

Bosentan in Clinical Practice for Treating Digital and Other Ischemic Ulcers in Spanish Patients with Systemic Sclerosis: IBER-DU Cohort Study

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ABSTRACT. Objective. To describe treatment outcomes and safety experience with bosentan in patients with systemic sclerosis (SSc) and digital ulcers (DU), in a clinical setting in Spain.

Methods. This was a multicenter, noninterventional retrospective cohort study. Data were collected retrospectively from patients with DU, with or without pulmonary arterial hypertension (PAH), who were initiating bosentan therapy in 2003 (n = 26) or 2004 (n = 41) and followed until May 2005. Data were obtained from centers prescribing bosentan. Relevant measures included number of DU, occurrence of new DU, overall DU clinical status (improved, stabilized, worsened), and bosentan-associated adverse events.

Results. Sixty-seven patients with SSc and DU or other ulcers were included. PAH was also present in 12 patients (18%). At the start of bosentan treatment, the median number of DU per patient was 3.0. The median change in number of DU was -3.6 and -5.0 at 12 and 24 months, respectively. Sixty-eight percent of the patients did not develop any new DU at 12 months. DU clinical status was reported at 12 months for 22 patients: 18 patients (81.8%) improved and 4 (18.2%) stabilized. The median treatment duration was 13.0 months. The main adverse event was increase of aminotransferase, observed in 5 patients (7%), leading to discontinuation of treatment in 3 patients (4.4%).

Conclusion. Previously reported results of bosentan efficacy in DU management are reproducible in clinical practice. This efficacy is maintained in the longterm followup. Bosentan treatment was well tolerated and adverse events were comparable with those observed in previous reports. (J Rheumatol First Release June 1 2011; doi:10.3899/jrheum.101266)

Key Indexing Terms:

DIGITAL ULCERS
ENDOTHELIN

SYSTEMIC SCLEROSIS

BOSENTAN
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Systemic sclerosis (SSc) is a rare chronic fibrotic connective tissue disease, characterized by cutaneous and visceral fibrosis. Widespread microvascular pathology is also a cardinal feature of SSc. Raynaud's phenomenon (RP) is an almost universal vascular manifestation of SSc (90%–95% of SSc

cases). SSc-associated RP is a structural disorder with intimal proliferation and vasculature obstruction on histology¹; it usually has an aggressive clinical course and can lead to digital ulcers (DU). Pathogenesis of SSc-associated vasculopathy entails both mechanisms of endothelial cell activation and dysregulation of the vasculature tone mediated by cytokines and growth, angiogenic², vasculogenesis-related³, and vasoactive factors⁴. All these molecules have 2 main targets, located in the vascular wall: the pericytes and the smooth muscle cells. A trigger stimulus starts an inflammatory process in the vascular wall, which is mediated by T and B lymphocytes, and possibly by autoantibodies⁴, resulting in endothelial cell damage, the key step of this pathogenic mechanism⁵. This damage produces an imbalance of interstitial turnover, leading to deposition of collagen and isolated mononuclear cell infiltrates. Intimal hyperplasia with severe and progressive vascular obstruction is the final pathologic consequence of these processes. Among the vasoactive factors, it is well known that increased endothelin activity plays a crucial role in the process of vascular injury⁶.

Occurrence of DU is the most common manifestation of SSc-associated vasculopathy. Studies have reported a fre-

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quency of DU between 50%^{7,8} and 58%⁹. DU is the consequence of an ischemic injury leading to necrosis of skin and subcutaneous tissues. This ischemic lesion is located more frequently in fingers, but hands, elbows, or heels may also be involved. DU lower a patient's quality of life¹⁰ because they are painful, disabling, and frequently lead to hospitalization^{11,12,13}. A study focused on both the severity and the definition of SSc-associated DU showed a lack of agreement among physicians (most of them rheumatologists)¹⁴. That study recommended a higher degree of uniformity in the definition of SSc-associated DU, mainly because DU-associated characteristics and development are frequently used as endpoints in clinical trials.

For many years, pharmacological management of DU has resulted in poor outcomes because the DU were often refractory to multimodal standard therapies. To date, established drugs such as calcium-channel blockers or prostaglandins and new treatments such as endothelin receptor antagonists and phosphodiesterase-5 inhibitors have been evaluated in randomized clinical trials¹⁵.

The endothelins are a family of 3 vasoactive peptides; endothelin 1 (ET-1) is the one studied most frequently. ET-1 is a potent vasoconstrictive factor that acts on connective tissue remodeling by means of chemotactic effects on macrophages and smooth-muscle cells⁴. ET-1 is widely expressed in SSc, especially in tissues affected by fibrotic changes^{16,17}. Pharmacological intervention on pathways triggered by ET-1 may block one of the receptors (ET_A or ET_B, single blockade) or both (dual blockade).

Bosentan is an oral dual ET-1 receptor antagonist, approved in the European Union to reduce the number of new DU in patients with SSc. Results of a study performed in a preclinical murine model of SSc suggested that bosentan may prevent endothelial alterations associated with SSc⁶. Further evaluation in 2 randomized placebo-controlled trials showed the efficacy of bosentan in reducing the number of new DU^{18,19} in patients with SSc who had ongoing DU.

We conducted a retrospective, clinical practice multicenter Spanish study of the safety experience and clinical outcomes of patients with SSc who received bosentan for the treatment of DU and other cutaneous ulcers.

MATERIALS AND METHODS

Patients. The IBER study involves a cohort of 418 patients who received bosentan in Spain. Patients for our study were selected as a subset of the IBER study patients.

Of the 418 patients in the IBER study, we determined that 67 patients with SSc had DU or other cutaneous ulcers. Ulcers were defined as a cutaneous lesion with an area of discontinuity of the epidermis, refractory to standard medical treatment, and prolonged in time. Patients were selected based on this ulcer definition, considering the opinion of the investigators on measures associated with ulcers such as the number, position, development, need for vasodilators, etc.

Methods. Data were collected from a careful review of the patients' clinical charts. Patients were followed from initiation of bosentan treatment in 2003 (n = 26) or 2004 (n = 41) until May 2005 (end of data collection), i.e., their

last visit, death, or loss to followup. Data were obtained from nearly all Spanish centers prescribing bosentan. For treatment and outcomes analyses, patients still under treatment at the end of the observation period were censored.

Study endpoints were (1) change in the number of ulcers over time; (2) occurrence of new ulcers; (3) overall clinical status of the ulcer (improved, stabilized, worsened); and (4) bosentan-associated adverse events.

In accord with local data privacy laws, information on sex and age were not collected.

The study was approved by the ethics committees of the participant centers. Written informed consent was obtained from all patients before the start of the treatment because bosentan was still not approved for the treatment of DU, and was administered in the setting of a compassionate use program.

Statistical analysis. Mean, median, range, and SD were calculated for quantitative variables. Absolute and relative frequencies were calculated for qualitative variables. The Kaplan-Meier actuarial method was used to estimate the duration in time-to-event variables with censored data.

RESULTS

Baseline characteristics. Among 418 patients treated with bosentan in the IBER study, a total of 67 patients (16%) with DU and other cutaneous ulcers were identified and included in our study (IBER-DU cohort). Baseline characteristics of the patients are listed in Table 1 with data on bosentan treatment and exposure. Twelve patients (18%) in this cohort also had pulmonary arterial hypertension (PAH), which was assessed by echocardiography.

Bosentan treatment and exposure. Twenty-two out of 67 patients (33%) initiated bosentan therapy before December 1, 2003, almost 3 years before the end of data collection, and 16 of these patients (72%) remained on bosentan treatment for at least 18 months. Thirty-nine out of 67 patients (58%) initiated bosentan therapy before June 1, 2004, almost 2 years before the end of data collection, and 35 of these 39 patients (89%)

Table 1. Baseline patient characteristics and exposure to bosentan. All data are number of patients (%), unless otherwise specified.

Measurement	N = 67
Etiology	
Ulcers with PAH	12 (17.9)
Ulcers without PAH	55 (82.1)
No. ulcers at baseline, n = 55*	
Mean ± SD	4.1 ± 4.4
Median (range)	3.0 (0–26)
Daily maintenance dose of bosentan, mg	
250	49 (73.1)
125	15 (22.4)
93.75	1 (1.5)
62.5	1 (1.5)
Unknown	1 (1.5)
Exposure to bosentan, mo	
Mean ± SD	13.1 ± 6.8
Median (range)	13.0 (3.2–28.0)
Treatment for ulcers	
Bosentan monotherapy	63 (94.0; 10 with PAH)
Bosentan plus prostanoids	4 (6.0; 2 with PAH)

* 12 missing data. PAH: pulmonary arterial hypertension.

continued bosentan treatment for at least 12 months. The median treatment duration was 13.1 months (range 3.2–28.0; Figure 1).

The majority of the patients were treated with an oral maintenance dose of 250 mg/day (125 mg bid; 49 patients) or 125 mg/day (15 patients). The 250 mg/day dose was increased from 125 mg/day, the dose administered during the first month to these patients. Sixty-three patients (94%) were receiving ≥ 1 non-PAH-specific concomitant therapy. The most commonly administered therapies were omeprazole, prednisone, aspirin, losartan, pentoxifylline, and diltiazem (data not shown). Four patients with PAH were treated with prostanoids concurrently with bosentan therapy.

Clinical outcomes. Information on the number of ulcers at baseline was available for 55 patients (82%) who had a mean of 4.1 ± 4.4 and a median of 3 ulcers (range 0–26) at baseline. Localization of DU at baseline was known in 48 patients (72%); among them, 33 (69%) had DU, 7 (14%) had hand ulcers, and 8 (17%) had ulcers on other sites (elbows, legs, or heels).

The change from baseline in the number of ulcers over time is shown in Figure 1. Compared with baseline, after 3 (n = 28), 6 (n = 30), 12 (n = 22), and 24 months (n = 5), patients had an average of 1.3, 2.7, 3.6, and 5.0 fewer ulcers, respectively. The median change in the number of ulcers per patient from baseline to 12 months was -2.0 (95% CI $-4.0, -1.0$). Half of these patients experienced a reduction ranging between 1 and 5 ulcers.

Data on occurrence of new ulcers are shown in Figure 2. More than 70% of patients experienced no new ulcers at 3 and 6 months, and 67% of the patients did not develop any new DU at 12 months, confirming the preventive effect observed in clinical trials of bosentan in patients treated for DU.

Overall, clinical ulcer status improved over time with bosentan treatment. Improvement was defined as a decrease of ≥ 1 ulcer. Ulcer clinical status was reported at 12 months for 22 patients: regarding the total number of ulcers, 18 patients (81.8%) improved and 4 (18.2%) stabilized, as determined by a physician on the basis of clinical experience in evaluating symptoms and signs. No patient showed an

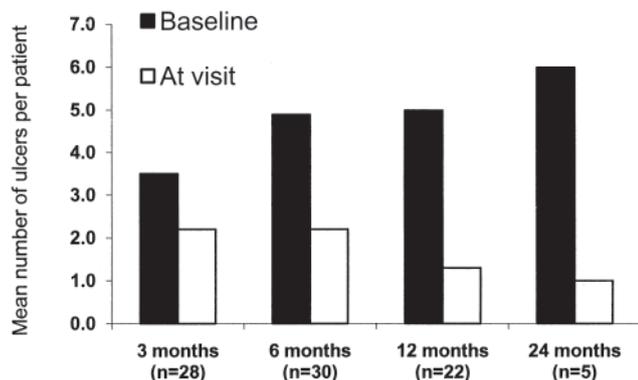


Figure 1. Mean number of ulcers per patient over time.

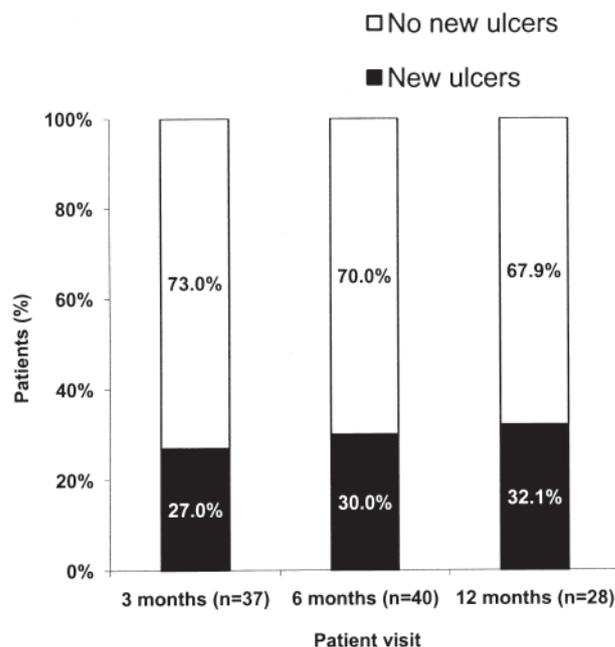


Figure 2. Occurrence of new ulcers.

increase in the total number of ulcers at 12 months of treatment.

After 3 (n = 28), 6 (n = 30), 12 (n = 22), and 24 months (n = 5), improvement was seen in 57.1%, 70%, 81.8%, and 100%, respectively, of the all patients with DU. Changes in clinical status of ulcers at 3, 6, 12, and 24 months as assessed by treating physician are illustrated in Figure 3.

Safety. Bosentan therapy was well tolerated and no unexpected adverse events were observed. Data on aspartate/alanine aminotransferase (AST/ALT) were collected only if abnor-

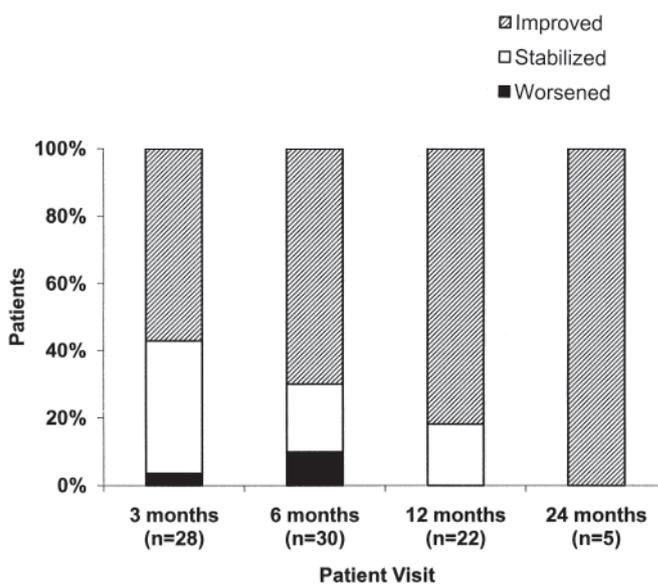


Figure 3. Change in total number of ulcers as assessed by treating physician (improvement: decrease of ≥ 1 ulcer).

mal. Five patients (7%) experienced AST/ALT increase > 3 times the upper limit of normal values. Among these patients, 3 discontinued bosentan and the other 2 patients experienced further stabilization of AST/ALT and could continue on bosentan therapy without additional adverse events.

The mean hemoglobin value at treatment initiation was 12.9 g/dl. Hemoglobin levels remained stable over the first 12 months of therapy. There was a slight decline in levels at 24 months (11.7 g/dl), but this hemoglobin level was not lower than the lower limit of normal. No other adverse events were observed.

Treatment discontinuation. A total of 15 patients (22%) discontinued treatment with bosentan prior to the data cutoff point, due to clinical worsening requiring change of treatment (n = 5), adverse events (n = 4), healing (n = 2), death (n = 2), pregnancy plans (n = 1), and personal reasons (n = 1). Causes of death were progression of lung disease in 1 patient and refractory progression of PAH in the other.

DISCUSSION

Limitations in generalizability or applicability of the results of randomized clinical trials because of limitations in inclusion criteria of the enrolled patients have been a matter of discussion²⁰ and in particular, in clinical trials on SSc²¹. These studies call for a better design of clinical trials in order to avoid large differences between the characteristics of the enrolled population and the real-world population. In the meantime, reports of real-world experience of treatments, approved as a consequence of the results of randomized clinical trials, are useful because they offer important information on the generalizability and applicability of our results.

The results of our study show that bosentan is effective when used in the treatment of SSc-associated DU. It is associated with a decrease in the number of ulcers over time, with effective prevention of the occurrence of new ulcers. It should be highlighted that our study, which recorded followup data at 12 and 24 months, also shows that the efficacy of bosentan is maintained in the long term, although data at 24 months are based on only 5 patients.

Two large randomized clinical trials^{18,19} showed the efficacy of bosentan in this setting and are the reason for its approval for this indication by regulatory agencies. These studies have recently been extensively reviewed²². The RAPIDS-1 study (Randomized Placebo-controlled Investigation of Digital ulcers in Scleroderma), a randomized double-blind placebo-controlled clinical trial, enrolled 122 patients and had the number of new ulcers developing as a main endpoint; a 48% reduction in the mean number of new DU in patients receiving bosentan was observed¹⁸. The RAPIDS-2 study¹⁹ enrolled 188 patients and also showed a reduction in the occurrence of new DU. In addition, both studies showed a significant benefit in hand function in the group of patients receiving bosentan. Although their main endpoints were different from ours (number of new ulcers in the RAPIDS studies and number of ulcers over time in our study),

the majority of our patients experienced no new ulcers, in agreement with the results of the 2 RAPIDS studies.

A controversial topic is the effectiveness of bosentan treatment in healing ongoing ulcers. Neither of the RAPIDS studies could formally demonstrate a significant effect of bosentan in that aspect. However, the results of our study showed a clinical improvement of the ulcers as a consequence of bosentan treatment. The results of the RAPIDS studies on this issue have been criticized for having used inappropriate tools to perform this analysis²³. Matucci-Cerinic and Seibold recommended better ulcer-specific measures of outcome in future clinical trials on DU management²³. Single reports^{24,25,26}, small retrospective studies^{27,28,29}, and a prospective study (Tsifetaki, *et al*)³⁰ all have reported the effectiveness of bosentan on SSc-associated DU. Tsifetaki, *et al* showed that cutaneous ulcers in 17 out of 26 patients (65%) healed after a median followup of 6 months³⁰, whereas we observed improvement in the total number of ulcers in 81.8% of patients at 12 months. However, the retrospective and noncontrolled design of our study, as well as the use of comedication, preclude drawing conclusions from our data on this issue.

Although RAPIDS-1 was extended with a 3-month study³¹, overall, RAPIDS-1 and RAPIDS-2 must be considered short-term studies because the followup was 4 months in RAPIDS-1 and 6 months in RAPIDS-2. Two longterm studies on bosentan efficacy in SSc-associated DU have been reported; these were nonrandomized trials and included 15³² and 26³⁰ patients and reported data at 30 and 36 months, respectively. In the aggregate, these studies showed that bosentan is related to a decrease in the number of DU in patients with SSc as compared with baseline, comparable with our results on this endpoint, and this efficacy was maintained in the longterm followup.

Adverse events we observed focused mainly on liver function, as expected in view of the literature on bosentan for DU treatment and data from a large postmarketing study on bosentan in patients with SSc-associated PAH³³. However, it should be highlighted that in our study, bosentan treatment resulted in increase of aminotransferase in < 10% of the patients and that only 3 out of 67 patients (4.4%) discontinued bosentan as a consequence of this increase. Moreover, no severe liver toxicity was observed (i.e., liver failure).

Our study has 3 main weak points. First, because of the lack of data on sex, age, and race, it is not possible to determine whether our patients are demographically similar to the populations treated in other clinical trials. Second, the data were retrospectively collected from medical charts, and the number of patients with available data declined over time. The most important dataset is at 12 months because at 24 months, few patients had available data. Lastly, we have no information on clinical subsetting (pure DU, digital pitting scar, calcinosis, or gangrene). This classification system has recently been shown to be a helpful clinical tool for evaluation and staging purposes in SSc-associated DU³⁴.

Our study shows that previously reported efficacy of DU management with bosentan in patients with SSc is reproducible in clinical practice, and that this efficacy is maintained in longterm followup. Bosentan-associated adverse events were mild and manageable, and elevated aminotransferase was comparable with levels observed in previous reports.

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