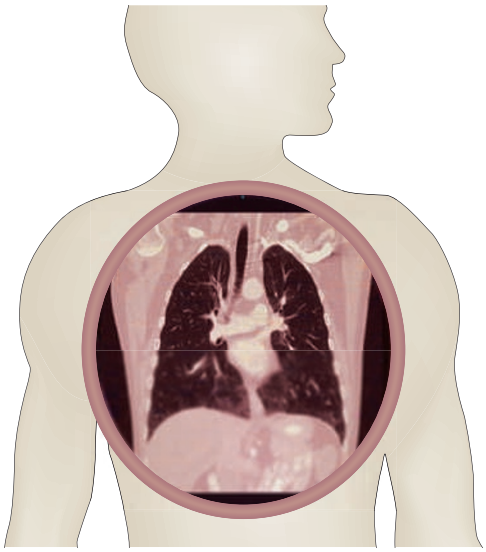
CONNECTIVE TISSUE DISEASES

Bosentan treatment unable to alter the progression of interstitial lung disease in patients with SSc

The main cause of disease-related mortality in patients with systemic sclerosis (SSc) is pulmonary complications, arising from interstitial lung disease (ILD) or pulmonary arterial hypertension, or both. Licensed for the treatment of SSc-associated pulmonary arterial hypertension, bosentan nonselectively antagonizes endothelin receptors. SSc is a systemic, fibrosing, connective tissue disease, so inhibiting endothelin-1, which can induce fibroblast chemotaxis and proliferation, promote collagen deposition, inhibit collagenase activity and enhance fibronectin levels, seems an attractive approach for the treatment of ILD. Furthermore, levels of endothelin-1 are increased in serum and in bronchoalveolar lavage fluid from patients with SSc-associated ILD. Bosentan is also known to be safe and well-tolerated in SSc patients. However, the first randomized, prospective, placebo-controlled trial to investigate the treatment of ILD associated with SSc using bosentan failed to alter the progression of SSc-associated ILD or stabilize or enhance exercise capacity, as reported in *Arthritis & Rheumatism*.

Despite ILD being a primary cause of death in SSc, the disease progresses relatively slowly, such that many patients have remarkably stable disease. "We thus sought a cohort enriched for risk of worsening disease and based this on duration of disease and extent of lung involvement by both physiologic testing, such as pulmonary function tests, and high-resolution computed tomography," explains Professor James Seibold, a member of the team behind the trial. The trial prospectively analyzed data from 163 randomized patients: 86 received bosentan (62.5 mg twice daily, increasing to 125 mg twice daily after 4 weeks) and 77 received placebo.



Patients were assessed during initial screening, randomization, and then after 3 months, 6 months, 9 months and, finally, at 12 months. "The trial was resoundingly negative," states Professor Seibold. No appreciable difference was observed between the treatment groups with regard to the primary end point, which was a change in the 6-minute walk distance (6MWD) up to month 12. In the bosentan-treated group, the mean change from baseline (± standard deviation) was −12 ± 100 m, whereas the placebo group showed a mean change of 9 ± 84 m.

A total of 48 patients from both groups failed to complete the 12-month treatment, mainly as a result of adverse events; worsening pulmonary function tests were the most common adverse event in both treatment groups, indicating that bosentan had no effect on this secondary end point. Other adverse events included skin ulcers, fatigue, infection of the upper respiratory tract, cough, arthralgia, peripheral edema, diarrhea, bronchitis, sinusitis and anemia. No deaths occurred during the course of the study. Elevated levels of liver aminotransferases were recorded in 11.3% of patients treated with bosentan, compared with 1.2% of patients receiving placebo. During the course of the study, most patients showed a relatively slow disease progression rate, with little change in forced vital capacity and diffusing capacity. Approximately 20–25% of cases, however, showed more marked disease progression, in keeping with the decline frequency over the period of 1 year reported in the literature, which confirmed the suitability of the cohort selection criteria.

The lack of effect shown by bosentan compared with placebo on this cohort 'enriched' for worsening disease indicates that treatment with this nonselective endothelin receptor antagonist is not effective at stabilizing or improving SSc-associated ILD. According to Seibold, "Since the trial was largely based on clinical descriptive data, the reasons for failure are unclear, although there are a number of possibilities. First, endothelin might not be a key mediator of disease progression. Second, the concept could have been right but the drug might have been wrong. Bosentan is a nonselective endothelin antagonist and has relatively weak receptor binding. There are hints of tachyphylaxis in longer-term studies in scleroderma. Third, endothelin's effects might be influenced by the microenvironment *in vivo* in ways that are not understood." Seibold points out that lessons from this trial might inform the design of future interventional studies for SSc-associated ILD, adding that "Other endothelin antagonists might be tested in the relatively near-term future."

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