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


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Abstract

Objectives: 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 SSC. The mean duration of RP was 19.1 ± 10.6 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 washout and then 4 weeks of crossover therapy. The safety and tolerability were assessed by monitoring adverse effects (AE), vital signs, clinical laboratory 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 (32.3%), myalgia (22.5%), fluid retention (10%), vasomotor changes (12%), fatigue (12%), deep ulcers (6%), 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 = 0.23). 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 pulmonology are ongoing. Hypersomnia-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 promoting 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

99 female patients with a mean age of 52.9 ± 10.6 years.

29 (74.4%) had limited and 10 (25.6%) had diffuse SSC.

The mean duration of RP was 19.1 ± 10.6 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.

Efficacy

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

- 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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