

# Bosentan Inhibits Digital Ulcers in Scleroderma

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.



**Bosentan blocks dual endothelin receptors, thereby preventing digital ulcers in patients with scleroderma.**

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 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<sub>B</sub> 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.

## Pamidronate Alters Immune Response in Scleroderma

BY NANCY WALSH  
New York Bureau

SAN DIEGO — A single infusion of pamidronate resulted in immunologic changes that, at least theoretically, could lead to a reduction in collagen production and fibrosis in scleroderma, Dr. Kenneth J. Warrington reported at the annual meeting of the American College of Rheumatology.

Immune activation plays a central role in the complex pathogenesis of scleroderma, with upregulation of certain profibrotic cytokines such as interleukin-4 (IL-4), IL-13, and transforming growth factor- $\beta$  (TGF- $\beta$ ).

Pamidronate is an aminobisphosphonate that inhibits bone resorption and is indicated for the treatment of hypercalcemia associated with malignancy as well as for bone metastases and Paget's disease. In recent years it has come to light that this agent also has immunomodulatory properties, acting as a ligand for a subset of T cells that express the  $\gamma\Delta$ -T-cell receptor.

When this subclass of T cells is activated by pamidronate, an alteration in the cytokine pattern occurs. There is an increase in production of interferon- $\gamma$  (IFN- $\gamma$ ), a cytokine that has antifibrotic properties. Up-regulation of IFN- $\gamma$  might alter the extracellular matrix deposition of collagen, said Dr. Warrington of the University of Tennessee, Memphis. "Therefore, administration of pamidronate could potentially restore the cytokine balance in scleroderma," he said.

This hypothesis was tested in a small pilot study that included 19 patients, three-quarters of whom were women and whose mean disease duration was 11 years. They were

given a single intravenous dose of 60 mg pamidronate and followed for 6 months, with cytokine production and lymphocyte activation being measured at 48 hours and at weeks 4, 8, 12, and 24 post infusion using enzyme-linked immunosorbent assay and flow cytometry.

At 48 hours there was a statistically significant increase in activated CD4 and CD8 lymphocytes; by week 4 the percentage of activated lymphocytes had returned to baseline levels. At weeks 4 and 8 a decrease in production of the profibrotic cytokine TGF- $\beta$  was observed in vitro, along with an increase in the production of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), which regulates the transcription of type 1 collagen.

And with a specialized cytokine secretion assay it was noted that the  $\gamma\Delta$ -T-cell subset was indeed directly activated by pamidronate to produce IFN- $\gamma$ . Cytokines from these T cells may then act indirectly on other cell subsets, inducing further activation downstream, Dr. Warrington said.

Safety was monitored throughout, and the drug was well tolerated. Four patients reported transient flulike symptoms at the 48-hour visit, a finding that has been reported previously with pamidronate. Clinical parameters overall were unchanged.

The findings of this study provide a basis for a follow-up study in which pamidronate would be infused repeatedly, with the goal of inducing sustained antifibrotic modulation of IFN- $\gamma$ , TNF- $\alpha$ , and TGF- $\beta$ , according to Dr. Warrington. This work was supported by grants from the Scleroderma Foundation and the National Institute of Arthritis and Musculoskeletal and Skin Diseases.

## Bosentan Ups Survival of Patients With Scleroderma-Associated PAH

BY BRUCE JANCIN  
Denver Bureau

STOCKHOLM — Survival of patients with systemic sclerosis-associated pulmonary arterial hypertension has improved markedly since the introduction of bosentan, Dr. Mark H. Williams said at the annual congress of the European Society of Cardiology.

Prognosis of scleroderma-associated pulmonary arterial hypertension (PAH) has traditionally been considered "very poor," with death often resulting from right heart failure, noted Dr. Williams of Royal Free Hospital, London.

He presented an observational study involving 92 patients with scleroderma-associated PAH diagnosed by cardiac catheterization. Of those, 45 who were diagnosed with World Health Organization functional class III PAH since bosentan (Tracleer) was approved for European marketing in 2002 received the dual endothelin receptor antagonist as first-line therapy.

The remaining 47 WHO class III patients, who were hemodynamically matched to the bosentan group but were treated during 1998-2002, served as controls. Of these, 27 received an intravenous prostanoid as first-line therapy; the other 20 were unable to obtain funding for this extremely costly form of therapy.

One-year survival in the bosentan group was 81%, compared

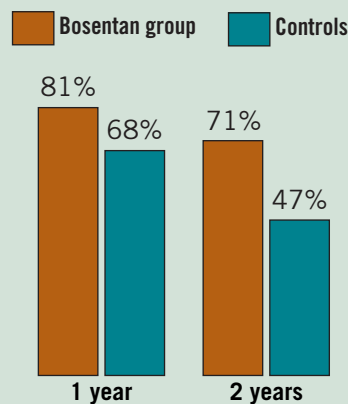
with 68% in the historic controls. Two-year survival was 71% with bosentan, compared with 47% in controls.

Bosentan, a nonselective dual endothelin receptor antagonist, stabilized cardiac hemodynamics, Dr. Williams said. Pulmonary vascular resistance, assessed in the majority of patients by repeat cardiac catheterization 9-12 months into treatment, climbed by 38% in the control patients but decreased by 1% in the bosentan group, compared with baseline.

Right artery and mean arterial pressures did not differ significantly between the two groups.

Dr. Williams has no conflict of interest regarding Tracleer or its manufacturer, Actelion.

### Scleroderma-Associated PAH Survival



Source: Dr. Williams