Successful treatment of systemic sclerosis digital ulcers and pulmonary arterial hypertension with endothelin receptor antagonist bosentan

Sir, We read with interest the recent reports describing the promising results of studies exploring the role of the dual endothelin receptor antagonist bosentan in pulmonary arterial hypertension (PAH) [1, 2]. We report the case of a patient with systemic sclerosis associated with PAH and ischaemic digital ulcerations who responded successfully to bosentan.

A 50-yr-old male dentist presented in 1995 with severe Raynaud’s syndrome and acral systemic sclerosis. Over 2 yr, he had developed severe pruritus, worsening upper
and lower limb ischaemia and digital ulcerations. The scleroderma progressed to a more diffuse form. In mid-1998 the patient developed progressive proteinuria (3 g/24 h) and impaired renal function. An echocardiogram showed an elevated systolic pulmonary artery pressure (PAP) of 45 mmHg. Hospitalizations for Iloprost infusions were required, and the digital ulcerations resolved.

By November 1999 the patient’s skin ischaemia had worsened; the sclerosis had progressed and numerous small ulcers had developed over his entire body. He experienced an almost fatal acute renal crisis (blood pressure 190/90 mmHg and proteinuria 6 g/24 h) and developed progressive dyspnoea on exertion with clinical signs of right heart failure. Right heart catheterization demonstrated severe PAH with a mean PAP of 55 mmHg (normal range 10–22), a right atrial pressure (RAP) of 18 mmHg (normal range 0–8), a cardiac index (CI) of 2.5 l/min/m² (normal range 2.8–4.2) and a pulmonary vascular resistance (PVR) of 874 dyn/s/cm⁵ (normal range 45–120), which was unresponsive to nitric oxide.

In October 2000, the patient’s haemodynamics had deteriorated further (mean PAP 70 mmHg, RAP 15 mmHg, CI 2.02 l/min/m², PVR 1417 dyn/s/cm³). The patient was enrolled in a double-blind, placebo-controlled study investigating the efficacy and safety of bosentan in patients with PAH (the BREATHE-1 study) [2]. At inclusion, the patient was in modified New York Heart Association (NYHA) functional class III, with a 6-min walk distance of 405 m. At baseline the patient had no skin ulcers; however, during the 16-week double-blind period he developed moderate left leg ulceration, resulting in difficulty performing the walk test. After the study had been unblinded, it was revealed that the patient had received placebo. He entered the open-label extension and active treatment with bosentan was started in January 2001. After four weeks of bosentan 62.5 mg twice daily (b.i.d.), the patient’s leg and small skin ulcers had healed.

After 6 months of bosentan at 125 mg b.i.d., the patient’s clinical symptoms had improved significantly: he could climb stairs, his 6-min walk distance was 508 m and he was in NYHA functional class II. Furthermore, his digital ulcers had healed completely and numerous telangiectasias could be observed all over his body, suggesting marked cutaneous vasodilation. His cutaneous fibrosis was significantly reduced, remaining distally on the hands and feet only. Tolerance of bosentan was good.

At the time of writing (June 2002), after 17 months of bosentan treatment, the patient’s clinical condition is satisfactory (6-min walk distance 480 m, NYHA functional class II, decreasing dyspnoea, no evidence of right heart failure), with progressive improvement of the skin (Fig. 1). Right heart catheterization has confirmed improvement of pulmonary haemodynamics (mean PAP 58 mmHg, CI 2.77 l/min/m², PVR 826 dyn/s/cm³).

Scleroderma is characterized by generalized vasculopathy, fibrosis of the skin, blood vessels and visceral organs, and inflammation. Digital ulcers develop in 15–25% of patients with scleroderma; these are intensely painful, slow to heal (3–15 months), and affect the quality of life significantly. Continuous or long-term treatment with vasodilators and antibiotics may be required to prevent recurrences and secondary infections and to suppress the need for digital amputation.

An excess of endothelin (ET-1) is an interesting hypothesis to explain the underlying pathology in this case. ET-1 is a potent endogenous vasoconstrictor and a mitogen for fibroblasts, smooth muscle and endothelial cells [4–6]. It is released by scleroderma fibroblasts in vitro [6] and may increase dermal fibrosis in systemic sclerosis [7]. In addition, ET-1 levels are increased in patients with systemic sclerosis [8] and evidence suggests that it plays a significant role in the pathogenesis of collagen vascular diseases [9]. ET-1 has also been implicated in the pathogenesis of PAH, as plasma ET-1 levels are elevated in patients with PAH and diffuse scleroderma [9]. Taken together, these results support a multiple role for ET-1 in the pathophysiology of scleroderma associated with PAH and skin ulcerations. The rapid response of this patient’s skin ulcers to treatment with bosentan, and possibly the improvement in...
in his cutaneous fibrosis, could be a result of bosentan’s activity as a dual endothelin receptor antagonist, opposing the vasoconstrictive and profibrotic effects of endothelin. This interesting case raises the prospect of a role for endothelin receptor antagonism in treating vasculopathy in connective tissue disease, and further studies with bosentan are warranted.

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Accepted 21 June 2002

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