. Observational studies found reduced severity and frequency of RP attacks,[48] however, a 2010 RCT found no benefits in patients unless they had pre-existing severe digital ulceration.[49] Bosentan can reduce the number of new digital ulcers in SSc, but doesn't heal ulcers nor improve RP.[50,51] EULAR SSc recommendations are for the use of bosentan only for SSc patients with multiple digital ulcers to reduce new ulcers.[21] Bosentan is not approved in Canada for this indication but is approved in PAH. Macitentan another ETA did not improve digital ulcers in patients with SSc added to background therapy.[52]

Conclusion

Treatment for RP includes lifestyle modifications, CCBs, and PDE5 inhibitors. For patients who are refractory to first-line treatments, intravenous prostanoids can be used but it is difficult to obtain iloprost in Canada as it is not approved and has no drug information number (DIN) in Canada, so it has to be approved by Health Canada and obtained from another country. Other therapies used in RP trials are in general unhelpful. Fortunately the majority of Canadians who have RP will never need pharmacological therapy.

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