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Effect of the endothelin type A–selective endothelin receptor antagonist ambrisentan on digital ulcers in patients with systemic sclerosis: Results of a prospective pilot study

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To the Editor

The dual endothelin receptor antagonist (ETRA) bosentan has been cited as useful in the prevention but not healing of digital ulcers (DUs) in patients with systemic sclerosis (SSc).^{1,2} This incomplete response may be explained by both pro- and antivasoconstrictive activities of the drug, given its relative nonselectivity for endothelin receptor types A and B. We sought to evaluate the effect of the relatively selective endothelin receptor type A antagonist ambrisentan³ on DU prevention and healing.

A prospective, open-label study enrolled SSc patients at Stanford University with 1 active DU located at or distal to the proximal interphalangeal joint that had developed within 12 weeks of screening. Institutional review board approval was obtained. All patients provided written informed consent. Patients received ambrisentan (up to 10 mg daily as tolerated) for 24 weeks. Stable doses of vasodilators, except phosphodiesterase-5 inhibitors, other ETAs, or prostacyclins, were permitted. Outcomes included the total number of DUs, the mean diameter of all DUs, and the number of new DUs that developed in the preceding 4 weeks comparing week 24 to baseline. Mean differences between baseline and week 24 were compared with the Student *t* test using a completer's analysis.

Twenty patients (80% female, 50% white, and 65% with diffuse cutaneous SSc; mean age, 49.3 ± 13.8 years; mean DUs, 3.1/patient) were enrolled, and 16 patients completed 24 weeks. Figure 1 shows a representative DU that healed during the study. The total number of DUs per patient decreased from 3.1 ± 2.1 to 1.3 ± 1.6 (*P* = .004; Fig 2). The mean maximum diameter of total and baseline DUs decreased from 3.3 ± 1.6 mm to 1.6 ± 1.5 mm and 0.1 ± 0.3 mm (*P* < .0001), respectively, at week 24. Fourteen (88%) patients experienced complete healing of all baseline DUs during the study. A mean of 3.2 new DUs per patient developed

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over 24 weeks. The mean number of new DUs that developed 4 weeks before week 24 was not different from the number that developed before baseline (0.44 ± 0.81 vs 0.45 ± 0.69), but they were small (mean diameter, 0.5–3.9 mm). Sixty-one ulcers were present at baseline, 54 developed during the study, and only 21 remained at week 24 (response rate, 94/115 [82%]). Three serious adverse events occurred; these were unrelated to the study drug. Peripheral edema occurred in 75% of subjects, but none experienced elevated liver enzymes.

This study evaluated the safety and efficacy of an ETRA with endothelin type A selectivity for the treatment of DUs in 20 patients with SSc. Bosentan received regulatory approval in the European Union for the prevention of new DUs, but studies did not find that bosentan promoted healing of existing DUs compared with placebo, and 12% to 14% of patients developed elevated liver enzyme levels.^{1,2} Ambrisentan significantly decreased DU burden and mean maximum diameter of lesions, and no patients developed elevated liver enzyme levels. These results concur with a study of 6 patients with SSc that found that ambrisentan, in combination with intravenous prostanooids, led to a reduction in number of DUs per patient from 2.67 ± 0.82 to 0.33 ± 0.52 ($P < .03$) after 24 weeks.⁴ Ambrisentan did not prevent the development of new DU over a 4-week time period after 24 weeks. A placebo-controlled study with more patients will be necessary to conclusively assess the effects of ambrisentan on DUs.

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References

1. Korn JH, Mayes M, Matucci Cerinic M, Rainisio M, Pope J, Hachulla E, et al. Digital ulcers in systemic sclerosis: prevention by treatment with bosentan, an oral endothelin receptor antagonist. *Arthritis Rheum*. 2004; 50:3985–3993. [PubMed: 15593188]
2. Matucci-Cerinic M, Denton CP, Furst DE, Mayes MD, Hsu VM, Carpentier P, et al. Bosentan treatment of digital ulcers related to systemic sclerosis: results from the RAPIDS-2 randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis*. 2011; 70:32–38. [PubMed: 20805294]
3. Maguire JJ, Kuc RE, Davenport AP. Defining the affinity and receptor sub-type selectivity of four classes of endothelin antagonists in clinically relevant human cardiovascular tissues. *Life Sci*. 2012; 91:681–686. [PubMed: 22634326]
4. Parisi S, Peroni CL, Lagana A, Scarati M, Ambrogio F, Bruzzone M, et al. Efficacy of ambrisentan in the treatment of digital ulcers in patients with systemic sclerosis: a preliminary study. *Rheumatology*. 2013; 52:1142–1144. [PubMed: 23463806]

Fig. 1.
Digital ulcer in a patient with systemic sclerosis during 24 weeks of ambrisentan therapy.

Fig. 2.

The mean number of total digital ulcers per patient was lower at week 12 (2.3 ± 1.9 ; $P = .07$) and significantly lower at week 24 (1.3 ± 1.6 ; $P = .004$) compared to baseline (3.1 ± 2.1).