Off-Label Drug Uses

Vardenafil: Raynaud Phenomenon

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This *Hospital Pharmacy* feature is extracted from *Off-Label Drug Facts*, a quarterly publication available from Wolters Kluwer Health. *Off-Label Drug Facts* is a practitioner-oriented resource for information about specific drug uses that are unapproved by the US Food and Drug Administration. This new guide to the literature enables the health care professional or clinician to quickly identify published studies on off-label uses and determine if a specific use is rational in a patient care scenario. References direct the reader to the full literature for more comprehensive information before patient care decisions are made. Direct questions or comments regarding *Off-Label Drug Uses* to jgeneral@kumc.edu.

BACKGROUND

Raynaud phenomenon, a vasospastic disorder, is characterized by sensitivity to cold temperatures, triggering the release of vasoconstrictors, including catecholamines, endothelin-1, or 5-hydroxytryptamine. Clinically, vasospasm or vasoconstriction may be associated with a change in the color of the fingers or toes, starting with one or several digits and spreading symmetrically to all fingers or toes. Attacks usually end with a sudden reflow of blood to the area, creating a reactive hyperemia. Criteria for primary Raynaud phenomenon (RP) are symmetrical attacks without necrosis, ulceration, or gangrene and no evidence of secondary causes. Typical onset of primary RP occurs in the early to middle teens as well as sometimes after the fourth decade of life. Symptoms may be mild. In contrast, criteria for secondary RP are associated with severe episodic attacks, usually asymmetrical or with ulcerations. Patients also may have other manifestations of connective tissue disease (eg, arthritis, systemic sclerosis).

Although a local fault in digital microcirculation is thought to be the primary cause, RP may actually be a systemic disease with multifactorial etiology. Vasospasms in the digits may also be accompanied by similar effects in other major organs (eg, lungs, kidneys). Repeated vasospasm attacks can possibly cause ischemic reperfusion endothelial injury, resulting in further vasospasms. The continuing cycle may result in further endothelial damage, particularly in severe cases.

Vasodilators may be of particular use in a disease characterized by vascular spasms; calcium channel

blockers (eg, nifedipine) are potent vasodilators and have been considered the gold standard of treatment,¹ but the use of other vasodilators has been suggested. Vardenafil, an agent marketed for the treatment of male impotence, is a competitive inhibitor of cGMP-specific phosphodiesterase type-5 (PDE-5); it enhances the effect of nitric oxide by causing increased levels of cGMP, resulting in smooth muscle relaxation in the corpus cavernosum. It is also a potent vasodilator and thus has been suggested for the treatment of RP.

PATIENT POPULATION

Adult patients with RP. The majority of patients were female.

DOSAGE AND DURATION:

Oral vardenafil has been administered as 10 mg twice daily for 2 weeks.

RESULTS

The use of vardenafil in the treatment of RP has been evaluated in a limited number of controlled and noncontrolled settings enrolling less than 100 patients, demonstrating benefit in reversing frequency and severity of symptoms. Though the use of sildenafil is mentioned in an evidence-based, international consensus-derived recommendation for treatment of pulmonary arterial hypertension (PAH), PDE-5 inhibitors are not mentioned in management of RP as a component of systemic sclerosis (SSc).^{1,2}

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Guidelines

Although guidelines specific to RP are not available, evidence-based, international consensus-derived recommendations (European League Against Rheumatism [EULAR] recommendations) have been published regarding the management of Raynaud's as a component of SSc. Level A evidence was documented for the use of nifedipine and intravenous iloprost to reduce the frequency and severity of SSc-RP attacks. Dihydropyridine-type calcium channel blockers (specifically oral nifedipine) should be considered first-line therapy with intravenous iloprost or other intravenous prostanoids used in the management of severe SSc-RP. Intravenous prostanoids, particularly iloprost, should be considered in the treatment of active digital ulcers in patients with SSc, particularly when calcium channel blockers have failed (Level A evidence). Bosentan has no confirmed efficacy in the treatment of active digital ulcers in SSc patients but is effective in the prevention of digital ulcers, particularly multiple ulcers, in SSc patients. Bosentan should be considered in diffuse SSc with multiple digital ulcers after the failure of other therapy (eg, calcium channel blockers, prostanoids).

These recommendations note that several other therapies used for the treatment of SSc-related RP (eg, nitrate preparations, antiplatelet agents, angiotensin receptor blockers, or antioxidants) have not been studied extensively, but may be beneficial in some cases. The use of PDE-5 inhibitors are mentioned in this statement for treatment of PAH, but they are not mentioned specifically in this addendum for the management of RP.^{1,2}

Controlled trials

In a double-blinded, placebo-controlled, crossover trial, 53 adult patients with primary and secondary RP were randomized to receive either vardenafil (10 mg twice daily) or placebo for 6 weeks. A washout period of 1 week separated the treatment phases. The majority of patients were female (79%) and had secondary RP (89%) related to SSc. Patients were followed for an additional 4 weeks after the last treatment phase. All vasoactive drugs were discontinued at 1 week prior study enrollment. Primary endpoints were the Raynaud Condition Score (RCS; a self-assessed, 10-item ranking scale) and digital blood flow (measured by the use of a laser Doppler perfusion imager). Treatment with vardenafil when compared to placebo was associated with a significant reduction in mean RCS (-0.45 ; $P = .03$), mean number of attacks (-0.51 ; $P = .005$), and cumulative duration

(-11.43 min; $P = .003$) of RP attacks per day. Clinical improvements in the vardenafil treatment phase were associated with a nonsignificant increase in digital blood flow ($+0.04$; $P = .14$) when compared to placebo. The authors concluded that these RP patients experienced improved clinical improvements with vardenafil.³

Noncontrolled trials

In an open-label study, 40 adult patients with RP (mean age, 49 years) of at least 1 year received vardenafil (10 mg twice daily) for 2 weeks. Approximately 93% of the patients were female. All vasoactive agents (eg, calcium channel blockers, nitrates, etc) were discontinued at least 1 week prior to enrollment. Peripheral blood flow in the index finger was measured by laser-Doppler flowmetry after adjustment to room temperature (24°C [75.2°F]) at baseline, 1 hour post first dose, and after 2 weeks of therapy. Measurements were also repeated during a cold exposure test (CET) at 4°C (39.2°F). Laser-Doppler flowmetry demonstrated improved digital blood flow during vardenafil in 70% of the patients. Significant increases in blood flow from baseline values occurred at both 1 hour after the initial dose (9.9%) and after 2 weeks of continuous therapy (12.9%). Significant increases in blood flow were also noted during a cold exposure test at 1 hour (11%) and after 2 weeks of therapy (19.7%). Patient self-ratings indicated that 68% of the patients reported an overall improvement in clinical symptoms of RP. A total of 60% also reported a reduction in total daily Raynaud attacks, and 50% reported a reduction in the overall number of attacks. Approximately half (53%) of the patients reported a reduction in the severity of attacks. The RCS was also significantly improved at 2 weeks when compared to baseline values (3.54 vs 5.05; $P < .001$).⁴

SAFETY

This is a limited safety profile. Refer to package labeling for complete prescribing information (eg, Warnings/Precautions, Adverse Reactions, Drug Interactions).

The most commonly reported side effects in the reviewed trials included headaches, flushing, dyspepsia, runny nose, visual abnormalities, and ischemia of the index finger.^{3,4} In an open-label study, 1 patient with ischemia of the index finger withdrew from treatment before completion of the study. Vardenafil caused a modest decrease in systolic blood pressure (not specified by authors) and had no effect on heart rate. No serious adverse events were recorded.⁴

THERAPY CONSIDERATIONS

Data from limited number of controlled and noncontrolled trials suggest that vardenafil may reduce the severity, duration, and frequency of attacks with RP. Larger, controlled trials compared with traditional therapy are needed to establish the benefit and safety of vardenafil in the management of RP.

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