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 SSc. The mean duration of RP was 19.8 ± 10.5 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 ± 12.5. Subjects that had at least 6 RP attacks per week were randomized to 20 mg tadalafil in placebo; daily for 4 weeks followed by a 2-week wash-out and then 4 weeks of crossover therapy. The safety and tolerability was 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 (22.3%), fluid retention (10%), vasomotor changes (15%), fatigue (5%), sleep disturbances (25%), and palpitations (5%). Subject rated 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) = -0.15, 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 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 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

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 SSc
• The mean duration of RP was 19.8 ± 10.5 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

<table>
<thead>
<tr>
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<th>Baseline</th>
<th>RP Frequency (per day)</th>
<th>RP Duration (min)</th>
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</thead>
<tbody>
<tr>
<td>Tadalafil</td>
<td>3.76</td>
<td>2.93</td>
<td>53.42</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.12</td>
<td>0.85</td>
<td>12.81</td>
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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


Acknowledgement

The study was an Investigator IND supported in part by a grant from Lilly ICOS LLC, Indianapolis, IN.