

Digital Ischemic Ulcers In Scleroderma Treated With Oral Treprostinil Diethanolamine: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study.

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Background/Purpose:

Prostacyclins are effective vasodilators for vascular features of systemic sclerosis (SSc, scleroderma) but systemic delivery requires the cumbersome logistics of intravenous infusion. Treprostinil diethanolamine (TDE) is an innovative salt form of the prostacyclin analog treprostinil for oral delivery as a sustained-release (SR) osmotic tablet for twice-daily dosing. The objective of this study was to evaluate the safety and efficacy of TDE SR for digital ulcers (DU) in patients with SSc.

Methods:

This was a randomized (1:1), placebo-controlled, parallel group, multicenter study of TDE in adult patients with SSc and presence of at least one DU meeting protocol definition as "active" at Baseline. Known PAH or bosentan therapy were excluded. Study drug was titrated to maximum-tolerated dose (up to 16 mg bid), with assessments at Weeks 5, 10, 15 and 20. The primary endpoint was change in net ulcer burden at Week 20. Secondary endpoints included patient DU pain, physician and patient global assessment and patient Raynaud symptoms by visual analogue scale (VAS), healing of cardinal ulcer, prevention of new ulcers, and measures of hand function and quality of life.

Results:

148 subjects (109 F/ 38M), mean age of 48.8 years and mean SSc disease duration of 10.5 years were enrolled in 27 centers. 64% of subjects had limited cutaneous SSc. Results for net ulcer burden were as follows:



Improvement ($p < 0.05$) occurred in several secondary endpoints, including physician global DU VAS, SHAQ-DI (Scleroderma Health Assessment Questionnaire-Disability Index) components related to hand function, dyspnea VAS, and patient impression of change in overall ulcer status and of Raynaud symptoms. While there were no differences in outcome in subjects classified clinically as either limited or diffuse SSc, exploratory analyses of

individuals who were anti-centromere antibody negative demonstrated a reduction in placebo-corrected mean net ulcer burden of -1.01 (P=0.01) at Week 20. Discontinuation due to adverse events occurred in 13% on TDE vs 8% on placebo with 82% and 86% completing the study, respectively.

Conclusion:

Administration of TDE SR to patients with DU did not result in a statistically significant reduction in net ulcer burden compared to placebo. A variety of secondary endpoints suggested utility for Raynaud symptoms. Critical tissue ischemia in SSc may involve factors other than afferent vasomotor perfusion. Future studies of healing will benefit from refinements in both outcomes assessments and identification and stratification of subjects.

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