Tadalafil: a new role in Raynaud's phenomenon?

"...tadalafil in combination with other vasodilators results in significant improvements not only in RP episodes but also in the healing of DUs and prevents the development of new DUs, thus improving the function and quality of life of the patients."

KEYWORDS: endothelial dysfunction ■ phosphodiesterase 5 inhibitor ■ Raynaud's phenomenon ■ scleroderma ■ tadalafil

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Raynaud's phenomenon (RP) is an exaggerated physiological phenomenon defined as episodic cold-triggered ischemic vasospasms of the digital arteries and precapillary arterioles. It can be idiopathic or may be a manifestation of underlying connective tissue diseases (CTDs) such as systemic lupus erythematosus, progressive systemic sclerosis (PSS; scleroderma), mixed connective tissue disease or rheumatoid arthritis. RP associated with CTDs is known as secondary RP [1]. It is more severe and causes tissue ischemia, resulting in digital ulcers (DUs). These DUs are often painful and cause progressive digital shortening with significant impairment of hand function and activities of daily living. DUs are a frequent complication in patients with PSS, with an estimated frequency of 17–30% [2].

"Management of secondary RP is difficult as these patients have severe and long-lasting vasoconstriction, leading to tissue ischemia."

Secondary RP is caused by the vasoconstriction of the arterioles and capillaries due to structural and functional defects. Structural changes range from endothelial cell injury to intimal proliferation, leading to narrowing of arterioles. Functional defect of the endothelium is caused by decreased levels of vasodilators such as nitric oxide (NO) and prostacyclin on one hand, and increased levels of vasoconstrictors such as endothelins on the other. These structural and functional defects cause increased propensity for vasoconstriction, leading to tissue ischemia [3].

Management of secondary RP is difficult as these patients have severe and long-lasting vasoconstriction, leading to tissue ischemia. Nonpharmacological measures such as discontinuation of smoking, avoidance of cold exposure and protection of exposed skin during cold weather, although helpful, are often inadequate in protection. Pharmacological therapy with vasodilators such as calcium channel blockers or angiotensin II receptor antagonists have variable and moderate efficacy at best. Prostacyclins such as iloprost and its analog epoprostenol have been shown to result in good control of RP episodes, as well as healing of DUs; however, its use is limited by continuous intravenous infusions. Moreover, its half-life is short and hence not suitable for long-term therapy [4]. Oral analogs of prostacyclins lack the efficacy of the intravenous prostacyclins and results have been disappointing [5]. Recent studies with the endothelin-1 antagonist, bosentan, have shown it to prevent new DUs; however, paradoxically healing of the existing DUs was slowed [6]. Thus, there is a need for a drug that is easy to administer, safe and efficacious in the treatment of secondary RP.

The phosphodiesterase-5 (PDE5) enzyme degrades cGMP, a molecule responsible for NO-mediated vasodilatation. PDE5 inhibitors, by inhibiting PDE5, increase the levels of cGMP, leading to vasodilatation. In addition, by inhibition of platelet activation it also improves microcirculation [7]. In a double-blind, placebo-controlled crossover trial involving 16 patients, sildenafil was effective in reducing the number of Raynaud's attacks, as well as their severity. It also increased the capillary blood flow velocity measured by laser Doppler [8].

The short and fast action of sildenafil is ideal for the treatment of erectile dysfunction; however, it may not be suitable for chronic conditions such as RP, where a round-the-clock effect is required. Tadalafil is longer acting (half-life: 17.5 h), more specific for PDE5 and does not have the PDE6 inhibitory property, responsible

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for visual side effects of the former. This longer half-life is ideal for the treatment of conditions such as secondary RP and additionally, by allowing less frequent administration, is more likely to improve patients' compliance. The first report of the efficacy of tadalafil in improving RP and healing of DUs was reported in 2005. Thereafter, a few more were reported, one even in a patient who was nonresponsive to sildenafil [9].

Based on these reports and the scientific rationale, we hypothesized that tadalafil improves secondary RP, its consequences and endothelial dysfunction. In our first single-center, randomized, double-blind crossover study in the winter of 2007–2008, 25 patients with secondary RP who had inadequate response to existing vasodilator therapy were randomized to tadalafil (20 mg every other day) or matching placebo as an add-on to their current vasodilator drug therapy for the initial 6 weeks, followed by a washout period of 7 days. Thereafter, patients were switched to the other arm for another 6 weeks. All the patients were receiving calcium channel blockers and 18 were receiving a combination of two or more vasodilators in addition. Compared with placebo, during tadalafil therapy significant improvement in mean daily frequency, mean daily duration and mean daily Raynaud's clinical score of RP were observed. Moreover, all 24 DUs completely healed during tadalafil treatment as compared with three out of 13 DUs during placebo treatment ($p < 0.0001$). Furthermore, only one new DU was reported during tadalafil therapy as compared with 13 during placebo therapy ($p = 0.0005$). Patient and physician global assessment of disease activity and PSS-specific health assessment questionnaire, and impact of DUs on daily activities, also improved significantly (both $p < 0.001$) during tadalafil therapy. This has led to overall improvement in physical as well as mental component scores of quality-of-life questionnaires (short form 36 version 2; SF-36v2) of the patient during tadalafil therapy. Tadalafil led to this overall improvement in RP and DUs due to improvement in the flow-mediated dilatation. Thus, in this small study we could prove that tadalafil was significantly better than placebo in decreasing the severity as well as complications of secondary RP [10]. Another study that assessed the improvement in sexual function in patients with PSS reported that tadalafil was not better than placebo in reducing RP attacks. In this study, tadalafil was evaluated as monotherapy, and all the vasodilators were stopped before initiation of tadalafil therapy. Moreover, the assessment of RP was not the primary outcome and this study was conducted during 2001–2002, with the results published in 2009 [11].

After the initial study, a major challenge was to evaluate the efficacy of tadalafil in a multicenter parallel-group study design. Therefore, we conducted a multicentric study across four centers in north and north-eastern India in the winter of 2009–2010. In this study, 53 patients (26 limited, 27 diffuse scleroderma, 50 females) with RP episodes (≥ four per week) despite being on vasodilators were recruited. A total of 26 patients were randomized to placebo and 27 to the tadalafil arm. Improvement in mean daily frequency, mean daily duration of RP and mean daily Raynaud's clinical score was significant in the tadalafil group as compared with the baseline RP parameters. The mean change in daily frequency, duration and severity of RP was significantly better in the tadalafil group as compared with the placebo group. A total of 18 patients in the tadalafil group had DUs, compared with 13 patients in the placebo group at baseline. Following treatment, DUs healed completely in 14 out of 18 patients in the tadalafil group, compared with five out of 13 patients in the placebo group ($p = 0.026$). New DUs appeared in one patient in the tadalafil group, compared with nine patients in the placebo group ($p = 0.004$). Questions related to dyspnea (Q2), Raynaud's phenomenon (Q4) and digital ulcers (Q5) of the PSS-specific health assessment questionnaire improved significantly in the tadalafil group. Adverse events were similar between the two groups and no serious adverse events was observed [12]. In an open-label study, a group from Italy demonstrated that tadalafil, in addition to decreasing the symptoms of RP, also decreases endothelin-1 levels, one of the most potent vasoconstrictors in physiologic systems [13].

> *"...tadalafil was significantly better than placebo in decreasing the severity as well as complications of secondary RP."*

Thus, it is clear that tadalafil in combination with other vasodilators results in significant improvements not only in RP episodes, but also in the healing of DUs, and prevents the development of new DUs, thus improving the function and quality of life of the patients. Tadalafil as a vasodilator can be safely combined with other vasodilators such as calcium channel blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. This has been confirmed by our two studies in

which all the patients received a combination of tadalafil with other vasodilators and tolerated the drugs without any significant hypotension or any other side effects. It has an advantage over calcium channel blockers as it does not lead to reflux, while it is easier to administer compared with prostacyclins.

The healing of the ischemic ulcers and prevention of appearance of new ulcers by tadalafil is encouraging. Tadalafil, by utilizing the available NO in a more efficient way, increases blood flow not only in the existing blood vessels, but also promotes angiogenesis. Its ability to promote matrix deposition as well as wound remodeling helps in healing ulcers [14]. These properties make it an excellent drug for the treatment of ischemic ulcers that are secondary to Raynaud's.

Tadalafil has some extra advantages that most other vasodilators do not have. PSS patients have pulmonary artery hypertension (PAH), and tadalafil has been proven to be effective in patients who have PAH with or without interstitial lung disease. Tadalafil decreases the right heart pressures and improves performance in these patients [15].

Tadalafil helps PSS patients by improving both PAH and Raynaud's. Early data from the bleomycin model and Peyronie's disease indicates that phosphodiesterase inhibitors may have an antifibrotic capacity. If this hypothesis stands the test of time, tadalafil may become the ideal disease-modifying drug in the management of scleroderma patients [16].

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