Concise Report

Long-term experience of bosentan for treating ulcers and healed ulcers in systemic sclerosis patients


Objectives. Our objective was to evaluate the efficacy and tolerability of bosentan in patients with systemic sclerosis (SSc) who develop ulcers and healed ulcers. We also wanted to analyse the effect of bosentan on other skin and general outcome measurements.

Methods. In the present prospective, observational, non-controlled study, we followed all patients with SSc who started treatment with bosentan for ischaemic ulcers and healed ulcers from January 2003 to June 2006 in our centre. We recorded skin and general outcome measurements at baseline and at 6 months.

Results. Fifteen patients were included. After a median follow-up of 24.7 months (range: 4–36), there was a significant decrease in the number of ulcers at baseline and at 6 months of treatment.

Conclusion. Bosentan may be a safe long-term alternative for treating the recurrence of skin ulcers and healed ulcers in SSc patients.

Introduction

Recurrent ulcers and healed ulcers are a manifestation of systemic sclerosis (SSc). These ulcers are painful, torpid and are frequently infected resulting in an incapacitating problem for many patients. Bosentan is an oral dual endothelin receptor antagonist, and its efficacy for preventing and treating of ischaemic ulcers has been evaluated in two well-designed studies, named randomized placebo-controlled investigation of digital ulcers in scleroderma (RAPIDS)-1 and RAPIDS-2, and also on the basis of several clinical observations [1–6]. Prospective studies have shown efficacy in the short term, while only a retrospective series of nine patients reached 24 months [3]. It is not clear whether long-term treatment addressed specifically towards ulcers may be effective or whether ulcers may recur once treatment is discontinued.

Our objective was to evaluate the long-term efficacy and tolerability of bosentan in patients with SSc who develop ulcers and have healed ones.

Patients and methods

This was an observational non-controlled, prospective study of patients with SSc and ulcers or healed ulcers refractory to conventional treatment and who were, therefore, eligible for off-label treatment with bosentan. Previously, all the patients gave their written informed consent and treatment was approved by the centre. The study was approved by the local ethics committee. Patients were enrolled in the study from January 2003 to February 2004. All patients were evaluated at baseline and at 6-month intervals. The efficacy parameters assessed are displayed in Table 2.

The difference between efficacy measures at follow-up visits and baseline was tested with the Wilcoxon’s signed-rank test. The trend of the efficacy with time was tested by Friedman’s test.

Results

Baseline patients’ characteristics

The study comprises 15 patients, 12 women (80%) and 3 men (20%), 5 with diffuse cutaneous SSc (dcSSc; 33.3%) and 10 with limited cutaneous SSc (lcSSc; 66.6%). All but one were adults with SSc; 48 yrs being the mean age at the beginning of the treatment (range: 11–72, s.d. 16.34) and 14.5 yrs being the mean disease duration. Seven patients presented anti-topoisomerase antibodies, six had anti-centromere antibodies and two did not present any of the above. The individual clinical characteristics of the 15 patients are displayed in Table 2.

It is a very heterogeneous group of patients, with various stages of skin and organ involvement. Fifteen (93.3%) patients had musculoskeletal findings while 13 (86.6%) had gastrointestinal symptoms. Six patients had interstitial lung disease and three had pulmonary artery hypertension (PAH), confirmed by right heart catheterization. Fourteen patients were being treated with calcium channel blockers (eight patients) and losartan (seven patients). Four patients carried a cervical electrical neurostimulator for the treatment of the RP. One patient was receiving inhaled iloprost for treating her PAH. Before bosentan treatment was started, four subjects had received i.v. prostaglandins (ivPG) and one i.v. cyclophosphamide.

Bosentan was prescribed off-label in 12 of the recruited patients and as approved in the three patients with PAH. The dose used was the standard one, 62.5 mg b.i.d. for 28 days and a maintenance dose of 125 mg b.i.d. including the child, since her body weight was over 40 kg.

Concomitant medications were not substantially modified during follow-up. Two patients needed to be treated with ivPG due to severe worsening because of an infection and the wintertime. Losartan could be interrupted in Patient 15 after 6 months of treatment.

The median follow-up time after bosentan was initiated was 24.7 months, (range: 4–36 months). Drop-outs before first...


assessments occurred in two cases: (i) Patient 8 developed a pleural effusion with interstitial lung disease, not clearly related to bosentan; (ii) Patient 1 withdrew bosentan on her own.

Table 1 shows the mean difference in the efficacy parameters between baseline and months 6, 12, 18, 24 and 30.

**Six-month assessment (n = 13).** The only significant improvement seen at this time point was in the number of healed ulcers (P < 0.05), although there were non-significant improvements in the number of ulcers, number of RP episodes (NRPE) (only collected in 10 subjects), duration of RP episodes (DRPE) (only collected in 10 subjects) and ulcer–healed ulcers visual analogue scale (U–HU VAS). A non-significant worsening was seen in modified Rodnan skin score (mRSs), oral opening, RP VAS, overall disease VAS (OD VAS), mean hand flexion (MHF), mean hand extension (MHE) and mean grip strength (MGS).

**One-year assessment (n = 13).** A statistically significant improvement was seen in the number of ulcers, NRPE (only collected in nine subjects) and RP VAS. A decrease in the number of healed ulcers, DRPE (only collected in nine subjects), RP VAS and OD VAS was also observed but without statistical significance. A non-significant worsening was noted in mRSs, oral opening and all the parameters of the hand.

**Eighteen-month assessment (n = 12).** A statistical improvement in the number of ulcers and healed ulcers, NRPE and DRPE (only collected in nine subjects) and RP VAS was noted. An improvement in mRSs, MHS, MGS, U–HU VAS and OD VAS was also observed, but did not reach statistical significance.

Worsening in oral opening and in MHE was observed. No changes were found in Scleroderma Health Assessment Questionnaire (SHAQ) or arthritis impact measurement Scales 2 (AIME2) scores at any assessment.

**Two-year assessment (n = 10).** A significant improvement in the number of ulcers, NRPE and DRPE (only collected in four subjects), RP VAS and MHF was noted. An improvement in the number of healed ulcers, mRSs, MGS, U–HU VAS and OD VAS was also observed, but without reaching statistical significance. A worsening in oral opening, MHE (P < 0.05), was observed.

**Thirty-month assessment (n = 5).** Patient 11 continued suffering severe RP and a cervical electrical neurostimulator was placed after 24 months of treatment with bosentan.

**Tolerability and side-effects.**

During the follow-up two patients died due to general deterioration and lung disease. Bosentan was definitively interrupted after 13 months only in Patient 10 due to toxic jaundice with complete recovery after a short time.

In two cases, bosentan was temporarily discontinued because of an increase of transaminases between 3 and 5 upper normal values in one case and because of a cholelithiasis with cholangitis.

NC, not collected by the patient; NP, not performed; AAT, anti-topoisomerase antibodies; AAC, anti-centromere antibodies.

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**Table 1. Efficacy of bosentan in the assessed parameter by periods of 6 months**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean at baseline (n = 15)</th>
<th>6 months (n = 13)</th>
<th>12 months (n = 13)</th>
<th>18 months (n = 12)</th>
<th>24 months (n = 10)</th>
<th>30 months (n = 5)</th>
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<td>mRS (mmHg)</td>
<td>75.0</td>
<td>70.1</td>
<td>110.0</td>
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<td>U–HU VAS (mm)</td>
<td>120.0</td>
<td>140.0</td>
<td>80.0</td>
<td>50.0</td>
<td>70.0</td>
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<td>RP VAS (mm)</td>
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<td>120.0</td>
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<td>40.0</td>
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<td>MHE (mm)</td>
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<td>80.0</td>
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**Table 2. Baseline patient characteristics**

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<td>11</td>
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<td>46</td>
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<td>F</td>
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<td>9</td>
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<tr>
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<td>SHAQ</td>
<td>1.1</td>
<td>1.1</td>
<td>0.1</td>
<td>0.1</td>
<td>-0.04</td>
<td>-0.04</td>
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P < 0.05.
in another one. In both patients, transaminase levels were normal after stopping treatment and sphincterotomy (in second case).

Three patients showed a mild transitory increase of transaminases (<3 times normal values). It was necessary to reduce the doses of bosentan temporarily only in one case. These six cases showed steatosis and two cholelithiasis as well, but only in one of them elevated transaminase levels were observed previous to the treatment, related to liver steatosis and cholelithiasis.

One patient had a myocardial infarction after 20 months. Percutaneous revascularization was performed.

Other minor side-effects were: headache (one patient), nasal congestion (two), discomfort (one), anaemia (two), decrease of 1–2 points of haemoglobin (six) and infection of ulcers (five).

Patient 2 decided, after 12 months, to stop bosentan. It was reintroduced after 6 months because of worsening desease.

Discussion

Ulcers and healed ulcers represent a disabling problem for patients suffering SSc. Ulcers frequently persist despite the widespread use of conventional therapy.

Bosentan is an antagonist of the receptor of the endothelin, indicated for the treatment of PAH [1]. RAPIDS-1 was the first double-blind study where the use of bosentan was compared vs placebo for preventing and treating ischaemic ulcers related to SSc [1]. Results showed a decrease in the rate of new ulcers. A statistically significant improvement was observed in the overall score hand function. The preliminary results from RAPIDS-2, which have not yet been published, [9] confirm the findings from RAPIDS-1.

The present study is the first prospective one with long-term follow-up that has evaluated not only the number of ulcers, but also the healed ones, VAS for U–HU, RP and OD, skin outcome measurements, and also functional and psychological scales. Recently, Launay et al. [3] published the first retrospective multicentre study with long-term follow-up (24.3 months) including nine patients. Previously, seven clinical observations of isolated case patients treated with bosentan had been reported [2, 4–6].

The present study is limited due to the small sample size and its uncontrolled and observational nature and should be viewed as descriptive, but it also has to be emphasized that most of these lesions were chronic and have not responded to previous treatments.

We focused on long-term follow-up analysing the total number of ulcers and healed ulcers as different stages of the same manifestation. We noted a decrease in the number of ulcers as well as of healed ones, and a trend to an improvement in the severity, measured by a U–HU VAS. Perhaps combining the severity of both ulcers and healed ulcers may have been definitive in not finding improvement in this VAS, as ulcers become healed ones eventually, but we believe that the most adequate measure of the phenomenon must include both parts. Patients do not differentiate easily the moment when a lesion is an ulcer and when it is healed, and VAS is based on patient judgement.

Although our series is small and heterogeneous, we have found better results in patients with cSSc than in those with lCSSc.

In this study, all parameters assessing the RP improved. There was a relevant decrease in the number of RP episodes and in the duration of such episodes. As we do, Launay et al. [3] also show an improvement in RP, but perhaps a long-term treatment is necessary to see a positive result of bosentan in RP. Probably, in the near future, bosentan, in monotherapy or in combination, will become usual in the armamentarium for treating RP and healed ulcers, as we do have now for PAH.

In relation to mRSSs, oral opening and functional hand measurements, we found no concluding results. We highlight that nine of the patients had baseline mRSS >14 and mean disease duration over 16 yrs [10]. Current evidence points to a greater, or faster, effect of bosentan on endothelium compared with its effect as an anti-fibrotic.

We have not observed any changes, in patients’ psychological perception of the disease, although a slight improvement was seen in the overall disease assessment.

Regarding toxicity, in this long-term follow-up study, we found many adverse events but no new unidentified adverse reactions, except for the unexpected toxic jaundice. We want to state that in all patients who had elevated transaminase, liver steatosis or cholelithiasis was detected. Many points of the precise role of bosentan in the treatment of ischaemic ulcers and other features of SSc need to be clarified, such as the time of starting, or what subset of patients should be treated. As RAPIDS-1 and RAPIDS-2 have shown, if bosentan seems to be more preventive than curative, then why do we limit its use for treating refractory ulcers [1, 9]? Should we use it before they become refractory? Bosentan is an expensive drug and its use is not free of adverse events, and so we must prescribe it reasonably and preferably by experts in this kind of disease. We should not forget that SSc is a very disabling and low prevalent disease, and it is not any less true that many drugs have been and are still being used for treating scleroderma patients without supporting studies proving the efficacy. We hope that joining the experience of all those we dedicate to the management of these patients all these questions could be elucidated.

Rheumatology key message

- Bosentan may be a safe long-term alternative for treating and preventing the recurrence of skin ulcers and healed ulcers in SSc patients.

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References