Clin Rheumatol (2013) 32:679–683
DOI 10.1007/s10067-013-2172-z

BRIEF REPORT

Low occurrence of digital ulcers in scleroderma patients treated with bosentan for pulmonary arterial hypertension: a retrospective case–control study

F. Cozzi · E. Pigatto · M. Rizzo · M. Favaro · E. Zanatta · S. Cardarelli · L. Riato · L. Punzi

Received: 28 September 2012 / Revised: 7 November 2012 / Accepted: 10 January 2013 / Published online: 24 January 2013

Abstract Digital ulcers (DU) are one of the most common and debilitating manifestations of vasculopathy in systemic sclerosis (SSc). Their prevention is important in order to improve patients' outcome and as a result of the economic impact they have on society. Randomised controlled studies have demonstrated that bosentan, an endothelin receptor antagonist, reduces the appearance of new DU. The aim of this retrospective study was to evaluate the occurrence of DU in a group of patients receiving long-term bosentan treatment for pulmonary arterial hypertension associated with SSc (PAH-SSc). Patients with PAH-SSc and treated with bosentan for at least 6 months (n=30) were evaluated. Thirty patients with SSc not treated with bosentan, but matched for sex, age, disease duration and cutaneous form of SSc, were considered as a control group. The occurrence of DU, defined as loss of tissue of varying degrees in the epidermis, dermis and subcutaneous tissue, was determined in the bosentan-treated and untreated groups. Mean duration of bosentan treatment was 3.6 years. DU were detected in six patients in the bosentan-treated group (20.0 %) and 16 patients (53.3 %) in the untreated group (p=0.0015). There were no significant differences in demographic or clinical characteristics between patients with or without DU at study end. The occurrence of DU in patients with PAH-SSc receiving long-term bosentan treatment was significantly lower than in untreated patients. The results from this long-term observational study provide valuable information on management of patients with PAH-SSc.

F. Cozzi (✉) · E. Pigatto · M. Rizzo · M. Favaro · E. Zanatta · S. Cardarelli · L. Riato · L. Punzi
Rheumatology Unit, Department of Medicine (DIMED), University of Padova, Via Giustiniani 2, 35128 Padova, Italy
e-mail: franco.cozzi@unipd.it

Keywords Bosentan · Case–control study · Digital ulcers · Systemic sclerosis

Introduction

Systemic sclerosis (SSc) is an autoimmune disease characterised by an obliterative vasculopathy which is responsible for some clinical manifestations such as digital ulcers (DU), pulmonary arterial hypertension (PAH) and scleroderma renal crisis [1]. DU are defined as the loss of substance of the skin and subcutaneous tissue due to acral vasospasm and microthrombosis; they are very painful and cause severe impairment of hand function [2].

DU occur in 35–60 % of patients with SSc [3–5]. In a series of 1,012 Italian patients with SSc, DU were detected in 48 % of cases [3]. In another large cohort of 2,080 SSc patients, followed in a single centre from 1972 to 1995, 58 % had a history of DU that was recurrent in 32 % of patients [4]. In a study performed in our Rheumatology Unit evaluating 333 consecutive patients enrolled from 1997 to 2007, DU were detected in 39.9 % of patients, with 12.3 % experiencing complications such as gangrene and loss of substance. Surgery to correct the damage caused by the DU was required in 8.7 % of patients [5]. In most patients, the onset of the first DU occurs within 5 years of the first clinical sign of disease [6]. Patients positive for anti-Scl70 antibodies have a risk of developing DU approximately 5 years earlier than patients positive for anticentromere antibodies (ACA) [7].

According to the recommendations of European League Against Rheumatism/Scleroderma Trials and Research group, the treatment of clinical manifestations of digital vasculopathy (RP and DU) is essentially based on three categories of drugs: calcium channel blockers, intravenous

prostanoids and an endothelin receptor antagonist (bosentan) [8]. Two randomised controlled trials have demonstrated that treatment with bosentan reduces the appearance of new DU in SSc patients [9, 10]. Other uncontrolled studies have shown that bosentan has a favourable effect on the healing of DU [11, 12].

Since 2003, bosentan has been used in our centre for the treatment of PAH associated with SSc and other connective tissue diseases. Bosentan has been demonstrated to be well tolerated and to both reduce blood pressure in the pulmonary artery and improve patients' functional capacity [13]. In this retrospective case–control study, the occurrence of DU in a group of SSc patients treated for a long period with bosentan for PAH was evaluated and compared with data from a group of SSc patients (matched for sex, age, disease duration, diffuse/limited cutaneous form and antinuclear antibody (ANA) specificity), but not treated with bosentan.

Patients and methods

From 2003 to 2011, 42 patients with SSc, being followed up at the Rheumatology Unit of Padova University (Italy) developed PAH. PAH was diagnosed using Doppler echocardiography, assuming 45 mmHg of systolic pulmonary artery pressure as minimal diagnostic value and confirmed in a proportion of patients ($n=12$) by right heart catheterisation.

Thirty-two patients initiated treatment for PAH with bosentan, six with sildenafil and four with ambrisentan. Bosentan was administered at a dose of 125 mg/day for the first month and then was increased to 250 mg/day. Sildenafil was administered at a dose of 60 mg/day, ambrisentan at a dose of 10 mg/day. Bosentan treatment was stopped after 3 months in two patients because of hepatotoxicity and was replaced by sildenafil in one patient and ambrisentan in the other. The other 30 patients received bosentan for a minimum of 6 months.

A matched set of 30 controls were identified from patients with SSc not complicated by PAH. They were matched to the treated group in terms of sex, age, disease duration, limited/diffuse cutaneous form and ANA specificity.

All patients underwent a complete clinical evaluation and laboratory tests, including ANA and ACA evaluations. ANA and ACA were detected by an indirect immunofluorescence technique, using HEp-2 cells as a substrate. Anti-extractable nuclear antigens antibodies (anti-Scl70, anti-U1RNP, anti-Ro/SSA, anti-La/SSB) were tested by a counterimmunoelectrophoresis technique, using control sera provided by the Center for Disease Control (Atlanta, USA). Anti-RNA polymerase III antibodies were detected using an immunoenzymatic test.

Skin thickening was assessed using the modified Rodnan skin score. Lung involvement (interstitial lung disease) was diagnosed if DLco was ≤70 % of predicted and forced vital capacity was ≤75 % of predicted or if interstitial changes were noted on chest radiogram or high-resolution computed tomography. Heart involvement was defined as the presence of conduction defects or arrhythmias on electrocardiography and/or left ventricular diastolic dysfunction on echocardiogram (alterations related to PAH were obviously not considered). The diagnosis of scleroderma renal crisis was confirmed in patients with rapidly progressive renal failure and/or malignant hypertension (systolic blood pressure ≥160 mmHg or diastolic BP ≥110 mmHg). Gastrointestinal involvement was diagnosed when symptoms related to gastro-oesophageal reflux, dysphagia and bowel alterations were present.

During follow-up, all patients were investigated for the presence of DU, defined as loss of tissue of varying degrees in the epidermal, dermal and subcutaneous layers; digital pitting scars were not considered as DU [14].

The aim of the study was to compare the prevalence of DU in the group of patients treated with bosentan for PAH with that in the untreated control group. Demographic and clinical characteristics of patients with and without DU were also evaluated.

Statistical analysis was carried out using the *t* test and the Pearson test. The significance level was set at $p<0.05$.

Results

The average duration of treatment in the 30 patients treated with bosentan for PAH associated with SSc was 3.6±2.2 years. Patients were mainly female ($n=22$) with a mean age of 67.2±10.5 years. The mean duration of SSc before starting treatment was 15.0±8.3 years. Twenty-three patients had the limited cutaneous form of SSc (skin score 5.4±1.7), and seven had the diffuse form (skin score 18.4±3.7). Demographic, clinical and serological data for the bosentan-treated group and the matched control group are reported in Table 1.

Thirty patients with SSc not complicated by PAH, matched to the treated group, were identified as controls. The control group comprised 22 women and eight men, mean age 67.8±9.9 years and mean duration of SSc 15.9±7.8 years. Twenty-three patients had the limited cutaneous form of SSc (skin score 5.8±1.5), and seven had the diffuse form (skin score 17.8±3.4). Demographic, clinical and serological data for the control patients are also reported in Table 1.

Comparison of SSc patients treated with bosentan and untreated patients showed no significant differences: ANA were positive in all patients, specific ACA was prevalent in

Table 1 Demographic, clinical and serological data of systemic sclerosis patients treated or not treated with bosentan

	Bosentan-treated group (n=30)	Matched control group (n=30)
Female/male	22/8	22/8
Age, mean±SD age (years)	67.2±10.5	67.8±9.9
Age of RP onset, mean±SD (years)	47.7±16.7	45.5±11.5
Age of SSc onset, mean±SD (years)	51.6±16.7	51±11.8
SSc duration, mean±SD, (years)	15±8.3	15.9±7.8
Limited/diffuse cutaneous form (n)	23/7	23/7
Skin score, mean±SD	8.5±5.9	8.3±5.2
Lung fibrosis (n)	17	12
Heart involvement (n)	11	7
SSc renal crisis (n)	2	1
Gastrointestinal involvement (n)	27	24
Antinuclear antibody (ANA) (n)	30	30
Anticentromere antibody (n)	22	20
Anti-Scl70 (n)	6	8
Aspecific ANA (n)	2	2

RP Raynaud's phenomenon, *SSc* systemic sclerosis

both groups (73.3 and 66.7 %) and mean skin score was similar in bosentan-treated and untreated groups (8.5 and 8.3). The most frequent visceral involvement of SSc in both groups was gastrointestinal involvement (90 and 80 %, respectively). Scleroderma renal crisis was rare in both groups (6.7 and 3.3 %, respectively). Pulmonary fibrosis occurred more frequently in the bosentan-treated group than in the control group (57 and 40 %, respectively), but it is important to note that when bosentan was introduced as a treatment for PAH, patients with pulmonary hypertension secondary to lung fibrosis were also treated. Heart involvement was also more frequent in patients treated with bosentan (37 and 23 %, respectively), probably because of alterations related to pulmonary fibrosis.

DU were detected in 20 % (6/30) of patients treated with bosentan and in 53.3 % (16/30) of patients in the control group. The lower occurrence of DU in bosentan-treated group was statistically significant (p=0.0015). DU frequency in patients treated with sildenafil was 28.6 %; in those treated with ambrisentan was 40 %. The small number of cases in these two groups precluded statistical analysis.

Comparison of the demographic and clinical data of patients with and without DU showed no significant differences between the two groups (Table 2). In patients with DU, a trend towards a longer disease duration (17.8 vs. 14.1 years), a greater prevalence of diffuse cutaneous form (31.8 vs.18.4 %) and a higher value of skin score (9.5 vs. 8.1) was observed.

Discussion

This case–control study aimed to retrospectively evaluate the occurrence of DU in a group of SSc patients treated for a long period with bosentan for PAH and compare them with a group of demographically and clinically matched SSc patients not treated with bosentan. The analysis demonstrated that prevalence of DU was significantly higher in the untreated control group (53.3 %) compared with those treated with bosentan (20 %). It should be emphasised that the patients in this study were characterised by advanced age and a long disease duration, which is representative of

Table 2 Demographic and clinical data of systemic sclerosis patients with or without digital ulcers

	Digital ulcers (n=22)	No digital ulcers (n=38)	p value
Female/male (n)	17/5	27/11	0.764
Age, mean±SD age (years)	66.1±8.5	68.7±10.9	0.094
Age of RP onset, mean±SD (years)	44.3±14.3	47.9±15.5	0.085
Age of SSc onset, mean±SD (years)	49.3±13.3	49.3±14.9	0.792
SSc duration, mean±SD, (years)	17.8±8.2	14.1±7.7	0.069
Limited/diffuse cutaneous form (n)	15/7	31/7	0.343
Skin score, mean±SD	9.5±6.7	8.1±5.8	0.380

patients with PAH. Moreover, many patients in this study—especially those in the bosentan-treated group—presented with a severe form of SSc, as demonstrated by the high prevalence of visceral involvements such as pulmonary fibrosis and cardiomyopathy.

DU are one of the most frequent and debilitating manifestations of vasculopathy in SSc. They cause chronic pain and impaired mobility of the hands, with functional limitation in performing domestic and professional activities [15] and have a negative impact on the quality of life [16]. DU management weighs heavily on both health care services because of the frequent need for hospitalisation and on society as a result of lost productivity for patients and caregivers [17]. DU prevention is, therefore, very important both for the patient's outcome and for the economic impact.

Endothelin (ET) has been implicated in the pathogenesis of scleroderma vasculopathy: studies have shown serum concentrations of ET to be elevated and increased expression of ET receptors in the lung tissue, skin and blood vessels of SSc patients [18–20]. ET receptor antagonists (bosentan and ambrientan) have been approved for the treatment of idiopathic PAH and of PAH associated to connective tissue diseases. Bosentan is also indicated to reduce DU in the number of new DU in patients with SSc.

Our results suggest that bosentan therapy was able to reduce the occurrence of DU during a long period of treatment (mean 3.6 years per patient). These data correspond to those observed by other authors in non-controlled studies. In 30 Greek patients with SSc complicated by DU, the mean number of DU per patient was significantly reduced during the follow-up and at the end of the study after treatment with bosentan for 36 months [21]. Similarly, in 15 Spanish patients with SSc and treated with bosentan for ischaemic ulcers, a significant decrease in the number of DU and a trend towards efficacy both in the number of healed ulcers and in the severity of ulcers were observed [22]. In a multicentre retrospective cohort study also performed in Spain, 67 scleroderma patients with DU were treated with bosentan from 2003 to 2005 and 68 % of them did not develop any new DU after 12 months [23]. In a Japanese observational study performed in 15 patients with PAH associated with connective tissue diseases, long-term bosentan treatment (40–96 weeks) was associated with improvements in DU ulcers, RP and Rodnan total skin score [24].

With regard to the comparison between patients with and without DU, in general the demographic and clinical characteristics were similar between the two groups. However, a longer disease duration, a greater frequency of diffuse cutaneous form and consequently a higher value of skin score were apparent in the group of patients with DU. These are relevant risk factors for developing DU, as previously demonstrated in large cohorts of SSc patients [25].

In addition to being a retrospective design, our study has some limitations including the small patient group and the lack of a score to better characterise DU severity; however, as data on the long-term potential of bosentan in prevention of DU are limited, these observational results are valuable. Randomised controlled trials to further establish the impact of long-term bosentan therapy would increase understanding of the role of this treatment in the management of DU.

Acknowledgments An English language copy editing service was provided by Lisa Thomas (Elements Communications, Westerham, UK), funded by Actelion Pharmaceuticals Ltd.

Disclosures None.

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