Bosentan for treatment of active digital ulcers in patients with systemic sclerosis (9 cases)

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Summary

Objectives > To describe the effect of bosentan and its dual inhibition of endothelin-1 ETA and ETB receptors on digital ulcers in patients with systemic sclerosis (SSc).
Methods > Patients receiving bosentan for SSc-related digital ulcers were identified in eight centers, and their characteristics and follow-up were recorded.
Results > Nine (six with diffuse and three with limited cutaneous forms of SSc) patients (median age: 54 years) had received bosentan for digital ulcers. Complete healing occurred in seven (median time to improvement: 4 weeks). Another experienced a significant decrease in the number of ulcers (from 22 to 5) in 8 weeks, while one had no improvement. After a median follow-up of 24.3 months, only one recurrence was observed. Raynaud phenomenon improved in all but one patient.
Discussion > These data suggest that some patients may benefit from bosentan to treat digital ulcers. The short time to healing in these
patients with rather chronic ulcers argues strongly in favor of its use. These results also strengthen the evidence that endothelin-1 plays an important role in the vascular manifestations of SSc.

**Conclusion** Bosentan can be effective in the treatment of digital ulcers in some SSc patients with SSc, probably especially those involving substantial ischemia. Bosentan is not a first-line drug in this indication yet and must be carefully used by specialists in SSc. Forthcoming results from the international RAPIDS-2 study should clarify the indications for bosentan in the treatment of SSc-related digital ulcers.

**What is already known**

- **Bosentan**, an inhibitor of the ETA and ETB receptors of endothelin 1, is efficacious in pulmonary hypertension associated with systemic sclerosis.

- An international randomized controlled trial showed that bosentan prevents the onset of new digital ulcers in patients with systemic sclerosis.

- Nonetheless, bosentan has not been shown to improve the speed of healing of existing ulcers.

**What this article adds**

- **Bosentan** can be efficacious in treating severe active digital ulcers in patients with systemic sclerosis.

- **Bosentan appears to act rapidly**, within approximately 4 weeks.

**Systemic scleroderma (SSc)** is an autoimmune disease characterized by cutaneous, visceral, vascular, and inflammatory effects, as well as fibrosis [1]. Raynaud’s phenomenon, nearly universal in SSc [2], is complicated by digital ulcers and necrosis in approximately 50% of patients [3]. Digital ulcers may heal slowly and only with difficulty, or may become infected [4] and significantly alter quality of life.

Few treatments for Raynaud’s phenomenon are useful for promoting healing of digital ulcers and necrosis in SSc patients [5]. Calcium channel blockers, widely used in Raynaud’s phenomenon, are ineffective against digital ulcers and necrosis. Intravenous iloprost is effective in treating ischemic complications of SSc [4, 6-8], but requires hospitalization to establish venous access for several days or even weeks.

Endothelin-1 plays a role in the pathophysiology of SSc and especially in its vascular complications, such as digital ulcers and pulmonary hypertension (PHT) [9-20]. Bosentan is an inhibitor of endothelin-1 ETA and ETB receptors and is indicated in the treatment of PHT, whether idiopathic or associated with SSc [21]. The Rapids-1 study showed that bosentan was also efficacious in preventing new digital ulcers in patients with SSc [22]. It did not find, however, that bosentan shortened the time required for healing active digital ulcers (secondary endpoint). An international study (Rapids-2) is underway to assess the curative and preventive effects of bosentan for ischemic digital ulcers in patients with SSc.

Several rare case reports suggest [23-25] that it may sometimes provide swift and spectacular benefits for some active digital ulcers. We analyzed the effect of bosentan prescribed for active digital ulcers in these patients. This off-label prescription was most often motivated by patients’ resistance to conventional treatment or their chronic trophic ulcers. Some patients were considered for the Rapids-2 study but did not meet its inclusion criteria.

**Methods**

We contacted eight departments of internal, vascular, and pulmonary medicine among those we knew to specialize in treatment of patients with scleroderma. We identified the patients in these departments who had SSc that met the criteria of the American College of Rheumatology [26] and who received bosentan specifically to treat active digital ulcers or necrosis.

Other patients (n = 3), excluded here, had received bosentan for very severe cutaneous damage and recurrent, treatment-resistant ulcers, but had not had an ulcer when they first started bosentan. The following clinical characteristics were recorded: sex, age, type of SSc according to Leroy’s classification [27], PHT, and pulmonary fibrosis based on high-resolution thoracic computed tomography. We also noted the presence and type of antinuclear antibodies and compiled the patients’ history of digital necrosis as well as the number and sites of digital ulcers or necrosis when they began bosentan treatment. Indications for bosentan were also recorded, including initiation date and dosage.

Date of initiation made it possible to calculate median duration of SSc (with debut of Raynaud’s phenomenon considered to define disease onset) and of the trophic disorders at the beginning of treatment as well as of ulcer healing with bosentan treatment.

Finally we recorded the median follow-up period, that is, the time from the beginning of bosentan treatment to the date of the last patient visit. Other treatments to help heal the trophic ulcers were also recorded. Results are expressed as medians (with their range).

**Results**

**Patients’ characteristics**

Nine patients (seven women and two men) met our selection criteria (table I). Their median age was 54 (20-69) years. According to LeRoy’s classification, six patients had a diffuse and three a limited cutaneous form of SSc. The mean duration of SSc from the onset of Raynaud’s phenomenon to the beginning of bosentan treatment was 14 (2-22) years.
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All patients underwent echocardiography, which did not suggest PHT in any of them. Four patients had pulmonary fibrosis; the others had normal pulmonary CT scans when they started bosentan. The three patients with limited cutaneous SSc had anticentromere antibodies and five of the six patients with diffuse cutaneous SSc had anti-Scl-70 antibodies.

Characteristics of digital ulcers and necrosis

Two patients had a history of digital necrosis. The nine patients had a total of 37 digital ulcers (patient 5 alone had 22) and one had digital necrosis of the hand, most often on the digital pulp. Table II details the specific site of all digital ulcers. These trophic ulcers had been developing for a median of 8 weeks (3-24) before patients began bosentan. Five patients had had previous treatment for these ulcers before beginning bosentan. Four had had iloprost — three of them for five days and one for 28 days (median duration: 5 days). Patient 4 received intravenous buflomedil for five days before beginning bosentan.

Effects of bosentan on digital ulcers and necrosis

Bosentan was prescribed according to the standard regimen, that is 62.5 mg b.i.d. for 4 weeks then 125 mg b.i.d. for all patients except patient 6; her dosage remained at 62.5 mg b.i.d. because of lower extremity edema. All patients continued their usual SSc drug, except for patient 2, who interrupted the oral buflomedil she had been taking for six years. The intravenous vasodilating treatments (iloprost and buflomedil) prescribed in 5 patients for the trophic disorders were stopped when bosentan was initiated.

Complete healing of the digital ulcers occurred in seven of the nine patients after a median of 4 (2-8) weeks of bosentan treatment (table II). The effect in patient 5, who had 22 cutaneous ulcers when starting bosentan, was manifested by a decrease in the number of ulcers; after 8 weeks of treatment, he had only five. A clear improvement was also observed in patient 8’s cutaneous sclerosis, especially of the face. On the other hand, the digital pulp ulcers in patient 9 did not heal. Moreover, he had numerous recurrences during the follow-up of approximately 9 months and required repeated iloprost treatment.

Mean follow-up after the first bosentan treatment was 24.3 (8.9-32.8) months. No patients discontinued bosentan treatment. Over this follow-up period, only patient 1 had a recurrence, of malleolar ulcers. There were no recurrences of digital ulcers. Raynaud’s phenomenon improved in all patients, especially during the winter, except for patient 9.

Adverse effects were limited to an episode of lower extremity edema (patient 6), and headaches for 15 days in patient 7. No hepatic cytolysis was observed.

Discussion

We report in this study the results of treatment with bosentan, an inhibitor of the ETA and ETB receptors of endothelin-1: eight patients with SSc showed swift improvement and recovery from active digital ulcers, while treatment failed for one. Our data reinforce and complement the six clinical cases previously described (table III). Evidence of its positive effects comes from the rapid improvement after a median of 4 weeks of bosentan treatment reported by Humbert and Cabane [23] (ulcers healed in 4 weeks) and by Snyder et al. (healing in two weeks) [25]. These results suggest that bosentan may promote the healing of active digital ulcers in some patients with scleroderma. These patients are most probably those with recurrent and/or multiple ulcers that have a significant ischemic component on which bosentan can act. For those whose ulcers were more mechanical, linked, for example, to fissures related to finger extension or to calcinosis or superinfection of a small wound, bosentan is much less likely to be efficacious and may even hamper reepithelialization, as Korn et al. suggest [22]. Systematic analysis of

**Table I**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Type SSc</th>
<th>Date of debut of Raynaud</th>
<th>Duration of SSc** (years)</th>
<th>Pulmonary fibrosis</th>
<th>Antinuclear antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>66</td>
<td>F</td>
<td>cutaneous diffuse</td>
<td>1991</td>
<td>11</td>
<td>1</td>
<td>Scl70</td>
</tr>
<tr>
<td>2</td>
<td>30</td>
<td>F</td>
<td>cutaneous diffuse</td>
<td>1988</td>
<td>14</td>
<td>0</td>
<td>Scl70</td>
</tr>
<tr>
<td>3</td>
<td>44</td>
<td>F</td>
<td>cutaneous diffuse</td>
<td>1988</td>
<td>15</td>
<td>0</td>
<td>Scl70</td>
</tr>
<tr>
<td>4</td>
<td>55</td>
<td>F</td>
<td>cutaneous diffuse</td>
<td>1985</td>
<td>19</td>
<td>1</td>
<td>Scl70</td>
</tr>
<tr>
<td>5</td>
<td>54</td>
<td>M</td>
<td>cutaneous diffuse</td>
<td>1984</td>
<td>19</td>
<td>1</td>
<td>Scl70</td>
</tr>
<tr>
<td>6</td>
<td>69</td>
<td>M</td>
<td>cutaneous diffuse</td>
<td>1994</td>
<td>10</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>20</td>
<td>F</td>
<td>cutaneous limited</td>
<td>2002</td>
<td>2</td>
<td>0</td>
<td>centromere</td>
</tr>
<tr>
<td>8</td>
<td>24</td>
<td>F</td>
<td>cutaneous limited</td>
<td>1995</td>
<td>8</td>
<td>1</td>
<td>centromere</td>
</tr>
<tr>
<td>9</td>
<td>58</td>
<td>F</td>
<td>cutaneous limited</td>
<td>1982</td>
<td>22</td>
<td>0</td>
<td>centromere</td>
</tr>
</tbody>
</table>

*None had pulmonary hypertension
**At initiation of bosentan treatment
the ulcers will certainly be important in determining whether bosentan should be prescribed for this indication. Although patient 9 had ulcers that seemed more ischemic than mechanical, bosentan failed for her; this suggests that other pathophysiologic mechanisms may play a role.

Bosentan was prescribed off-label, that is, for indications not listed in its approved indications. The reason is that these patients did not meet the inclusion criteria for Rapids-2 or that some of the centers included here were not participating in that trial. Some patients received a vasodilating agent (either iloprost or buflomedil) before the bosentan prescription but it is unlikely that the benefits observed are related to the earlier administration of these drugs. Bosentan treatment was only initiated in the absence of response or after a very moderate response to these treatments. It is thus very improbable that the recovery seen soon after initiating bosentan can be attributed to a delayed effect of these conventional treatments.

The second notable element is the absence of recurrence of these

### Table II
**Indications and effects of bosentan**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Cutaneous lesions at initiation of bosentan treatment</th>
<th>Date of initiation of bosentan</th>
<th>Effects</th>
<th>Time until bosentan effects appeared (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ulcer of pulp of left middle finger</td>
<td>21/10/2002</td>
<td>Ulcer healed</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>3 ulcers of right index finger</td>
<td>NK/12/2002</td>
<td>Ulcers healed</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>3 digital ulcers (the main one is on the pulp of the right fourth finger)</td>
<td>NK/03/2003</td>
<td>Ulcers healed</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>Extensive necrosis of the dorsal face of the right middle finger</td>
<td>12/10/2004</td>
<td>Necrosis healed</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>3 pulpal ulcers on the left hand (index, middle, and fourth fingers)</td>
<td>NK/05/2003</td>
<td>Ulcers healed</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>22 ulcers (right and left feet, knees, hands and elbows)</td>
<td>NK/07/2004</td>
<td>Reduction in number of ulcers to 5</td>
<td>8</td>
</tr>
<tr>
<td>7</td>
<td>Digital ulcer of the pulp of the right fourth finger</td>
<td>06/10/2004</td>
<td>Ulcer healed</td>
<td>2</td>
</tr>
<tr>
<td>8</td>
<td>Active foot ulcers (2) (pulp of second toe and external face of foot)</td>
<td>NK/07/2003</td>
<td>Ulcers healed</td>
<td>8</td>
</tr>
<tr>
<td>9</td>
<td>2 periungual ulcers of the right hand</td>
<td>NK/10/2004</td>
<td>No improvement</td>
<td></td>
</tr>
</tbody>
</table>

*The bosentan regimen was 62.5 mg b.i.d. for 4 weeks then 125 mg b.i.d. except for patient n° 6 (62.5 mg b.i.d. maintained and no increase because of edema of the lower extremities). NK: not known.

### Table III
**Summary of case reports in the literature**

<table>
<thead>
<tr>
<th>Study</th>
<th>Type SSc</th>
<th>Indication for bosentan</th>
<th>Effect of bosentan</th>
<th>Time to effect</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humbert and Cabane [23]</td>
<td>Diffuse</td>
<td>PHT</td>
<td>Healing of ulcer on leg and other small ulcers</td>
<td>4 weeks</td>
<td>17 months. No recurrence of ulcers Improvement of cutaneous sclerosis</td>
</tr>
<tr>
<td>Ramos-Casals et al. [24]</td>
<td>NM</td>
<td>PHT</td>
<td>Healing of digital ulcers</td>
<td>NM</td>
<td>12 months. No recurrence</td>
</tr>
<tr>
<td>Cutting limited</td>
<td>Digital ulcers and necrosis</td>
<td>Complete healing</td>
<td>NM</td>
<td>4 months. No recurrence</td>
<td></td>
</tr>
<tr>
<td>Cutting limited</td>
<td>Raynaud’s phenomenon severe and small digital ulcers</td>
<td>Healing of small ulcers</td>
<td>NM</td>
<td>5 months. No recurrence</td>
<td></td>
</tr>
<tr>
<td>Cutting limited</td>
<td>Severe Raynaud digital ischemia and ulcers</td>
<td>Healing of digital ulcers and ischemia</td>
<td>4 months</td>
<td>NM</td>
<td></td>
</tr>
<tr>
<td>Snyder et al. [25]</td>
<td>Diffuse</td>
<td>PHT</td>
<td>Improvement then healing of digital ulcers</td>
<td>2 weeks</td>
<td>NM</td>
</tr>
</tbody>
</table>

PHT: pulmonary hypertension; NM: not mentioned.
digital ulcers during bosentan treatment, although they had previously been both active and recurrent. This was somewhat expected, since the Rapids-1 study showed significant efficacy for bosentan compared with placebo in preventing new ulcers in SSc [22]. Compared with intravenous iloprost, bosentan had the same advantages as for PHT, principally that it can be taken orally on an outpatient basis. Of course, it requires the same rules for monitoring tolerance – specifically, a hepatic work-up, hemoglobin assays, regular pregnancy tests, and effective contraception. It may also help avoid long and costly hospitalization. Moreover, its prescription can be sequential in some patients, essentially those who have digital ulcers principally in the winter with no problems during the summer. This study has several limitations, in particular, its retrospective nature, but also its inability to include all French patients with scleroderma treated with bosentan for digital ulcers; accordingly we were unable to include other cases of treatment failure. These probably exist, and the reasons may be the same as those found in Rapids-1 [22]: the type of ulcer, whether it is infected, its site, and its longevity all play a role in the failure of bosentan to affect some ulcers. Bosentan may become a first-line treatment option during SSc. Nonetheless, its exact place in the management of digital ulcers in patients with SSc will be clarified by the results of the Rapids-2 study, expected soon. Until then, these cases make it possible to assess the beneficial effects of bosentan while limiting its off-label use to severe digital ulcers refractory to conventional treatment. Prescribing should only be considered and administered by experienced teams.

Conflicts of interest:
• Eric Hachulla has received fees from the following pharmaceutical companies: Actelion, Pfizer, Schering, LFB, ZLB Behring.
• Patrick Carpentier has received fees from Actelion. David Launay, Luc Mouthon, Nadine Boulanger report no possible conflicts of interest.
• The other authors had no conflict of interest.

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