Successful treatment of patients with severe secondary Raynaud’s phenomenon with the endothelin receptor antagonist bosentan

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Secondary Raynaud’s phenomenon (RP) in patients with systemic sclerosis (SSc) and other collagen vascular diseases is a serious manifestation of microvascular damage that may precede the onset of visceral and/or cutaneous sclerosis for years. Recent studies have demonstrated that the endothelin receptor antagonist bosentan prevents the development of new digital ulcers in SSc. We investigated the potential benefits of bosentan in patients with secondary RP associated with pre-scleroderma and with SSc, independent of digital ulcers. Three patients with secondary RP received bosentan 62.5 mg twice daily for 4 weeks followed by 125 mg twice daily for 12 weeks during the winter season. Pain (visual analogue scale), Raynaud’s disease activity (Scleroderma Health Assessment Questionnaire), number and severity of daily Raynaud’s attacks (diary) and peripheral thermoregulation (thermography) were assessed during treatment periods. Pain, Raynaud’s disease activity, number and severity of Raynaud’s attacks significantly decreased during treatment periods. Thermography after 16-week treatment demonstrated improved peripheral thermoregulation. Although this is a small observational study, treatment with bosentan appears to measurably reduce the daily impact of Raynaud’s disease and improve peripheral thermoregulation in patients with secondary RP, independent of digital ulcers.

Introduction

Raynaud’s phenomenon (RP), a painful condition induced by cold and stress, is defined as an episodic ischaemia of distal extremities, particularly the digits. Excessive vasoconstriction leads to pallor and cyanosis followed by hyperaemia. The majority of affected individuals have primary RP, a functional vascular defect, usually not complicated by tissue loss. In 1–2% of patients, however, it represents the key initial clinical symptom of connective tissue disease including systemic sclerosis (SSc) and mixed connective tissue disease (MCTD). SSc is a multistage connective tissue disorder characterized by microvascular dysfunction, immune activation and excessive deposition of extracellular matrix within the skin and visceral organs [1]. RP associated with structural alterations of the nailfold capillaries and with disease-specific anti-nuclear antibodies (ANA) is defined as pre-scleroderma [2, 3] that may precede the onset of systemic disease by several years. Present in more than 95% of SSc patients, secondary RP is frequently complicated by severe functional disability, infarction and digital ulcerations [1]. Therapeutic management of severe RP remains a challenge. Although various vasodilators including calcium-channel blockers, angiotensin converting enzyme inhibitors and intravenous prostaglandin analogues are beneficial, an effective therapy remains elusive.

Endothelial cell injury is considered an initial event in the pathogenesis of SSc-related vascular disease [1, 4]. Endothelial cells are the first to undergo apoptosis in SSc skin, a process most likely induced by anti-endothelial cell auto-antibodies [4]. Subsequent loss of physiological vasodilating mediators (i.e. prostacyclin, nitric oxide) may result in abnormal responses to vasoconstrictors including endothelin-(ET)-1. ET-1, the most potent endogenous vasoconstrictor, was originally identified by its effect on vascular smooth muscle cells. It is released by endothelial cells following cell damage, and increased serum levels are detectable in SSc patients. ET-1 stimulates smooth muscle cell proliferation and fibroblast matrix biosynthesis [5, 6]. Thus, ET-1 appears to be crucial in the pathogenesis of RP and in the subsequent development of structural alterations in SSc. Bosentan, an oral endothelin receptor antagonist, is beneficial in the treatment of both idiopathic pulmonary arterial hypertension (PAH) and PAH associated with SSc [7]. Structural abnormalities in PAH resemble vascular lesions in SSc-associated RP, and recently—although not yet approved for this indication—bosentan has been shown to prevent the development of new digital ulcerations in RP patients with SSc [8]. This observational study was conducted to examine the effects of bosentan in a small number of patients with pre-scleroderma and with SSc, independent of a history of digital ulcerations.

Patients and methods

Subjects

Three patients with a history of severe RP for various periods in the context of pre-scleroderma/limited SSc were included. PAH was excluded in all patients. Previous therapies in all subjects consisted of oral calcium-channel blockers and repeated intravenous prostaglandin analogues without sustained benefit (Table 1).

Patient 1: A 46-yr-old woman with a history of severe RP since 1993 in the setting of pre-scleroderma (RP, functional and...
structural abnormalities of the microvasculature/nailfold capillaries, disease-specific circulating ANAs 1:5120, nucleolar pattern).

Patient 2: A 35-yr-old man with a history of severe RP since 1999 in the setting of MCTD diagnosed in 2002 (RP, functional and structural abnormalities of the nailfold capillaries, disease specific ANAs 1:5120 reacting with U1 small nuclear ribonucleoprotein). Cutaneous and visceral organ involvement were absent in patients 1 and 2.

Patient 3: A 64-yr-old woman with a history of progressing RP since early adulthood in the setting of limited SSc (CREST syndrome, i.e. calcinosis cutis, Raynaud’s phenomenon, oesophageal dysfunction, sclerodactyly, telangiectasia) diagnosed in 1988. In 2002, the patient presented with sclerodactyly, periarticular calcinosis (elbows) together with facial telangiectasias. A discrete impairment of oesophageal motility was the only visceral organ involvement detectable. A painful non-healing ulcer developed on the distal left index finger in 2003. Sympathectomy was performed without significant improvement, and subsequently, the middle and end-phalanx was amputated.

Treatment and evaluation protocol

All subjects gave their written informed consent to participate in this observational trial. Subjects received bosentan 62.5 mg twice daily for 4 weeks followed by 125 mg twice daily for the following 12 weeks. Treatment was initiated during late autumn (November 2003). At each monthly visit, Raynaud’s activity was evaluated by using a modified Scleroderma Health Assessment Questionnaire (SHAQ) [8, 9]. This questionnaire excluded questions related to the use of assistive devices. In addition, patients were advised to fill out a visual analogue scale (VAS, range 0–10) to determine pain severity [8, 9]. Furthermore, patients used diaries to record the number, duration and severity of pain of daily Raynaud’s attacks starting one week prior to the initiation of therapy.

Peripheral thermoregulation was assessed by thermography of both hands at controlled room temperature (22°C). Skin temperature recovery was examined 20 min after cold challenge (20°C water bath). Arterial pulse oscillography and digital arterial pressure was recorded (Vasoquant VQ 4000) for individual fingers at room temperature and after cold provocation. All tests were performed at baseline and week 16. Liver function tests were performed monthly according to bosentan treatment recommendations. No increase of transaminases was observed.

Results

All patients completed the 16-week treatment period without occurrence of major adverse events. The primary outcome variable was the assessment of Raynaud’s activity and pain severity. At baseline, all three patients were strongly compromised due to daily Raynaud’s attacks. Patient questionnaires revealed a Raynaud’s activity of 94, 85 and 58%, while the VAS assessed pain severity was 10, 7.2 and 6.9, respectively. Both parameters significantly decreased during treatment period in all patients (Fig. 1a, b). Similarly, the number of average daily attacks (patient 1: 8/day at week 0, 2/day at week 16; patient 2: 5/day at week 0, 1/day at week 16; and patient 3: 5/day at week 0, 0/day at week 16) and duration (patient 1: 4 min/attack at week 0, 1 min/attack at week 16; patient 2: 20 min/attack at week 0, 10 min/attack at week 16 and patient 3: 20 min/attack at week 0, 0 attacks at week 16) decreased in all patients, as recorded by the diaries (Table 1). After 16 weeks of treatment, thermography of both hands at room temperature paralleled the improved thermoregulation in all patients. (Fig. 1c). Skin temperature recovery 20 min after cold challenge significantly improved in patient 3 (data not shown). No significant changes,
however, in arterial pulse oscillography and digital arterial pressure in individual fingers were evident (data not shown). Due to favourable wound healing during bosentan treatment in Patient 3 further amputation of the left index finger, as initially intended, became unnecessary. Taken together, these data suggest that bosentan may effectively reduce symptoms of secondary RP.

**Discussion**

Individuals with RP suffer from severe pain, with significant impairment of hand function and with serious impact on activities of daily living foremost during winter seasons. The results of previous studies [8] showing that bosentan prevents digital ulcers in SSc, prompted us to use bosentan in a small number of patients with severe RP in the setting of pre-scleroderma and limited SSc independent of a history of digital ulcerations. All patients had previously received calcium-channel blockers and intravenous prostaglandin analogues without sustained benefit.

We are aware of the limitations inherent to this study; i.e. it is uncontrolled, observational and involves a small number of patients only. Moreover, endpoints are mainly subjective and placebo responses cannot entirely be ruled out. Yet, pain, Raynaud’s disease activity and number/severity of Raynaud’s attacks significantly decreased, reflected by improved thermoregulation in all patients after the 16-week treatment period. Moreover, all patients preferred to repeat bosentan therapy during the following winter seasons instead of receiving infusions with prostaglandin analogues. Thus, despite the obvious limitations of our study, the response to bosentan in severe secondary RP appears beneficial.

In previous trials, no major effects of bosentan on RP have been recognized [8]. This somewhat conflicting result could be explained by the fact that in patients with multiple digital ulcerations as included in the RAPIDS trials end stage microvascular damage and severe sclerodactyly are usually present so that immediate effects of bosentan on RP may not be obvious any more.

Infusions with prostaglandin analogues are invasive and require hospitalization. This is associated with dose-related side effects and with complications related to intravenous application. The advantages of bosentan are its oral administration on an out-patient basis, and its lack of severe side effects. The application of bosentan in secondary RP, potentially as an interval therapy during winter seasons, may thus represent a valuable future therapeutic alternative in a condition that can affect patients for many years. Moreover, since bosentan appears to interfere with a key pathogenic process in SSc, it is conceivable that treatment in the setting of pre-scleroderma may potentially decelerate progression towards systemic disease. Clearly, further studies are necessary to substantiate our findings.

**Key messages**

- Bosentan may prove beneficial in severe secondary RP associated with pre-scleroderma and systemic sclerosis independent of digital ulcers.
- Bosentan is a less invasive therapeutic option in comparison to most standard therapeutic regimens used in severe secondary RP.
- Interval therapy during winter seasons could be a valuable therapeutic strategy.
- Until now, bosentan has not been approved in the described indication.
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References