Randomized Placebo-Controlled Crossover Trial of Tadalafil in Raynaud's Phenomenon Secondary to Systemic Sclerosis

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ABSTRACT. ***Objective.*** Raynaud's phenomenon (RP) is an important clinical feature of systemic sclerosis (SSc) for which consistently effective therapies are lacking. The study was designed to assess the safety, tolerability, and efficacy of tadalafil, a selective, long acting type V cyclic GMP phosphodiesterase (PDE-5) inhibitor, in this clinical syndrome.

Methods. We performed a prospective, randomized, double-blind, placebo-controlled, crossover study comparing oral tadalafil at a fixed dose of 20 mg daily for a period of 4 weeks versus placebo in women with RP secondary to SSc.

Results. Thirty-nine subjects completed the study and were evaluable. There were no statistically significant differences in Raynaud Condition Score (RCS), frequency of RP episodes, or duration of RP episodes between treatment groups. Placebo response was a confounding factor. Tadalafil was well tolerated.

Conclusion. Tadalafil appears to be safe and well tolerated but lacks efficacy in comparison to placebo as a treatment for RP secondary to SSc. (First Release Sept 15 2009; J Rheumatol 2009;36:2264–8; doi:10.3899/jrheum.090270)

Key Indexing Terms:
RAYNAUD PHENOMENON   SYSTEMIC SCLEROSIS   TADALAFIL   PDE-5 INHIBITOR

Raynaud's phenomenon (RP) is an important clinical issue in patients with systemic sclerosis (SSc) and significantly affects both function and quality of life. The mechanism of RP secondary to SSc is complex and includes contributions from dysfunctional endothelium, abnormal smooth muscle cell responses, fixed luminal obstruction, local platelet activation, and extravascular neuroregulation[1]. Vasoactive therapy of RP secondary to SSc is not uniformly effective, and interventional clinical trials report variable results[2-4].

Endothelial injury is a hallmark of SSc and is associated with reduced production of nitric oxide (NO)[5]. A diverse body of evidence suggests that type V cyclic GMP phosphodiesterase (PDE-5) has an important central role in smooth muscle tone regulation. The cyclic nucleotide monophosphate cGMP is an important intracellular regulator of smooth muscle tone. Nitric oxide, a crucial mediator of smooth muscle relaxation is produced by nitric oxide synthase. NO signals the conversion of GTP into cGMP and furthers intracellular accumulation of cGMP[6]. cGMP is broken down by PDE-5. Inhibition of PDE-5 results in increased available intracellular cGMP, which leads to vasodilatation. There are 3 PDE-5 inhibitor compounds available: sildenafil, vardenafil, and tadalafil. Although most of the literature addresses their use in male erectile dysfunction, experience with use in RP has been reported. Benefit from sildenafil in severe RP and digital ischemia has been suggested in both case reports and series[7,8]. A 40 patient open label trial of vardenafil in RP[9] and a double-blind, placebo-controlled, crossover trial of sildenafil in 18 patients with RP[10] also describe improvement.

Tadalafil has a chemical structure that differs significantly from sildenafil and vardenafil and has little activity against most of the other PDE isoenzymes. Tadalafil has a prolonged mean terminal elimination half life (17.5 h) and efficacy lasting up to 36 h, thus making chronic daily dosing practicable. Steady-state plasma concentration is achieved within 5 days of once daily dosing[11]. Another distinctive feature of tadalafil is the fact that its pharmacokinetics are not affected by food or alcohol intake, age, presence of diabetes, or mild to moderate hepatic insufficiency[6,12-16].

Our pilot trial was designed to test the efficacy and tolerability of once daily tadalafil in the treatment of RP secondary to SSc.

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MATERIALS AND METHODS

Study design. The primary objective of our study was to evaluate efficacy and tolerability of tadalafil in women with RP secondary to SSc. The study was a prospective, randomized, double-blind, placebo-controlled, crossover study evaluating oral tadalafil at a fixed dose of 20 mg daily for a period of 4 weeks versus placebo in women with RP secondary to SSc.

The sponsor of this pilot trial was primarily committed to investigation of the potential benefits of tadalafil in sexual dysfunction. Accordingly, this single center trial incorporated a co-primary outcome measure of possible effects on quality of female sexual function, which is reported separately[17]. All the participants in our trial were hence women and were sufficiently healthy to agree to attempt sexual activity at least once weekly. The 20 mg daily dose of tadalafil was chosen based on sponsor data from other trials suggesting excellent tolerability.

Enrollment began in October to permit study during cold weather months; however, the last enrolled subject exited in June of the following year. The potential for influence of variable weather was examined by comparing results for patients starting the study in October-November with those enrolling during the months of February-March.

There were a total of 5 study visits: 1 screening visit (Visit 1), 3 intermediate visits (Visits 2, 3 and 4), and an exit visit (Visit 5) (Figure 1). During the screening visit (Visit 1) subjects signed informed consent and were instructed on the use of paper diaries to record daily Raynaud Condition Score (RCS)[18], duration and frequency of RP attacks. At 2 weeks prior to randomization subjects received a phone call to reinforce appropriate use of RP diaries. The total duration of the run-in period (between screening and randomization) was 2 weeks. At Week 0, subjects who recorded at least 6 RP attacks per week during the run-in period were randomized to a uniform dose of 20 mg of tadalafil or matching placebo and entered the first 4-week treatment block. This was followed by a 2 week washout period and then by 4 weeks of crossover therapy.

Our study was approved by the UMDNJ-Robert Wood Johnson Medical School Institutional Board for Human Studies.

Subjects. All patients fulfilled the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) classification criteria for SSc[19]. To be eligible, patients had to be at least 18 years old, be able to sign informed consent, and have documented evidence of at least 6 RP attacks per week during the 2-week pre-treatment period. Exclusion criteria included the following: active smoking status, clinically significant evidence of hepatobiliary disease, serum creatinine > 1.8 mg/dl, history of myocardial infarction within the previous 6 months, unstable angina, congestive heart failure of any etiology, current chronic or intermittent use of nitrates or nitrites for angina pectoris or any other condition, significant central nervous system diseases within the last 6 months (stroke, spinal cord injury, etc.), World Health Organization (WHO) Class III or IV pul-

monary hypertension, primary RP or RP secondary to a condition other than SSc, surgical sympathectomy involving the upper limb performed within the previous 12 months, participation in another study with an investigational drug or device during the 30 days prior to study entry, or during the study, use of HIV protease inhibitors, ketoconazole or rifampin. Also, the study excluded subjects who were pregnant or attempting to become pregnant before or during the study and subjects who were lactating or were < 6 months postpartum. All subjects of childbearing potential had to have a negative pregnancy test result prior to enrollment. A woman of childbearing potential was defined as a female who is biologically capable of becoming pregnant. All women of childbearing potential in a heterosexual relationship had to agree to practice a medically acceptable form of contraception during the entire study.

All study patients were required to discontinue certain prespecified concomitant medications before starting the 2-week pretreatment period. These medications included drugs used in the treatment of RP [e.g., calcium channel blockers (CCB), other PDE-5 inhibitors, sympatholytic drugs, arginine, papaverine, nitrates, nitrites and other vasodilators]. CCB and angiotensin converting enzyme inhibitors (ACEI) being used for the treatment of conditions other than RP could be continued at the same dose if the patient was stabilized on the drug. Hypertension developing during the study could be treated with ACEI and/or diuretics. Drug therapies for the underlying disease, SSc (e.g., methotrexate), could be continued if the patient was already receiving them, but new treatment was not allowed during the study. Medications specifically prescribed for psychoses, bipolar disorder, and depression were prohibited. Cyclosporine was specifically prohibited. Palliative therapies (e.g., nonsteroidal antiinflammatory drugs, proton pump inhibitors) were continued. If a patient had been receiving any other medication for some period of time prior to the commencement of the study, as a matter of necessity for the treatment of a medical condition, then the medication was permitted for the duration of the study, based on the judgment of the investigator. If a subject withdrew or was dismissed from the study after any use of the study medication, the exit procedures of the last visit (Visit 5) were implemented. Withdrawn or dismissed patients were replaced as needed to assure full numbers of completed patients.

Treatment regimen. Patients were assigned at random to receive either active treatment with a fixed dose of 20 mg of tadalafil or matching placebo daily for 4 weeks, followed by a 2-week washout period, followed by another 4 weeks of crossover therapy.

Outcome measures. The primary measure of outcome was efficacy of tadalafil for RP. The chosen measures of efficacy were RCS[18], duration and frequency of RP attacks as recorded in a paper diary by the patient. Patients were instructed to record every RP episode along with the time (min) that the attack lasted. At the end of each day, patients completed the RCS, a 10-cm visual analog scale, which is a validated measure of the overall
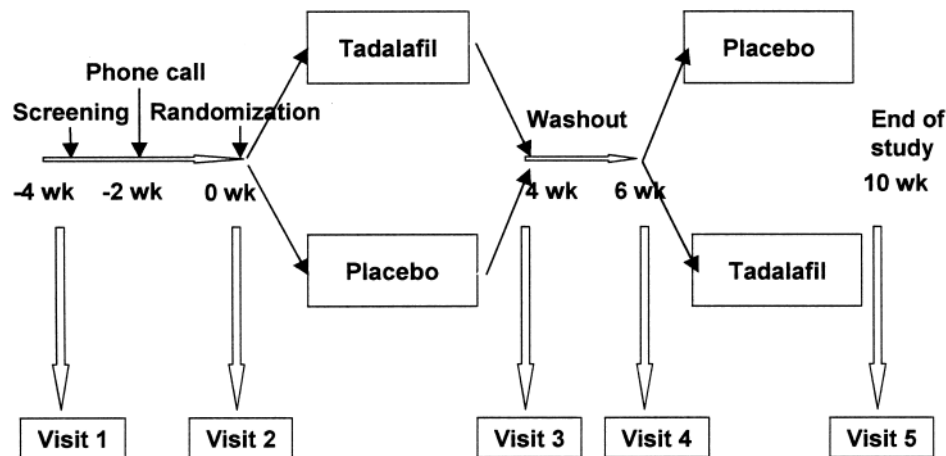

Figure 1. Study design.

effect of the RP (including frequency, severity, effect on activities of daily living)[18]. These measures were obtained weekly during the 2-week pretreatment block and during the 2 4-week treatment blocks. The diaries were collected at each visit. Measures of efficacy were reported as mean change from the baseline. The average RCS was calculated as the arithmetic mean of the daily scores for every given interval. The average daily duration of RP attacks was calculated by dividing the total duration of the attacks during a given interval by the number of diary days. Similarly, the average daily number of attacks was calculated by dividing the total number of RP attacks by the number of diary days for a certain interval. Digital tip ischemic ulcerations were followed as a secondary outcome measure.

Quality of female sexual function was a co-primary outcome; hence, all patients were sexually active women sufficiently well to attempt sexual activity at least once per week. Safety and tolerability of tadalafil were assessed by monitoring adverse events (AE) and severe adverse events (SAE), changes in vital signs, clinical laboratory tests (complete blood count, serum chemistry, urinalysis, and urine pregnancy test), electrocardiogram, and examination at each study visit. The incidence of study-emergent AE was tabulated by treatment group, event, and body system. Events occurring between Visit 3 and 4 (washout period) were summarized with the treatment received at Visit 2.

Statistical analysis. The primary analysis was performed on all patients that completed the study. Measures of efficacy are reported as mean change from the baseline. The paired sample t-test was used to compare the intervention to the placebo group, using a significance level of 0.05. The information about the sample size was based on data from a 2-group, parallel, placebo-controlled trial of oral iloprost for treatment of RP in patients with SSc[20]. A sample size of 40 patients would provide 88% power to detect a 15% difference between placebo and tadalafil in the percent change from baseline RCS at a 0.05 level of significance. It was envisaged that 40 subjects would be enrolled in the study, but 45 patients signed consent to assure the number of evaluable cases at study completion. All data management and statistical analysis were performed with SPSS for Windows 16.0 (SPSS Inc., Chicago, IL). The overall incidence rates of AE were compared between treatments using Pearson's chi-squared tests. There was no subgroup analysis available.

RESULTS

Characteristics of the study subjects. Of the 45 patients who signed consent, 39 completed the study. Three of the patients who signed consent had fewer than 6 RP episodes per week during the 2 week run-in period between Visit 1 and Visit 2 and were considered ineligible. Three other patients were discontinued during the first treatment period due to noncompliance with the protocol (1 subject) and investigator's discretion due to labile clinical circumstances (2 subjects). Thus, 39 patients receiving tadalafil or placebo were evaluated and fulfilled all visits required for full protocol participation.

The final study population consisted of 39 women with a mean age of 52.9 [standard deviation (SD) 10.6; range 40.3-63.3] (Table 1). Subjects were mostly Caucasian, and 75% were classified as having limited SSc (Table 1). The mean RP duration prior to enrolling in the study was 12 years (SD 10 yrs). The frequency of RP attacks and the mean RCS at baseline were comparable to previous large randomized clinical trials in RP[3,20,21].

Table 2 illustrates the use of concomitant medications before and after the initiation of the trial. Calcium channel blockers (CCB) and selective serotonin reuptake inhibitors

Table 1. Baseline characteristics of the study patients.

Demographic and Clinical Variables	
Patients, n	39
Age, yrs	52.9 ± 10.6
Ethnicity, n (%)	
Caucasian	36 (92.3)
African	1 (2.6)
Other	2 (5.2)
Disease classification, n (%)	
Limited SSc	29 (74.4)
Diffuse SSc	10 (25.6)
RP duration, yrs	11.8 ± 10
Average RP attacks/wk, baseline	20.7 ± 12.3
Average RCS in cm, baseline	3.76 ± 1.83

SSc: systemic sclerosis; RP: Raynaud's phenomenon; RCS: Raynaud Condition Score.

Table 2. Concomitant medications.

Medication	Before Study, Patients, n (%)	During Study, Patients, n (%)
CCB	22 (56.4)	7 (17.9)
Antiplatelet agents	12 (30.7)	12 (30.7)
ACEI/ARB	10 (25.64)	8 (20.5)
ERT	9 (23)	9 (23)
SSRI	6 (15.4)	0
Glucocorticoids	6 (15.4)	4 (10.2)
Statins	4 (10.2)	4 (10.2)

CCB: calcium channel blockers; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; ERT: estrogen replacement therapy; SSRI: selective serotonin reuptake inhibitor.

were the most frequently discontinued agents during the study.

Study-specified measures of efficacy for RP are presented in Table 3. There were trends to improvement during this trial in RCS, RP frequency, and RP duration which were unrelated to treatment. All differences were not significant.

We performed several post hoc analyses of potential confounding effects. There was no period effect — specifically no differences in change of RCS either in comparison to baseline or between treatment arms for patients randomized to receive active drug first or to receive placebo first. There was no detectable relationship to environmental temperature during the conduct of this study. This is not surprising. Although our study enrolled between October and April, any given subject completed participation within 10 weeks and did not bridge between very cold and very warm weather. There were no differences in RCS either in terms of absolute values or in terms of change from baseline between subjects studied in October through November versus February through March. In this patient population, there were too few digital ulcers to permit analysis of healing or prevention. Two subjects had a single digital ulcer at entry, which

Table 3. Results of the mean RCS, mean RP frequency, and mean RP duration in a crossover trial of tadalafil in RP secondary to SSc.

	Baseline	Tadalafil (change from baseline)	Placebo (change from baseline)	p
RCS, cm	3.76 ± 1.83	2.43 ± 2.01 (−1.33)	2.53 ± 2.22 (−1.23)	NS
RP frequency, per day	2.93 ± 1.67	2.08 ± 1.72 (−0.85)	2.1 ± 1.78 (−0.83)	NS
RP duration, min	53.42 ± 56.38	40.61 ± 63.81 (−12.81)	47.0 ± 77.60 (−6.42)	NS

RCS: Raynaud Condition Score; RP: Raynaud Phenomenon; NS: not significant.

was still present at the exit visit. No physiologic measures of digital perfusion were included in this trial.

Safety and tolerability. No SAE were reported for the duration of our study. The most frequently encountered AE during the treatment phase were headache, back pain, fluid retention, and vasomotor changes (Table 4). The common AE were similar in the placebo and tadalafil group. Back pain was reported more frequently in the treatment group but this is a well known, idiosyncratic side effect of PDE-5 inhibitors. Overall, tadalafil at 20 mg daily was well tolerated among all the study subjects who received the active drug, with the majority of reported AE being mild to moderate in intensity and with the exception of back pain, judged unrelated to the treatment. Measurements of vital signs, physical findings, electrocardiograms, and laboratory measures were not different between the treatment and the placebo group during the study.

DISCUSSION

We were not able to demonstrate evidence of efficacy of tadalafil by any of our clinical measures of RP. These outcome measures included duration of daily attacks, frequency of RP recorded in a diary, and RP severity as measured by a patient-completed daily RCS. While all measures showed improvement, there were no statistical differences between placebo and tadalafil in any of these variables. At the dose used for the duration of this study (20 mg daily), tadalafil was associated with no severe adverse events. The reported AE were minor.

Tadalafil was reported to increase blood flow and reduce symptoms in a single case of secondary RP not responding to sildenafil[22]. Effects of tadalafil on the pulmonary circulation are described in both high-altitude pulmonary edema[23]

Table 4. Summary of adverse events in 39 subjects with SSc.

	Placebo	Tadalafil
Headache	7	6
Back pain	2	7
Fluid retention	1	2
Vasomotor changes	2	2
Fatigue	1	1
Sleep disturbances	0	2
Palpitations	0	2

and idiopathic pulmonary arterial hypertension (PAH)[24]. Tadalafil is highly selective for the pulmonary circulation and has a longer lasting effect of all available PDE-5 inhibitors on lung and systemic hemodynamics in PAH[25].

There are several limitations to our study. Our subjects had a mean disease duration of 12 years which is longer than the average 8-9 years reported in other RP trials[3,20]. It has been noted that severity of RP tends to increase with disease duration which may be due to cumulative intimal damage over time. Our study sample might thus be less likely to note a measurable difference when exposed to a drug in which actions are largely dependent on endothelial integrity. However, all our subjects were sufficiently healthy to volunteer as sexually active women and only 2 had active digital ischemic ulcers. If our study reflected a selection bias, we speculate that we were enriched for patients with generally less severe SSc vasculopathy.

With a sample size of 39 patients, our study has 88% power to detect a 15% treatment effect. Placebo effect, reported in previous large RP trials to be as high as 46%[20], remains a prominent issue in RP secondary to SSc trial design. Previous studies in RP secondary to SSc have been limited by lack of adequate assessment tools that are sensitive to change over the time course of a short clinical trial. The RCS is the only measure that has been validated. Although uniformly used in RP trials, diary collection of RP information is likely to introduce a recall bias and to be an inaccurate method of assessing the exact status and severity of the peripheral circulation. In the large trial of oral iloprost (308 subjects), mean RCS at entry was 4.21–4.35 units (comparable to that of our study population[20]. Drug and placebo response were 1.32 and 1.00 units respectively — again an effect comparable to our study (Table 3).

A similar crossover trial of tadalafil 20 mg every other day versus placebo has been reported in abstract and showed significant improvement in the mean daily frequency and duration of RP and in the mean daily RCS[26]. The mean age of the subjects in this latter trial was lower than the mean age in our subjects (36.71 vs 52.9), and the study design allowed continuation of established therapies for RP (24 of 24 continued CCB; 18 of 24 participants also continued ACE inhibitors and angiotensin receptor blockers). The magnitude of change on active therapy of mean RCS, RP duration and frequency between baseline and treatment was

similar to our study. However, placebo response was notably absent — a surprising finding for which we offer no explanation[26].

Our study did not permit inclusion of physiologic measures of the digital blood flow in response to tadalafil daily. Peripheral vascular response to PDE-5 inhibitors has been assessed objectively. One study reported a 400% increase in capillary blood flow velocity assessed by laser Doppler anemometry after 4 weeks of sildenafil[10] and another reported an increase of 9.9% in blood flow using laser Doppler flowmetry in an open label trial using vardenafil[9]. However, a recent study of 20 patients with RP (including only 1 subject with RP secondary to SSc) who received a single dose of 10 mg of tadalafil had digital blood flow measured by laser Doppler flowmetry at rest and during 2 heat and cold exposure cycles[27]. Tadalafil had no measurable effect on digital blood flow at baseline, during heating or in response to cold exposure. The physiological response or lack thereof to chronic daily use of tadalafil has not yet been studied in a controlled fashion.

Other studies have suggested that treatment with vasodilators of RP secondary to SSc may not benefit all patients, possibly due to the relative contribution of fixed changes related to the underlying SSc vasculopathy. Additional larger studies are needed to identify a subgroup for which PDE-5 inhibitors may be beneficial or to assess whether or not there is therapeutic efficacy associated with specific agents within this class. In conclusion, the results of our study do not support the use of tadalafil as a therapy for RP secondary to SSc at a dose of 20 mg daily. Placebo response continues to be a significant limitation in RP trials.

REFERENCES

1. Herrick A. Pathogenesis of Raynaud's phenomenon. Rheumatology 2005;44:587-96.
2. Thompson A, Shea B, Welch V, Fenlon D, Pope J. Calcium-channel blockers for Raynaud's phenomenon in systemic sclerosis. Arthritis Rheum 2003;44:1841-7.
3. Dziadzio M, Denton C, Smith R, Howell K, Blann A, Bowers E, et al. Losartan therapy for Raynaud's phenomenon and scleroderma: clinical and biochemical findings in a fifteen-week, randomized, parallel-group, controlled trial. Arthritis Rheum 1999;42:2646-55.
4. Pope J, Fenlon D, Thompson A, Shea B, Furst D, Wells G, et al. Iloprost and cisaprost for Raynaud's phenomenon in progressive systemic sclerosis. Cochrane Database Syst Rev 2000;2(CD000953).
5. Kahaleh B. Vascular disease in scleroderma: mechanisms of vascular injury. Rheum Dis Clin North Am 2008;34:57-71.
6. Uckert S, Hedlund P, Andersson K, Truss M, Jonas U, Stief C. Update on phosphodiesterase (PDE) isoenzymes as pharmacologic targets in urology: present and future. Eur Urol 2006;50:1194-207.
7. Colglazier C, Sutej P, O'Rourke K. Severe refractory fingertip ulcerations in a patient with scleroderma: successful treatment with sildenafil. J Rheumatol 2005;32:2440-2.
8. Gore J, Silver R. Oral sildenafil for the treatment of Raynaud's phenomenon and digital ulcers secondary to systemic sclerosis. Ann Rheum Dis 2005;64:1387.
9. Caglayan E, Huntgeburth M, Karasch T, Weihrauch J, Hunzelmann N, Krieg T, et al. Phosphodiesterase type 5 inhibition is a novel therapeutic option in Raynaud disease. Arch Intern Med 2006;166:231-3.
10. Fries R, Shariat K, von Wilmowsky H, Bohm M. Sildenafil in the treatment of Raynaud's phenomenon resistant to vasodilatory therapy. Circulation 2005;119:2980-5.
11. Porst H. Phosphodiesterase type-5 inhibitors: a critical comparative analysis. EAU Update Series 2004;2:56-63.
12. Rosen R, Kotsis J. Overview of phosphodiesterase 5 inhibition in erectile dysfunction. Am J Cardiol 2003;92 Suppl:9M-18M.
13. Sung B, Hwang K, Jeon Y, Lee J, Heo Y, Kim J, et al. Structure of the catalytic domain of human phosphodiesterase 5 with bound drug molecules. Nature 2003;425:98-102.
14. Boin F, Wigley F. Understanding, assessing and treating Raynaud's phenomenon. Curr Opin Rheumatol 2005;17(6):752-60.
15. Wright P. Comparison of phosphodiesterase type 5 (PDE5) inhibitors. Int J Clin Pract 2006;60:967-75.
16. Forgue S, Phillips D, Bedding A, Payne C, Jewell H, Patterson B, et al. Effects of gender, age, diabetes mellitus and renal and hepatic impairment on tadalafil pharmacokinetics. Brit J Clin Pharmacol 2007;63:24-35.
17. Impens AJ, Rothman J, Schiopu E, Cole JC, Dang J, Gendrano N, et al. Sexual activity and functioning in female scleroderma patients. Clin Exp Rheumatol 2009; Suppl 54: [in press].
18. Merkel PA, Herlyn K, Martin RW, Anderson JJ, Mayes MD, Bell P, et al. Measuring disease activity and functional status in patients with scleroderma and Raynaud's phenomenon. Arthritis Rheum 2002;46:2410-20.
19. Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum 1980;23:581-90.
20. Wigley F, Korn J, Csuka M, Medsger TJ, Rothfield N, Ellman M, et al. Oral iloprost treatment in patients with Raynaud's phenomenon secondary to systemic sclerosis: a multicenter, placebo-controlled, double-blind study. Arthritis Rheum 1998;41:670-7.
21. Gliddon A, Doré C, Black C, McHugh N, Moots R, Denton C, et al. Prevention of vascular damage in scleroderma and autoimmune Raynaud's phenomenon: a multicenter, randomized, double-blind, placebo-controlled trial of the angiotensin-converting enzyme inhibitor quinapril. Arthritis Rheum 2007;56:3837-46.
22. Baumhaekel M, Scheffler P, Boehm M. Use of tadalafil in a patient with a secondary Raynaud's phenomenon not responding to sildenafil. Microvascular Res 2005;69:178-9.
23. Maggiorini M, Brunner-La Roca H, Peth S, Fischler M, Bohm T, Bernheim A, et al. Both tadalafil and dexamethasone may reduce the incidence of high-altitude pulmonary edema: a randomized trial. Ann Intern Med 2006;145:497-506.
24. Affuso F, Palmieri E, Di Conza P, Guardasole V, Fazio S. Tadalafil improves quality of life and exercise tolerance in idiopathic pulmonary arterial hypertension. Int J Cardiol 2006;108:429-31.
25. Ghofrani H, Voswinckel R, Reichenberger F, Olschewski H, Haredza P, Karadas B, et al. Differences in hemodynamic and oxygenation responses to three different phosphodiesterase-5 inhibitors in patients with pulmonary arterial hypertension: a randomized prospective study. J Am Coll Cardiol 2004;44:1488-96.
26. Shenoy P, Agarwal V, Kumar S, Choudhary SK, Jha LK, Singh U, Misra R. Efficacy of tadalafil in secondary Raynaud's phenomenon resistant to vasodilator therapy: a double blind randomized cross over trial [abstract]. Arthritis Rheum 2008;58 Suppl:s402.
27. Friedman EA, Harris PA, Wood AJJ, Stein CM, Kurnik D. The effects of tadalafil on cold-induced vasoconstriction in patients with Raynaud's phenomenon. Clin Pharmacol Ther 2007;81:503-9.