CASE REPORT

Management of digital vasculopathy in systemic sclerosis: benefits of multiple courses of endothelin-1 receptor antagonists

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SUMMARY

Two patients with scleroderma and recurrent digital ulcers (DUs) were treated with bosentan for 6 months. Treatment was associated with a reduction in the number of new DUs; however, DUs recurred on treatment discontinuation. This case report illustrates the positive response of digital vasculopathy to bosentan and describes the benefits of multiple bosentan treatment courses in these patients.

BACKGROUND

Systemic sclerosis (SSc, scleroderma) is an autoimmune connective tissue disease characterised by vascular abnormalities and excessive collagen deposition in affected tissues (including the skin) and is associated with significantly reduced life expectancy.¹ Digital ulcers (DUs) occur in 30–60% of patients with SSc during the course of their disease.^{2–5} The aetiology of DUs is complex and multifactorial. The principal mechanisms underlying DU formation are ischaemic, inflammatory and mechanical damage either alone or in combination. DUs are often painful and slow to heal. They pose a major source of disability that affects domestic and professional activities and has a negative impact on quality of life.^{3–6–7} As a result of persistent DUs, patients frequently require long-term antibiotic treatment for coexisting infections and hospitalisation for management of associated complications including surgical interventions (local debridement, amputation or digital sympathectomy).

The endothelin-1 receptor antagonist (ERA) bosentan has been shown to prevent SSc-related DUs in two randomised, double-blind, controlled clinical trials (RAPIDS-1 and RAPIDS-2).^{8–9} Both trials indicated that bosentan reduced the number of new DUs by 30–48% compared with placebo, but did not increase the healing rate of existing DUs. Bosentan has been licensed in Europe to reduce the number of new DUs in patients with SSc and ongoing DU disease since May 2007.^{10–11} The licensed dose of bosentan in the management of DUs in patients with SSc is 62.5 mg twice daily for 4 weeks, increased to 125 mg twice daily thereafter.¹⁰ The short-term net pharmacological effect of bosentan is as a vasodilator, while the longer term activity may be related to its effect on vascular remodelling, in particular on fibroblast and smooth muscle cell proliferation.¹²

Here we describe two cases where multiple courses of bosentan were used successfully to treat patients with DUs.

CASE PRESENTATION

Patient 1

A 44-year-old woman with anti-Scl-70 antibody-associated, diffuse cutaneous SSc first diagnosed in 1995 was subsequently diagnosed with digital vasculopathy in 2000. She was initially prescribed several oral vasodilators including losartan, diltiazem and fluoxetine, but achieved a suboptimal response. She continued to experience an increasing number of DUs and she was treated with regular intravenous prostacyclin (iloprost) infusions and antibiotics for recurrent DU-associated infections. Intravenous access was difficult and therefore a subcutaneous implantable vascular access port (Portacath) was inserted in 2008. She also had a 6-week course of sildenafil in early April 2009, with partial healing of existing ulcers and formation of new ulcers. She was subsequently prescribed bosentan in June 2009.

TREATMENT

Patient 1

Bosentan was initiated at the licensed dose with appropriate blood monitoring towards the end of June 2009 and treatment continued for 6 months. Iloprost infusion was continued after the 6-month course of bosentan. The patient subsequently received two more 6-month courses of bosentan starting in December 2010 and December 2011. A 12-month course of treatment initiated in mid-2012 is currently ongoing.

OUTCOME AND FOLLOW-UP

Patient 1

Before the first bosentan 6-month treatment course was initiated, the patient had two DUs. Only one new DU developed during the treatment and the baseline DUs healed within 6 weeks of treatment initiation. Following completion of the treatment course (December 2009), the patient developed two DUs and, therefore, prostacyclin infusion was continued. In December 2010, with a net DU burden of four, approval was received from the patient's local primary care trust to proceed with a second 6-month course of bosentan. She responded well with resolution of all DUs during bosentan treatment and with no further DUs developing. In addition, she did not require prostacyclin infusion. Shortly after completing the second course of bosentan (4–6 weeks), the patient developed eight new DUs (figure 1). A third 6-month course of bosentan was prescribed in December 2011 and all

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Figure 1 Digital ulcers of patient 1 pretreatment and 4 months after starting treatment.

DUs healed during treatment with no new DUs occurring. After treatment was discontinued for the third time, new DUs developed and the patient was subsequently prescribed a 12-month course of bosentan in mid-2012, which is currently ongoing. Interestingly prostacyclin infusion was not required during the bosentan treatment courses.

CASE PRESENTATION

Patient 2

A 43-year-old woman was diagnosed with anti-Scl-70 antibody-associated, diffuse cutaneous SSc in 2004. Since 2006 the major disease manifestation was severe digital vasculopathy with recurrent DUs. Previous treatments had included two 6-week courses of sildenafil in September 2009 and February 2010, intravenous prostacyclin (iloprost) and antibiotics. Intravenous access was difficult requiring several central venous cannulations including Hickman line and Portacath. A digital sympathectomy on the left middle finger was undertaken in 2008.

TREATMENT

Patient 2

Bosentan was initiated at the licensed dose with appropriate blood monitoring in May 2010 and continued for 6 months. A second 6-month course of bosentan was prescribed in October 2011 and a third 12-month course of bosentan was prescribed in December 2012 and is currently ongoing.

OUTCOME AND FOLLOW-UP

Patient 2

Prior to starting the initial 6-month course of bosentan, the patient had four DUs. No new DUs were observed during the treatment and all existing DUs improved within 4 weeks of starting bosentan treatment. On discontinuation, three new DUs developed and therefore, a second 6-month course of bosentan was started in October 2011. She subsequently received a further 6-month course and, again, new DUs developed on

discontinuation. The patient started a 12-month course of bosentan in December 2012 and no new DUs occurred. Effect of treatment was similar to patient 1, all elective prostacyclin infusions were cancelled by the patient during bosentan treatment and in the intervals between the treatment courses.

DISCUSSION

DUs are a frequent, debilitating complication of SSc.^{3 6 7} DU management weighs heavily on healthcare services because of the frequent need for hospitalisation for specialised medical and surgical treatments, as well as on society as a result of lost productivity for patients. The two pivotal clinical studies, RAPIDS-1 and RAPIDS-2, form the basis for approval of bosentan for this indication by regulatory agencies.^{8 9} Bosentan is often prescribed for a limited period of 6 months. However, as demonstrated in the cases described here, new DUs can develop following treatment discontinuation resulting in the need for repeated courses of therapy. Here we demonstrate that patients continue to benefit from multiple courses of bosentan, with prevention of new DUs and resolution of total ulcer burden. The need for invasive treatment including intravenous prostacyclin infusions was also reduced during treatment with bosentan.

Following the approval of bosentan for prevention of DUs in SSc, the DUO registry was initiated as a European Medicines Agency (EMA) commitment to describe the disease course, clinical details and outcome of SSc patients with ongoing DU disease irrespective of treatment regimen. Data from the registry reported that there is wide variation in the use of ERAs and DU-specific therapies across Europe with a low rate of ERA use in the UK.¹³ While this may suggest differences in healthcare economic structure across Europe, it also highlights the need for a coordinated approach in establishing the best management practice for these patients.

There is growing evidence to support prolonged use of bosentan in SSc-associated DU disease.^{14–18} The mean duration of bosentan therapy in these studies ranged from 1 to 3.6 years. These studies support the results from both RAPIDS-1 and RAPIDS-2 with

significant reduction in occurrence of DUs and improvement in quality-of-life scores relating to hand function and dexterity. Importantly, long-term bosentan therapy was well tolerated. The results from these studies suggest that patients with persistent DUs, such as those described here, may benefit from prolonged courses of bosentan therapy.

Learning points

- In addition to bosentan reducing and preventing the development of new digital ulcers (DUs), existing DUs healed during the 6-month courses of bosentan therapy; however, new DUs developed on treatment discontinuation.
- Repeated courses of bosentan continue to be effective and reduce the need for intravenous prostacyclin therapy.

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