



Controlled Trial of Tadalafil in Raynaud Phenomenon (RP) secondary to Systemic Sclerosis (SSc)

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Abstract

Objective :
Type V cGMP phosphodiesterase inhibitors (PDE-5) are reported as useful in the treatment of RP and for the ischemically threatened digit in SSc. Controlled trials are lacking.

Methods:
39 patients with SSc and RP were recruited for a randomized, double-blinded, placebo-controlled, cross-over study of tadalafil at 20 mg daily. Quality of female sexual function was a co-primary outcome hence all patients were women. The mean age was 52.9 ± 10.6 years. Of the 39 subjects, 29 (74.4%) had limited and 10 (25.6%) had diffuse scleroderma. The mean duration of RP was 11.8 ± 10 years. Eligible subjects recorded daily diaries of RP episodes and Raynaud Condition Score (RCS) for 2 weeks. The average number of RP attacks per week was 20.7 ± 12.3. Subjects that had at least 6 RP attacks per week were randomized to 20 mg tadalafil or placebo daily for 4 weeks followed by a 2 week wash-out and then 4 weeks of crossover therapy. The safety and tolerability were assessed by monitoring adverse effects (AE), vital signs, clinical laboratories and physical examination findings. Efficacy was assessed utilizing a daily paper diary including RCS. Duration and frequency of RP attacks were secondary efficacy outcomes.

Results:
There were no severe AEs. Common AEs included headache (32.5%), myalgia (22.5%), fluid retention (10%), vasomotor changes (7.5%), fatigue (5%), sleep disturbances (5%) and palpitations (5%). 5 subjects reported no AEs. Measures of efficacy are reported as mean change from baseline. All differences were not significant: RCS (t (38) = -0.36, p = 0.71), RP Frequency (t (38) = -0.08, p = 0.93) and RP Duration (t (38) = -1.15, p = 0.25). There were too few digital ulcers to permit analysis. Several validated questionnaires of quality of female sexual function showed no effects (data not presented).

Conclusions:
Tadalafil is a long acting PDE-5 inhibitor amenable to once daily dosing. It appears to be well tolerated in women with SSc and RP. The present data do not support its use as a therapy for RP secondary to SSc although studies in pulmonary hypertension-SSc are in progress. Placebo effect remains a prominent issue in RP clinical trial design.

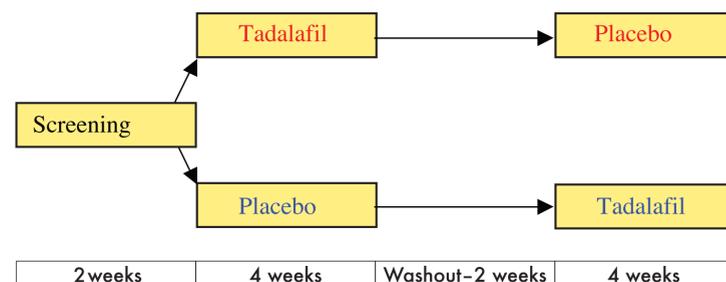
Background and Rationale

- Raynaud phenomenon is present in 95% of patients with SSc
- Severity, frequency and duration of Raynaud attacks have great impact on activities of daily living and may cause digital ulceration
- Vasodilators have been used to treat RP with variable success and side effects
- There are currently no approved therapies for RP
- Type V cGMP selective inhibitors are effective microvascular and macrovascular dilators by prolonging the bioavailability of cGMP — a key downstream mediator of NO
- PDE-5 inhibitors have been reported as useful in the treatment of RP and ischemically threatened digit in SSc
- Randomized controlled studies are lacking
- This present study was designed to assess safety and efficacy of Tadalafil in patients with RP secondary to SSc

Patients and Methods

- 39 female patients with a mean age of 52.9 ± 10.6 years
- 29 (74.4%) had limited and 10 (25.6%) had diffuse scleroderma
- The mean duration of RP was 11.8 ± 10 years
- The average number of RP attacks per week was 20.7 ± 12.3

This study is a randomized, double-blinded, placebo-controlled, cross-over study of tadalafil at 20 mg daily.



- Subjects that had at least 6 RP attacks per week were randomized to 20 mg tadalafil or placebo
- Primary objective was to assess safety and tolerability of Tadalafil (AEs, vital signs, labs)
- Efficacy was assessed utilizing a daily paper diary including RCS, with duration and frequency of RP attacks being secondary outcomes
- Quality of female sexual function was a co-primary outcome; we used sexual activity diaries and a sexual function questionnaire FSFI (Female Sexual Function Index)

Results

Safety and Tolerability

- No severe AEs were noted
- Common AEs included:

headache	32.5%
myalgia	22.5%
fluid retention	10%
vasomotor changes	7.5%
fatigue	5%
sleep disturbances	5%
palpitations	5%

Efficacy

Measures of efficacy are reported as mean change from baseline and revealed:

	RCS (cm)	RP Frequency (per day)	RP Duration (min)
Baseline	3.76	2.93	53.42
Tadalafil	-1.33	-0.85	-12.81
Placebo	-1.23	-0.83	-6.42

All differences were not significant:

- RCS (t (38) = -0.36, p = 0.71)
- RP Frequency (t (38) = -0.08, p = 0.93)
- RP Duration (t (38) = -1.15, p = 0.25)

There were too few digital ulcers to permit analysis. Several validated questionnaires of quality of female sexual function showed no effects.

Conclusions

- Tadalafil appears to be well tolerated in women with RP and SSc
- Long half life makes it amenable to once a day dosing
- In the absence of a clinical effect on RP, our data does not support the use of Tadalafil as a therapy for RP secondary to SSc
- Based on the sample size, our study had 60% power for a 20% treatment effect
- Placebo effect remains a prominent issue in RP clinical trial design

References

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