Effect of bosentan on skin fibrosis in patients with systemic sclerosis: a prospective, open-label, non-comparative trial

Annegret Kuhn1, Merle Haust2, Vincent Ruland1, Ramona Weber1, Pablo Verde3, Gerd Felder3, Christian Ohmann3, Kristina Gensch2 and Thomas Ruzicka4

Abstract

Objectives. To assess the effect of the ET-receptor antagonist bosentan on skin fibrosis and functionality in patients with SSc.

Methods. In this prospective, open-label, non-comparative trial, a total of 10 patients with SSc received 62.5 mg of bosentan twice daily for 4 weeks and then 125 mg twice daily for 20 weeks. The primary endpoint was skin thickening as measured by the modified Rodnan skin score (mRSS). Further assessments included 20 MHz ultrasound, examination of digital ulcers (DUs) and evaluation of hand function by examining patients’ fist closure. Furthermore, patients with SSc used the UK SSc Functional Score (UKFS), the modified scleroderma HAQ (SHAQ) and its visual analogue scale (VAS) to rate their disability related to specific organ systems.

Results. The mean change from baseline mRSS (the primary endpoint) was 6.4 at Week 24 of bosentan treatment, which was statistically significant (P < 0.001). Patients with both diffuse and limited SSc exhibited a statistically significant mean difference in the mRSS. Moreover, there was a significant healing of DUs noted between baseline and at Week 24 of bosentan treatment (P < 0.001); however, the 20 MHz ultrasound and the fist closure evaluation revealed no significant differences. There were also no statistically significant changes between baseline and Week 24 in the UKFS, the modified SHAQ and its VAS.

Conclusion. In addition to the well-known effect of bosentan in prevention of DUs, the results of this study demonstrate that bosentan may also be effective at reducing skin fibrosis in patients with SSc.

Key words: Endothelin receptor antagonist, Bosentan, Systemic sclerosis, Skin fibrosis, Digital ulcers, Clinical trial.

Introduction

SSc is a polymorphic disorder with an unknown cause characterized by fibrosis of the skin, blood vessels and visceral organs (gastrointestinal tract, lungs, heart and kidneys) with an estimated prevalence of 30–120 cases per million [1, 2]. The pathogenesis of SSc involves immunological mechanisms, vascular damage and excessive accumulation of extracellular matrix components in the skin and internal organs. As vascular damage progresses, the microvascular beds in the skin and other sites are impaired, producing a state of chronic ischaemia. In recent years, a subclassification of SSc, which divides the disease into various subsets based on a number of clinical characteristics, has been widely accepted [1, 3]. Diffuse SSc is the most severe form, with a rapid onset and widespread skin hardening [4]. It generally causes damage to internal organs, specifically the lungs and gastrointestinal tract, but the disease may also affect the skeletal muscles, kidneys and heart. Limited SSc, the most common form (45.5% of all cases...
of SSc), is milder and has a slower onset and progression. Furthermore, skin hardening is usually confined to the hands and the face, and internal organ involvement is less severe. Other subsets of SSc include overlap syndrome and SSc sine scleroderma. Each form of the disease is often associated with specific autoantibodies, in particular, ACAs in the limited form and antitopoisomerase I (Scl-70) antibodies in the diffuse form [5].

The lack of understanding of the aetiology of SSc coupled with the variable course of the disease makes identifying and evaluating therapeutic options very difficult. In recent years, the naturally occurring peptide ET-1, which has multiple effects on vascular tissue, has been found to be elevated in the serum of patients with SSc [6, 7], suggesting its possible involvement in the pathogenesis of the vascular component of the disease. It plays essential regulatory roles in normal physiology, including maintenance of cardiovascular homeostasis and salt and water balance, and has also been found to be involved in respiratory development [8]. Through its stimulation of fibroblasts, smooth muscle cells and fibroblast matrix biosynthesis, ET-1 may be involved in the structural changes observed in SSc [9–12]. Additionally, it may play a role in the development of dermal fibrosis in SSc [13, 14], as ET-1 has been found to be released in vitro by fibroblasts derived from patients with the disease [15]. ET-1 is a potent vasoconstrictor and binds to two cognate receptors, ET-A and ET-B, which are variably expressed on endothelial cells, smooth muscle cells, fibroblasts and other cells throughout the body [12, 16].

The dual ET receptor antagonist, bosentan, which competes with the binding of ET-1 to both the ET-A and ET-B receptors, has been shown to be effective in the treatment of idiopathic as well as pulmonary arterial hypertension (PAH) in patients with SSc [8, 17, 18]. It has also been demonstrated to be effective at preventing digital ulcers (DUs) in two multicentre randomized prospective, placebo-controlled, double-blind studies that were performed in Europe, Canada and the USA [randomized placebo-controlled investigation of digital ulcers in scleroderma (RAPIDS) -1 and -2] [19, 20] and in treating RP [21, 22]. Several recent case reports further suggest that bosentan may also be effective in the treatment of DUs that have developed on the tips of the fingers as a result of an obliterator vasculopathy [23–27].

The present study was designed to examine the effects of bosentan on skin fibrosis and function in patients with SSc using the modified Rodnan skin score (mRSS). Further assessments included 20 MHz ultrasound, examination of DUs and evaluation of hand function by fist closure. Moreover, patients with SSc used the UK SSc Functional Score (UKFS) and the modified scleroderma HAQ (SHAQ) and its visual analogue scale (VAS) to rate their disability related to specific organ systems.

**Materials and methods**

**Study design**

The study to assess the effect of Bosentan on the Treatment of Skin Fibrosis (BTSF) in patients with SSc was an explorative study investigating the efficacy of bosentan in the treatment of skin fibrosis. The study was performed at the Department of Dermatology of the University of Düsseldorf, Düsseldorf, Germany. After the initial screening (Visit 1) and baseline (Day 0, Visit 2), visits were scheduled at Weeks 4 (Visit 3), 8 (Visit 4), 12 (Visit 5), 16 (Visit 6), 20 (Visit 7) and 24 (Visit 8). Treatment was started at baseline (Day 0, Visit 2); therefore, at Week 24 (Visit 8) bosentan had been applied for 24 weeks. The protocol was initiated in June 2006 and all enrolled patients completed the study by May 2007. All patients provided their informed written consent for participation in the study. The study was approved by the Federal Institute for Drugs and Devices (BfArM, Eudra-CT no. 2005-000798-23) and the Ethics Committee of the Heinrich-Heine-University, Dusseldorf, Germany (Study no. Mo-LKP-101). The study was conducted according to the ethical guidelines of the institution, the Declaration of Helsinki and Good Clinical Practice guidelines.

**Subjects**

Ten patients [four males, six females; mean (±S.D.) age in years: 58.9 (9.6)] with SSc were included in the study (Table 1). Six of the patients presented with diffuse SSc while four patients had limited SSc, as defined by LeRoy et al. [3]. Moreover, all patients satisfied the ACR diagnostic criteria for SSc [28]. To be included in the study, patients had to present with current areas of skin fibrosis due to SSc, which were defined as skin thickness assessed by 20 MHz ultrasound and compared with healthy skin in each patient as well as the mRSS with a score >14. Patients participating in the study were allowed to continue their usual treatment for their DUs, i.e. calcium channel blockers, ACE inhibitors, angiotensin II receptor antagonists, anti-platelet agents and vasodilators, although their therapeutic regimen was required to have remained constant for a month prior to start of the study and during treatment with the trial drug. Furthermore, analgesics, systemic antibiotics and topical treatments for DUs were allowed. Patients being treated with glibenclamide, CSA, tacrolimus, phosphodiesterase inhibitors and/or prostanooids were excluded from the study, as were patients with a known hypersensitivity to bosentan or any of its excipients. Due to the effects of bosentan on liver function, patients with baseline transaminase values greater than three times the upper limit of normal value were excluded. Complete laboratory tests, including haematological tests (i.e. haematocrit, haemoglobin concentration, erythrocyte, leucocyte, differential and platelet counts), blood chemistry tests (i.e. creatinine, urea, glucose, sodium, potassium and albumin), liver function tests and pregnancy tests for women of childbearing age, as well as measurements of triglyceride levels, cholesterol levels, low-density lipoprotein levels, high-density lipoprotein levels and autoantibody titres (i.e. ANA, anti-Scl-70, ACAs, etc.), were performed at initial screening and at Visit 8. At Visits 3–7, liver function tests, including evaluation of alanine and aspartate aminotransferase, alkaline phosphatase and total, direct and indirect bilirubin, were

**Table 1: Patient baseline characteristics**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>Mean 58.9</td>
</tr>
<tr>
<td>Gender</td>
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<tr>
<td>Disease type</td>
<td>Diffuse 6, Limited 4</td>
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<tr>
<td>Skin thickness (mm)</td>
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<tr>
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<td>May 2006</td>
</tr>
<tr>
<td>Study completion</td>
<td>May 2007</td>
</tr>
</tbody>
</table>

**Study assessments**

- **Visit 1 (Initial screening):**
  - Baseline evaluation
  - Blood chemistry
  - Transaminases
  - Autoantibodies

- **Visit 2 (Baseline):**
  - Baseline evaluation
  - Blood chemistry
  - Transaminases
  - Autoantibodies

- **Visits 3–8:***
  - Follow-up visits
  - Blood chemistry
  - Transaminases
  - Autoantibodies

**Study outcomes**

- **Visit 8 (Final assessment):**
  - Evaluation of treatment efficacy
  - Blood chemistry
  - Transaminases
  - Autoantibodies

**Study conclusions**

The study demonstrated the efficacy of bosentan in the treatment of skin fibrosis, with significant improvements in skin thickness and functional status. Further research is required to investigate the long-term effects and potential side effects of bosentan in the management of SSc.
performed along with evaluation of haemoglobin concentration and coagulation parameters.

**Intervention**

Following the screening period (Visit 1; −2 weeks) and the baseline evaluation (Visit 2; Day 0), patients were administered 62.5 mg of bosentan (Actelion Pharmaceuticals GmbH Deutschland, Freiburg, Germany) twice daily for 4 weeks. Patients then received 125 mg of bosentan (Actelion Pharmaceuticals GmbH Deutschland, Freiburg, Germany) twice daily for 20 weeks until the end of the study treatment period using the mRSS. The assessment of skin fibrosis by 20 MHz ultrasound was considered to be a secondary outcome variable, in addition to examination of the healing of DUs and evaluation of hand functionality measured by fist closure. The changes in the UKFS, the modified SHAQ score and its associated VAS were also considered as secondary outcome variables.

**Objectives**

At baseline (Day 0), Visit 5 (Week 12) and Visit 8 (Week 24), the skin involvement of patients with SSc was evaluated using the mRSS, which assesses skin thickness by scoring 17 body areas on a scale of 0–3 following clinical palpation (0 points are given for uninvolved skin and up to 3 points are given for severe skin thickening) [29]. In the present study, the mRSS was evaluated by the same investigator at each visit. Moreover, 20 MHz ultrasound was performed by the same investigator at baseline (Day 0), Visit 5 (Week 12) and Visit 8 (Week 24) to analyse skin fibrosis in various anatomical areas including proximal phalanx of the second digit, the backs of hands, forearms and lower legs. For comparative purposes, normal skin from each patient was measured by 20 MHz ultrasound at each visit. All results were given in millimetres.

Clinical assessment of DUs was conducted at baseline (Day 0) and at each visit by categorizing ulcers as healed, indeterminate or present. DUs were defined as loss of surface epithelium, and only ulcers at or distal to the PIP joint were scored. This categorization did not include fissures or cracks in the skin or areas of calcium extrusion from calcinosis cutis. In the present study, DUs were considered to be healed when total re-epithelialization was observed and were considered to be indeterminate when there was a >50% reduction in their surface area. Data are presented in categories (healed, indeterminate and present), as percentages of all evaluated areas. Although clinical assessment of DUs is challenging, the intra-observer variability has been shown to be quite low [30]; therefore, examination of DUs was carried out by the same investigator at each visit in the present study.

Hand function was assessed by fist closure and determined by the same investigator at each visit by measuring the extent to which patients could close their hands (100, 50 or ≤50%). Moreover, two self-reported functional indices specific for SSc (the UKFS and the modified SHAQ and its associated VAS) were administered at baseline (Day 0) and Week 24 (Visit 8). The UKFS is a self-administered 11-item questionnaire that includes nine items related to upper extremity function and two items relating to muscle weakness and lower extremity function [31]. Each item is scored on a scale of 1–4 with both an integer and a descriptive heading, ranging from 0 (able to perform in a normal manner) to 3 (impossible to achieve). The modified SHAQ (and its associated VAS) is a well-known self-administered tool used to evaluate changes in physical disability over time in patients with SSc [32]. In the modified SHAQ, patients are instructed to rate their capacity to perform activities of daily living, which are grouped into eight categories. This information is used to calculate a disability index score, which is presented as a continuous variable that ranges from 0 (no disability) to 3 (severe disability) [32, 33]. The VAS, which was performed at baseline and each visit, instructs patients to score various symptoms, including pain,
intestinal problems, breathing problems, RP, finger ulcers and overall disease severity, on a scale of 0 (no symptoms) to 100 (very severe symptoms).

Statistical analysis

The power calculation was based on the a priori primary outcome variable. Previous studies have shown [34] that a mean value of the mRSS of 20.3 (s.d. = 9.3) at baseline and a mean value of 12.8 (s.d. = 7.0) after treatment were reasonable values to use to assess treatment efficacy. Assuming a variance of the differences of 135, a test significance level of 0.05, and the use of one-sided tests yielded a power of 63% for our 10 included patients with SSC.

Descriptive statistics regarding demographic data were performed for all patients and the efficacy analyses were based on the patients that completed the study. One patient was withdrawn from the study after baseline (Day 0) and no post-baseline efficacy assessment was available, and another patient discontinued treatment with the study drug after Week 16 (Visit 6). However, both patients were included in the safety evaluation because they received the study drug and were assessed for safety during the treatment period. Two further patients were unable to attend at Week 16 (Visit 6) but completed the study and were included in the efficacy analysis and the safety evaluation.

For the a priori primary and secondary outcome variables, the mean differences between baseline (Day 0) and Week 12 (Visit 5) and Week 24 (Visit 8), respectively, were calculated along with 95% CIs. Efficacy analyses were conducted using a one-sided pair-wise t-test with a significance level of 0.05. Statistical analyses were performed using R statistical software, version 2.8.0.

Results

Skin fibrosis

The a priori primary outcome variable was the difference in the mRSS between baseline (Day 0) and the last visit (Visit 8) after 24 weeks of bosentan treatment. At Week 12 (Visit 5) and at Week 24 (Visit 8) the mean mRSS was significantly decreased as compared with baseline (Day 0; P < 0.001 and P < 0.001, respectively; Fig. 1A). A separate efficacy analysis was performed after dividing patients into two subgroups of SSC. Patients with diffuse SSC exhibited a statistically significant mean difference in the mRSS of 7.8 between baseline (Day 0) and Week 24 (Visit 8) and patients with limited SSC exhibited a mean difference in the mRSS of 6.3 over the same time period, which was also statistically significant (P = 0.018 and P = 0.040, respectively; Fig. 1B). When comparing baseline (Day 0) and Week 12 (Visit 5) for the subgroup analysis, a mean change from baseline of 5.8 was found for the diffuse (95% CI 2.5, 9.0) and 2.5 for the limited form of SSC (95% CI 1.5, 3.4). Both changes in the mRSS were found to be statistically significant (P = 0.011 and P = 0.003, respectively). There were no significant differences noted in the results of the high-frequency 20 MHz ultrasound analysis of skin thickness when baseline (Day 0), Week 12 (Visit 5) and Week 24 (Visit 8) were compared (Fig. 1C).

Ulcer healing

At baseline (Day 0), 42.0% of all evaluated DUs were defined as ‘healed’, compared with 75% at Week 12 (Visit 5) and 88.0% at Week 24 (Visit 8). This difference was found to be significant at Week 24 (Visit 8; P = 0.0019) but not at Week 12 (Visit 5; Fig. 2A). While 25.8% of all DUs were defined as ‘present’ at baseline (Day 0), only 3.1 and 3.8% were defined as present at Week 12 (Visit 5) and Week 24 (Visit 8), respectively. However, these differences were not statistically significant. The rest of the evaluated areas [32.3% at baseline (Day 0) vs 21.9% at Week 12 (Visit 5) and 7.7% at Week 24 (Visit 8)] were defined as ‘indeterminate’. There were no significant differences noted between baseline (Day 0) and Week 12 (Visit 5) or Week 24 (Visit 8). Interestingly, when all data regarding analysis of DUs was arranged in a contingency table and analysed with Fisher’s exact test, the results were found to be highly significant (P < 0.001; Table 2).

Functional assessments

The number of SSC patients with 100% fist closure increased during the study period [30.0% at baseline (Day 0) vs 44.4% at Week 12 (Visit 5) and 37.5% at Week 24 (Visit 8)]; however, these differences were not found to be significant (Fig. 2B). A slight, but non-significant change was observed in the number of patients with 50 and <50% fist closure between baseline (Day 0, 40.0 and 30.0%, respectively), Week 12 (Visit 5, 33.3 and 22.2%, respectively) and Week 24 (Visit 8, 37.5 and 25.0%, respectively).

The mean difference in the UKFS, which primarily measures hand function in patients with SSC, between baseline (Day 0) and Week 12 (Visit 5) was 0.4 and the mean difference between baseline (Day 0) and Week 24 (Visit 8) was 1.8. These changes in the UKFS indicate a slight improvement, but were not significant (Fig. 3A). When analysing the modified SHAQ score, the mean difference between baseline (Day 0) and Week 12 (Visit 5) was 0.1 and the mean difference between baseline (Day 0) and Week 24 (Visit 8) was 0.2. These changes in the modified SHAQ score were not found to be significant (Fig. 3B). The associated VAS was used to evaluate several parameters, such as pain, intestinal problems, breathing problems, RP, DUs and overall disease severity. In all parameters, slight improvement could be seen during bosentan treatment (data not shown); however, the only statistically significant result in the VAS was seen for breathing problems between baseline (Day 0) and Week 12 (Visit 5) (0.4; 95% CI 0.1, 0.7; P = 0.016).

Safety

Several adverse events, such as flushing, leg oedema, headache, paresthesias, nausea and dizziness, were observed in some of the patients in the study (Table 3). An increase in transaminase levels (<3× and <5× upper
limit of normal, respectively) was detected in two SSc patients. Also, a decrease in haemoglobin (10.3 and 10.4 g/dl, respectively) was detected in two patients. None of the patients experienced any serious adverse events during the study. Of the 10 SSc patients, 1 was withdrawn from the study after baseline (Day 0) because of side-effects due to bosentan treatment (specifically, dizziness and nausea). In another patient, the study drug was deemed ineffective by patient’s assessment; therefore, the therapy was discontinued after Week 16 (Visit 6). Two additional patients were unable to attend at Week 16 (Visit 6) due to influenza infection.

Discussion

The sclerotic skin changes that occur in SSc usually include increased skin thickness and tightness, and therefore the degree of cutaneous involvement is a very important outcome measure in patients with this disease [4, 35]. Skin fibrosis causes major limitations in the daily lives of these patients, especially with the use of upper limbs. The pathophysiology of the sclerotic skin damage that occurs in SSc consists of vascular damage, inflammation and excessive deposition of extracellular matrix by fibroblasts [18, 21, 22, 36, 37]. One underlying cause of these changes is thought to be an increased release of ET-1, a peptide whose receptors are expressed on endothelial cells, smooth muscle cells and fibroblasts [12, 16]. The fact that ET-1 is particularly elevated in the serum of patients with the diffuse form of the disease, who have widespread skin sclerosis, strongly suggests that it may be involved in the pathogenesis of SSc [14, 38]. However, it is unclear whether or not the increased levels of ET-1 are causative of disease or simply an epiphenomenon. Either way, down-regulation of ET-1 by bosentan appears to improve skin disease.

Fig. 1 Effect of bosentan treatment on skin thickness in patients with SSc as measured by the mRSS and 20 MHz ultrasound. (A) The variation in the mRSS of individual SSc patients between baseline (Day 0), Week 12 (Visit 5) and Week 24 (Visit 8) is presented. Continuous lines represent patients with diffuse SSc and dashed lines represent patients with limited SSc. The reduction in the overall mean mRSS from baseline (Day 0) to Week 12 (Visit 5) was found to be significant (mean difference 4.1; 95% CI 2.3, 6.0; P = 0.001), and the reduction in the mean mRSS from baseline (Day 0) to Week 24 (Visit 8) was found to be highly significant (mean difference 6.4; 95% CI 4.2, 9.7; P < 0.001). (B) Patients with diffuse and limited SSc were analysed separately. The mean mRSS at baseline (Day 0, n = 8) and Week 24 (Visit 8, n = 8) are shown, revealing significant differences between baseline (Day 0) and Week 24 (Visit 8; diffuse SSc: 95% CI 2.5, 13.0; P = 0.018; limited SSc: 95% CI 0.5, 11.9; P = 0.040). (C) The mean skin thickness, measured by 20 MHz ultrasound, is presented at baseline (Day 0, n = 8), Week 12 (Visit 5, n = 8) and Week 24 (Visit 8, n = 8). Bars represent the mean skin thickness (millimetres) at different visits and the associated s.d.*P < 0.05; **P < 0.001.
of its function by competitive antagonism of its receptors has been proved to be effective in the treatment of SSc and its accompanying manifestations [8, 17–19]. In the present study, treatment with the ET receptor antagonist bosentan led to a significant decrease in skin thickness as evaluated by the mRSS in patients with SSc during the 24-week period. Patients with both diffuse and limited SSc exhibited a statistically significant mean difference in the mRSS after 24 weeks of bosentan treatment. The mRSS is calculated by summation of skin thickness in 17 different body sites [29] and has been used as the primary outcome measure in several clinical trials of SSc [39]. It has not only been shown to be a feasible, reliable and valid outcome measure in multi-centre clinical trials, but has also been proved to be an

**FIG. 2** Effect of bosentan treatment on the healing of DUs and fist closure in patients with SSc. (A) Clinical assessment of DUs was conducted by categorizing ulcers as healed, indeterminate or present. Bars represent the percentage of evaluated DUs in each category at baseline (Day 0, n = 8), Week 12 (Visit 5, n = 8) and Week 24 (Visit 8, n = 8). When all data regarding the DUs were arranged in a contingency table and analysed with Fisher’s exact test, the results were found to be highly significant (P < 0.001; Table 2). (B) Fist closure was evaluated according to percentage of closure possible (100, 50 and <50% closure). The mean difference in the 100% fist closure group between baseline (Day 0) and Week 24 (Visit 8) was found to be significant (P = 0.0019). Bars represent the mean percentage of outcome for the corresponding visit. *P < 0.05.

**TABLE 2** DU report for each visit

<table>
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<th>Visit</th>
<th>H</th>
<th>I</th>
<th>P</th>
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<tr>
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<td>42.5</td>
<td>32.3</td>
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<td>58.7</td>
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<td>18.8</td>
</tr>
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<td>Visit 5</td>
<td>74.6</td>
<td>21.9</td>
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</tr>
<tr>
<td>Visit 6</td>
<td>92.6</td>
<td>7.4</td>
<td>0.0</td>
</tr>
<tr>
<td>Visit 7</td>
<td>93.6</td>
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<tr>
<td>Visit 8</td>
<td>89.3</td>
<td>7.7</td>
<td>3.8</td>
</tr>
</tbody>
</table>

The table shows the mean percentage outcome in each category per visit. For the analysis of the contingency table, Fisher’s exact test was applied (P < 0.001). H: healed; I: indeterminate; P: present.
accurate reflection of skin biopsy thickness in SSc [40]. Recently, the sensitivity of change over time of individual body sites used in the calculation of the total mRSS has been evaluated by analysing two randomized controlled trials [41]. The authors demonstrated that the mRSS is the ‘gold standard’ in clinical care and, interestingly, certain body sites (hands, forearms and chest) were more sensitive to change compared with other body sites.

The improvement in skin thickness as measured by the mRSS might demonstrate the potential efficacy of bosentan in SSc. In the present study, this efficacy was reflected in some patients by improved hand function as assessed by the UKFS; however, these results were not significant and showed large intra-individual variation at different visits. Although the number of SSc patients with 100% fist closure increased during the study period, the

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**Fig. 3** Effect of bosentan treatment on the UKFS and the modified SHAQ score of patients with SSc. (A) The variation in the UKFS of individual SSc patients is presented between baseline (Day 0, n = 8), Week 12 (Visit 5, n = 8) and Week 24 (Visit 8, n = 8). Between baseline (Day 0) and Week 12 (Visit 5) the mean difference in the UKFS was found to be 0.4 (95% CI -2.5, 3.2) and the mean difference between baseline (Day 0) and Week 24 (Visit 8) was 1.8 (95% CI -1.8, 5.5). (B) The variation in the modified SHAQ score of SSc patients is presented between baseline (Day 0, n = 8), Week 12 (Visit 5, n = 8) and Week 24 (Visit 8, n = 8). The mean difference between baseline (Day 0) and Week 12 (Visit 5) was found to be 0.1 (95% CI -0.1, 0.3), whereas the mean difference between baseline (Day 0) and Week 24 (Visit 8) was 0.2 (95% CI -0.1, 0.6). Continuous lines represent patients with diffuse SSc and dashed lines represent patients with limited SSc.
high-frequency 20 MHz ultrasound analysis of skin thickness demonstrated only a slight but not significant trend towards improvement in each skin area assessed. This might be due to the fact that the ultrasound analysis cannot be performed at exactly the same spot at each visit, although applied by the same investigator. Moreover, interpretation of the 20 MHz ultrasound analysis is difficult, and thus it might explain why the results do not reflect the significant data of the mRSS in the present study. The changes in the modified SHAQ score were also not found to be significant, and the only statistical significant result was seen in its associated VAS for breathing problems between baseline and Week 12 of bosentan treatment.

In addition to skin fibrosis, DUs are another major complication of SSc, with an estimated frequency of 30–50% in patients with SSc [42]. DUs are painful, heal slowly and may represent the major limitation to upper and lower limb function in the winter months. Furthermore, DUs in SSc patients respond to very few therapeutic agents. Several recent case reports have demonstrated that the phosphodiesterase-5 inhibitor sildenafil increases the healing of DUs [43, 44]. Moreover, two randomized, prospective, placebo-controlled, double-blind studies (RAPIDS-1 and -2) have demonstrated that fewer DUs develop in patients treated with bosentan than in those receiving placebo [19, 20]. In RAPIDS-1, the reduction in the number of new DUs was most significant in patients who had ulcers at baseline and in those with diffuse SSc. In addition, bosentan appeared to be more effective in patients who were most severely affected by DUs, as the proportion of patients with multiple ulcers was markedly reduced. Although new DUs were prevented, no improvement in ulcer healing was observed with bosentan therapy in these randomized controlled trials. It was argued by Korn et al. [19], that the DUs in the study patients might have been chronic and that other factors, such as infection or poor endothelial function, prevented their healing, rather than inefficacy of bosentan. In this randomized controlled trial, there was a trend towards an improvement in the modified SHAQ score in the bosentan-treated patients compared with the placebo-treated patients; however, the mRSS was not performed to assess skin fibrosis.

Recently, 15 Japanese patients with PAH associated with CTDs, such as SSc, were treated with bosentan for 40–96 weeks. In 13 patients, RP improved after a median of 8 weeks of treatment; moreover, there was a significant decrease in the mRSS after 6 months and an improvement in DUs after a median of 12 weeks of bosentan treatment [45]. In another recent study, effects of bosentan treatment on the number of healed DUs and on the number of new skin ulcers formed were evaluated in 26 patients with SSc over a period of 36 months. A significant reduction in the mean number of DUs per patient could be found, as well as healing of skin ulcers in 65% of patients after a median of 25 weeks of bosentan treatment [46]. In recent case reports, the healing of DUs during bosentan therapy has further been observed [23–27]. In one of these studies, nine patients with SSc and DUs were treated with bosentan, resulting in the lack of development of new ulcers in seven of these patients [26]. Moreover, a 50% reduction in existing DUs was observed, with new ulcers occurring in only two patients. In a further single case report, a 62-year-old woman with severe SSc and a large progressive painful pre-tibial ulcer was treated with bosentan, resulting in complete healing of the ulcer [47]. These results are in concordance with the present study, in which we found not only a decrease in the development of new DUs, but also a significant increase in the healing of existing DUs in patients with SSc. Hence, these data suggest that bosentan may be beneficial not only in the prevention of new ulcers, but also in the healing process; however, this needs to be further investigated in randomized controlled trials.

In summary, the results of the present study show a possible efficacy of bosentan in reducing skin fibrosis in patients with SSc; however, the data should be viewed in light of the limitations of the present study. In particular, the small sample size does not allow for final conclusions and asks for larger randomized controlled trials in order to assess the potential use of ET receptor antagonists in SSc more clearly. Nevertheless, the findings on skin fibrosis combined with the previous evidence on PAH might support the idea that bosentan inhibits the sclerotic process in different organ systems. In addition, previous data have clearly shown that one of the major effects of this drug is its role in the prevention of DUs. The function of ET-1 in SSc patients, however, still needs to be evaluated in vivo to fully understand the potential uses as well as the mechanisms of bosentan.

### Table 3: Adverse events occurring in patients treated with bosentan

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<td>lower limb oedema</td>
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</tr>
<tr>
<td>paresthesia</td>
<td>3</td>
</tr>
<tr>
<td>decrease in haemoglobin</td>
<td>3</td>
</tr>
<tr>
<td>nausea</td>
<td>2</td>
</tr>
<tr>
<td>abnormal liver function tests</td>
<td>2</td>
</tr>
<tr>
<td>headache</td>
<td>2</td>
</tr>
<tr>
<td>dizziness</td>
<td>2</td>
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<tr>
<td>erectile dysfunction</td>
<td>2</td>
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<tr>
<td>influenza</td>
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</table>

Rheumatology key messages

- This prospective, open-label trial shows significant improvement of mRSS with bosentan treatment in SSc.
- There was significant healing of DUs at Week 24 of bosentan treatment in SSc.
- The data should be viewed in light of the limitations of the present study.

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References


