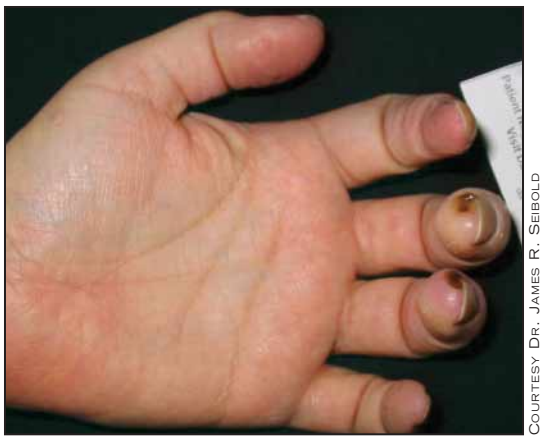

COURTESY DR. JAMES R. SEIBOLD

Bosentan group patients had 2.3 new ulcers versus 4.4 new lesions in the control group.

Bosentan Prevents Scleroderma Ulcers

BY NANCY WALSH
New York Bureau

SAN DIEGO — A second randomized clinical trial has confirmed that treatment with bosentan can help prevent the formation of digital ulcers in patients with scleroderma, Dr. James R. Seibold reported at the annual meeting of the American College of Rheumatology.

A total of 188 patients from 41 centers in North America and Europe were enrolled in the Randomized Placebo-Controlled Investigation of Digital Ulcers in Scleroderma (RAPIDS-2). All had scleroderma and at least one recent active digital ulcer, and their mean disease duration was 8.7 years.

At baseline, patients randomized to the placebo and bosentan groups had a mean of 3.6 and 3.7 digital ulcers, respectively. By 24 weeks, a mean of 2.7 new ulcers were seen in the placebo group, compared with a mean of 1.9 in the active treatment group, Dr. Seibold said in a late-breaking poster session. This difference was statistically significant.

Statistically significant differences were already apparent by week 12, at which time the placebo group had a mean of 1.3 new digital ulcers, whereas the bosentan group had a mean of 0.8 new ulcers.

The effects were particularly marked in patients with more severe peripheral vascular injury, said Dr. Seibold, director of the University of Michigan Scleroderma Program, Ann Arbor.

Among patients who had more than 3 ulcers at baseline, those receiving placebo developed 4.4 new ulcers during the 24 weeks of the trial, while those receiving bosentan had 2.3 new ulcers, which was a statistically significant difference, he said.

"These data suggest that if a patient with scleroderma were to present at a physician's office with three digital ulcers, he or she would be likely to develop an additional four to five ulcers over the next 24 weeks, and the risk of that occurring would be reduced by nearly 50% on bosentan," Dr. Seibold said in a discussion of the trial at a satellite symposium.

Bosentan treatment did not, however, shorten the time to healing of active digital ulcers. In 6 months, only 50% of ulcers had healed despite treatment with topical and systemic antibiotics and adjustments to therapy for Raynaud's phenomenon. "These data are quite instructive in terms of getting a handle on how intractable this problem is. We are treating the untreatable," he said.

The study also evaluated the effects of treatment on hand functionality as measured by the Scleroderma Health Assessment Questionnaire. Most notable was a significant improvement in patients' ability to dress. On this domain, change from baseline was –0.35 in the bosentan group; a change of –0.22 is considered clinically meaningful.

The findings of this study are in agreement with those in RAPIDS-1, which evaluated bosentan in 122 patients with scleroderma for 16 weeks, and found a 48% reduction in the mean number of new ulcers (Arthritis Rheum. 2004;50:3985-93).

Serious adverse events were uncommon. As in RAPIDS-1, more patients in the active treatment group had elevations of liver enzymes greater than 3 times the upper limit of normal (10.5%) than in the placebo group (1.1%).

Bosentan (Tracleer) is a dual endothelin receptor antagonist. Endothelin-1 and its receptors, particularly the ET_B receptor, are overexpressed in scleroderma, and the vasoconstrictive and pro-proliferative effects of endothelin-1 contribute to the vasculopathy associated with the disease. The RAPIDS data "support the contention that chronic endothelin receptor antagonism has an important effect on vascular integrity and function in systemic sclerosis," he said.

Dr. Seibold disclosed that he has received research grants and consulting fees from Actelion Pharmaceuticals Ltd., the sponsor of the trial. ■