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Long-term Efficacy snd Safety of Bosentan in Patients with Digital Ulcers Related to Systemic Sclerosis

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ABSTRACT

Objective: *Two pivotal studies, RAPIDS-1 and RAPIDS-2 (RAndomized, double-blind, Placebo-controlled study with bosentan on healing and prevention of Ischemic Digital ulcers in patients with systemic Sclerosis) revealed that Bosentan reduces the development of new Digital Ulcers (DUs) in patients with Systemic Sclerosis (SSc). However, data regarding the long-term use of this dual endothelin antagonist receptor in the treatment of DUs is scarce.* ***Methods:*** *We conducted a prospective observational case-control study, between 2014 and 2020 that enrolled 80 SSc patients with at least one active DU at baseline compatible with a vascular etiology or recurrent DUs within the previous 3 months. DUs number, patients' subjective perception of DUs' pain and/or Raynaud's phenomenon, nail fold video-capillaroscopy, and Health Assessment Questionnaire (HAQ) were reassessed every 6 months, for up to 60 months after treatment initiation.* ***Results:*** *At week 24, bosentan therapy was associated with a significant reduction in the number of DUs ($p<0.001$) and significant improvement of quality of life ($p<0.001$), patients' subjective perception of DUs' pain ($p<0.001$) and Raynaud's phenomenon ($p<0.001$) compared to baseline and benefits were maintained up to month 60. Long-term use of bosentan also improved the Microangiopathy Evolution Score (MES) and the difference was statistically significant between bosentan-treated and the control group ($p=0.005$). Accelerated development of new DUs was described 6 months after temporarily stopping bosentan. Following the re-initiation of treatment, the mean number of DUs rapidly decreased.* ***Conclusion:*** *Bosentan has long-term efficacy in DUs prevention in SSc patients, a tolerable safety profile, and might improve microvascular remodeling.*

Keywords: Systemic sclerosis, Digital ulcers, Bosentan, Efficacy, Safety, Long-term

INTRODUCTION

SSc is a rare connective tissue disease in which vascular dysfunction, tissue fibrosis, and immune dysregulation are key events [1]. The near-universal initial clinical manifestation of SSc is the Raynaud phenomenon and associated digital vasculopathy, indicating that endothelial dysfunction is an early, if not primary event in SSc pathogenesis [2,3]. DUs are a serious manifestation of SSc-related digital vasculopathy and are a marker for disease severity [4]. They occur as a result of structural vascular disease as well as vasospasm [5].

Up to 30%-50% of SSc patients will suffer from at least one ischemic digital ulcer; 66% of the patient have recurrent ulcers throughout the natural history of an SSc patient [5,6]. Moreover, patients with SSc and DUs develop internal organ involvement 2 to 3 years earlier than those without DUs [7,8]. Complications of DUs include irreversible tissue

loss, as well as other significant complications such as osteomyelitis, gangrene, and amputation [9]. In addition, the degree of functional impairment is considered as well. Patients with chronic, recurrent DUs are prone to experience the highest disease burden and should be accordingly recognized and intensively managed [10]. These ischemic lesions decrease patients' quality of life because they are painful, disabling, and frequently lead to hospitalization [11].

Bosentan, an oral inhibitor of endothelin-1, is widely used for the prevention of new DUs in SSc [12]. Two large randomized clinical trials showed the efficacy of bosentan in this setting and are the reason for its approval for this indication by regulatory agencies [13,14]. However, there are insufficient data about the long-term use of this drug. Single reports small retrospective studies and two prospective studies, all have reported the efficacy of bosentan for SSc-associated DUs' prevention [15-22]. Although there have been considerable advances in the management of SSc-related vasculopathy, the authors noted that large trials can provide a superior approach by analyzing a more precise estimate of the treatment effect. Moreover, there is a need to consider moving away from short-term trials to longer-term, event-driven trials with composite endpoints that better reflect the ultimate goals of reducing morbidity and mortality rates of SSc-related DUs.

Because of the short-term beneficial results observed with bosentan in patients with SSc and digital ulcers, we aimed to investigate the potential benefit and safety of long-term treatment in a larger group of patients treated with bosentan.

MATERIALS AND METHODS

Study Design

This was a prospective, observational, case-control study conducted in 2 university hospitals in Bucharest from September 2014 to December 2020, which enrolled 80 SSc patients with DUs, who received bosentan therapy. All 80 patients were assigned to receive bosentan according to standard recommendations (62.5 mg twice daily for 4 weeks and 125 mg twice daily till the end of study up to month 60). All patients were evaluated at baseline and 6 months intervals. The control group included 20 patients with SSc-related DUs, who did not receive bosentan treatment. The two groups were well matched concerning demographic features and baseline disease characteristics. The sample size was calculated with an error of 0.05 and a power of 80%.

Selection of Patients

Adults (≥ 18 years of age) were eligible for inclusion if they had a diagnosis of SSc based on ACR/EULAR criteria and at least one active DU compatible with a vascular etiology or recurrent DUs in the last 3 months [23]. They were also required to have a documented history of vasodilators such as calcium antagonists, prostacyclins, or PDE-5 inhibitors providing inadequate control of the DUs. All patients signed informed consent.

Assessing Vascular Damage Progression

Nailfold Videocapillaroscopy (NVC) was performed with CAM1Capiscope with a 200 × magnification lens. All assessments were performed by the same rheumatologist, using qualitative and semi-quantitative scoring systems. All images were scored for each patient at baseline and then every 6 months. Capillaroscopic findings were described following qualitative classification of scleroderma microangiopathy damage described by Cutolo as early, active and late patterns [24]. A semiquantitative rating scale to score the altered microvascular parameters was adopted (score 0-3) [25]. The Microangiopathy Evolution Score (MES) (sum of three scores: loss of capillaries, disorganization of the microvascular array, and capillary ramifications) was also performed [26].

OUTCOME MEASURES

Patients were evaluated on an outpatient basis every 6 months. The primary outcome of the study was the long-term efficacy and safety of bosentan. Secondary outcomes included the evolution of the Raynaud phenomenon, the NVC dynamic changes, and health-related quality of life during bosentan treatment. The severity of RP and DUs were measured using visual analog scales and the impact of DUs on quality of life through the Health Assessment Questionnaire (HAQ). Safety was assessed based on recorded adverse events and laboratory measures (cell blood count, Aspartate Transaminase (AST), and Alanine Transaminase (ALT) according to standard recommendations).

Statistical Analysis

The statistical analysis was performed with SPSS 27.0 Quantitative variables were described with mean ± Standard Deviation (SD) or median and interquartile range for normally distributed or non-normally distributed continuous data, respectively. Qualitative variables were described with frequencies and percentages. Levene's test for equality of variance was performed to compare the paired groups. Treatment efficacy is shown as the mean difference from baseline of all patients remaining at the assessment point in time. The difference between efficacy measures at follow-up visits and baseline was tested with Wilcoxon's signed-rank test. $p<0.05$ was considered statistically significant.

RESULT

The current study enrolled a total of 80 patients (64 females and 16 males), with a mean age of 52.6 (± 12) years, 50% of patients with diffuse cutaneous involvement, most of them with a late NVC scleroderma pattern (54/80) and with antitopoisomerase-1 antibodies (48/80). 55% of the patients had interstitial lung disease, 16% of the patients had pulmonary hypertension and 5% had scleroderma renal crisis. The average disease duration before the bosentan therapy was 7.8 (± 7.9) years.

The median duration of treatment was 25.95 (± 19.4) months. While 16.25% of patients completed 6 months of therapy, most of the patients (18.75%) completed 12 months of treatment, but only 13.75% completed the entire duration of the study of 60 months. 28.75% of the patients had temporarily stopped bosentan due to logistic issues or to increased liver enzymes according to recommendations. The mean duration of the pause was 6.9 (2.2) months; 69.56% of those patients restarted bosentan and were re-evaluated every 6 months.

The number of DUs at baseline was 4.55 (± 2.8). MES was 5.1 (2.19), mean VAS for DUs was 78.6 (46.4), mean VAS for Raynaud was 71.7 (46.32), and mean HAQ at baseline was 1.62 (0.55).

DUs Assessment

Patients receiving bosentan had a clinically significant reduction in the mean number of DUs ($p<0.001$) after the first 6 months of treatment. A plateau was reached after the first 6 months since there were no significant differences between the other 2 consecutive follow-up evaluations (Figure 1). However, the benefits of Bosentan persisted until the end of the study when compared to baseline ($p<0.001$).

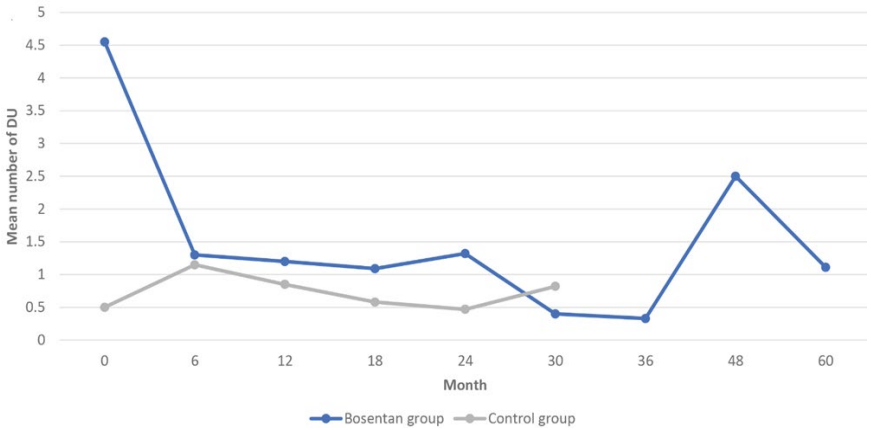

Figure 1 Long term evolution of the mean number of digital ulcers in the bosentan treated group compared with the control group

Digital Ulcers (DU)

VAS for DUs decreased significantly after 6 months ($p<0.001$) and the effect was kept till the end of the study ($p<0.001$) (Table 1). VAS for Raynaud also decreased significantly after the first follow-up ($p<0.001$) (Table 1). As a consequence of the decrease in the total number of DUs and Raynaud's severity, compared to baseline, a significant improvement of life quality was noticed in the first 3 years of treatment ($p<0.001$).

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

Para-meters	Baseline	6 months		12 months		18 months		24 months		30 months		36 months		48 months		60 months	
	Mean ± SD	Mean ± SD	p -value	Mean ± SD	p -value	Mean ± SD	p -value	Mean ± SD	p -value	Mean ± SD	p -value	Mean ± SD	p -value	Mean ± SD	p -value	Mean ± SD	p -value
No DUs	4.55 (± 2.8)	3.4 (± 2.0)	0.00	0.2 (± 1.8)	0.48	0.3 (± 2.2)	0.44	0.1 (± 1.0)	0.60	0.2 (± 1.3)	0.32	-0.1 (± 0.8)	0.50	-0.9 (± 3.5)	0.27	1.2 (± 3.9)	0.33
VAS for Ray-naud	71.7 (± 46.32)	33.7 (± 28.7)	0.00	6.5 (± 18.3)	0.00	4.8 (± 15.3)	0.14	0.4 (± 13.7)	0.91	-0.3 (± 11.7)	0.92	-2.6 (± 11.3)	0.51	-3.8 (± 11.6)	0.14	4.9 (± 15.7)	0.32
VAS for DUs	78.6 (± 46.4)	48.0 (± 28.6)	0.00	2.4 (± 22.3)	0.00	6.7 (± 16.9)	0.00	-4.7 (± 22.5)	0.00	6.1 (± 29.1)	0.00	0.8 (± 23.2)	0.00	-4.6 (± 20.1)	0.00	-0.6 (± 21.8)	0.00
HAQ	1.62 (± 0.55)	0.4 (± 0.5)	0.00	0.0 (± 0.4)	0.80	0.0 (± 0.4)	0.66	0.0 (± 0.4)	0.89	0.0 (± 0.5)	0.99	0.0 (± 0.2)	0.78	0.2 (± 0.7)	0.23	0.0 (± 0.5)	0.94
Mean MES	5.1 (± 2.19)	-0.4 (± 0.8)	0.01	-0.4 (± 0.7)	0.01	-0.4 (± 0.7)	0.05	-0.2 (± 0.4)	0.16	0.2 (± 0.4)	0.16	-0.6 (± 0.7)	0.05	0.5 (± 0.7)	0.50	-2.5 (± 0.7)	0.12

DUs: Digital Ulcers; VAS: Visual Analog Scale; HAQ: Health Assessment Questionnaire; MES: Microangioapthy Evolution Score; SD: Standard Deviation; mean: mean difference from baseline; (*p<0.05)

Microvascular Alterations

The benefits of bosentan on the progression of microangiopathy had not been clearly defined during the first 2 years of treatment, but on the other hand, beyond that period, no significant increase of MES between 2 consecutive evaluations could be noticed until the end of the study (Table 1). Overall, based on the fact that MES values between baseline and month 60 are not statistically different, we could conclude that bosentan slows down the progression of endothelial dysfunction. The difference was statistically significant when compared to the control group, but only for the first 18 months of treatment (p<0.001) (Figure 2).

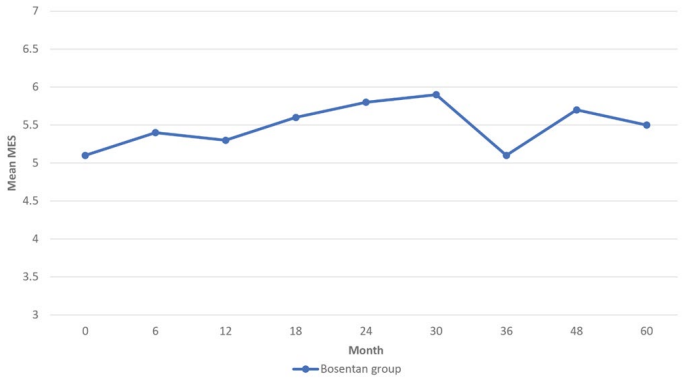

Figure 2 Long term evolution of nailfold capillaroscopic changes evaluated through microangiopathic evolution score

Microangiopathy Evolution Score (MES)

MES values were significantly higher in the bosentan treated group compared to control up to month 18 (p<0.001), but after month 24 mean values are comparable between the 2 groups. This strengthens the idea that long-term treatment with bosentan could slow down the progression of microangiopathy.

The Effect of Temporarily Stopping the Bosentan Treatment

23 patients (28.75%) discontinued bosentan therapy due to logistic reasons. The median duration of discontinuation was 6.9 months (± 28.75). A significant increase of new DUs was described 6 months after (p=0.025). Following reinitiation of bosentan, the mean number of DUs has rapidly decreased (p=0.008). There was no significant difference regarding the number of new DUs between patients who temporarily discontinued bosentan for 6 or 12 months. Subgroup analysis revealed the same pattern.

Safety and Tolerability

Bosentan was stopped due to lack of efficacy in 3 (3.75%) cases (significant increase of new DUs number at follow-up requiring digital amputation).

The most frequent adverse events in the bosentan-treated group are shown in Figure 3. Adverse events led to premature discontinuation of the study medication in 10 (12.5%) patients. In 13.75% of the patients, the bosentan dose was reduced and in 12.5% of the cases treatment was temporarily stopped and then restarted.

The most frequent adverse events leading to withdrawal were abnormal liver tests (15% of the patients) but in only 5% of the cases, it was permanently interrupted (increased hepatic aminotransferase levels more than eight times the upper limit of normal). In 2 cases treatment was withdrawn because of severe thrombocytopenia, in the other 2 because of dyspnea worsening and low blood pressure.

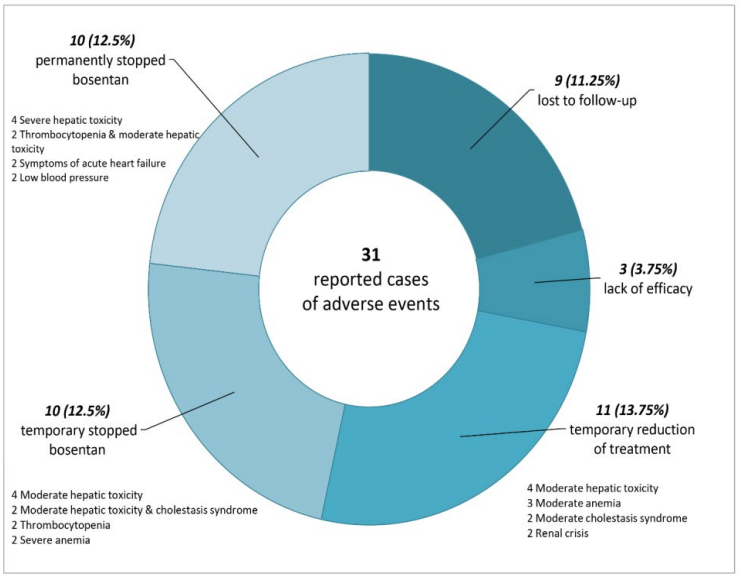

Figure 3 Long term safety and rate of retention of bosentan in the study group

13.75% of patients required a reduction of the dose because of increased hepatic aminotransferase levels less than eight times the upper limit of normal (4 cases), cholestasis (2 cases), renal crisis (2 cases), anemia (3 cases). In 12.5% of the cases treatment was temporarily stopped (elevated liver enzymes 5%, cholestasis-2.5%, thrombocytopenia 2.5%, anemia-2.5%).

9 patients were lost to follow-up. 5% of subjects died within the first year after initiating bosentan and 5% during the second year after treatment onset. None of the reported deaths have been considered related to study medication, but rather to the progression of the treated concomitant diseases.

DISCUSSION

Ulcers and healed ulcers represent a disabling problem for patients with SSc. Ulcers frequently persist and often recur despite the widespread use of conventional therapy. Two large randomized double-blind, placebo-controlled trials that have been extensively reviewed showed the efficacy of bosentan in decreasing the overall incidence of new digital ulcerations in SSc patients [13,14,23,27]. Bosentan treatment reduced the occurrence of new DUs in patients with SSc between 30% and 48% compared to placebo but did not affect DU healing. Nonetheless, RAPIDS-1 and RAPIDS-2 must be considered short-term studies because the study duration was no longer than 24 weeks.

Evidence for the long-term use of bosentan for DUs prevention is available from three case-series reports [21,22,28]. Tzifetaki, et al., outlined their experiences gained from the use of bosentan in 26 patients for up to three years. They revealed that the mean number of digital ulcers showed a continuous decline over the entire study, from nearly six at baseline to less than four after three years [21]. In another study report, a Spanish team describes their experiences of

using bosentan in 15 patients with a median follow-up of 25 months. After one year a significant improvement was observed in the mean number of ulcers, the severity of Raynaud's episodes, and some patient-reported assessments. These effects were maintained at 18 months although no changes were found in qualitative assessments of functional performance or disease impact. After two years, further improvements were noted in other parameters although there was a worsening in hand functionality [22]. A report of 15 patients treated with bosentan for pulmonary arterial hypertension included eight patients with DUs. In these patients, healing was evident at a median of 12 weeks after treatment (range six to 14) and no one developed new digital ulcers throughout the entire duration of treatment (12 months) [19]. Quality of life data from another subset of patients with DUs and receiving treatment with bosentan for pulmonary arterial hypertension has also been reported. A significant improvement of the short form 36 score and visual analog scale score for pain, vascular disease, ulceration, and overall disease severity were demonstrated at week 48 [29].

The present study is a prospective controlled one with a long-term follow-up that has evaluated the total number of ulcers, but also the patients' perception of DUs and Raynaud and their impact on health-related quality of life. We focused on long-term follow-up, analyzing the total number of ulcers, new and healed ulcers as different stages of the same manifestation. Results of this study showed that bosentan is effective in SSc-associated DUs long-term prevention. Our research has proven that bosentan treatment leads to a significant decrease in the number of ulcers at month 6, with efficient prevention up to month 60. The patient's perception of Raynaud's severity and DUs also significantly improved at month 6 and was maintained till the end of the study. Significant improvement of HAQ scores compared to baseline is noticed only in the first 3 years. The most reasonable explanation is the fact that the progression of other organ involvement influences the quality of life.

In RAPIDs 2 study the reduction of new DUs with bosentan did not translate into measurable decreases in pain or disability compared with placebo. Perhaps, combining the severity of both ulcers and healed ulcers in our study may have been definitive in finding improvement in VAS and HAQ. Patients do not differentiate easily the moment when a lesion is an ulcer and when it is healed, and VAS is based on patient judgment.

Previous studies have evaluated the role of disease evolution and various treatments on microcirculation in SS using semi-quantitative scoring systems for video capillaroscopy [24-26,30]. Specifically, MES is a reliable tool to assess the progression of vascular damage in patients with SSc [26]. A study of bosentan in patients with SSc and pulmonary arterial hypertension indicated that bosentan in SSc may help the de-remodeling process of the capillary microcirculation [30]. After 12 months of bosentan, the NVC pattern changed in seven out of nine patients from "late" into an "active" SSc pattern. The disappearance of avascular areas and capillary hemorrhages were the most striking results. The authors concluded that bosentan may improve the NVC pattern in SSc as the presence of new capillaries suggests that it may favor angiogenesis. Guiducci, et al., suggest that bosentan may improve and stabilize the microvasculature in long-term treatment, modulating the structural modifications detected by NVC [30].

Our study confirms these data. During the first two years, MES seems to significantly increase suggesting the progression of vascular damage. After that, a plateau is reached with no significant difference between baseline and month 60, possibly related to increased density of capillaries due to angiogenesis. Further studies on a larger number of patients are warranted to confirm these data and to get a correct profile of the drug capacity to restore the capillary network.

Safety data from the longer-term studies are poorly described. In the larger study with 26 patients, three patients discontinued treatment; two due to raised liver enzymes and one due to reduced blood cell count [21]. In the Spanish report with 15 patients treatment was discontinued in one due to toxic jaundice which later resolved. In two other cases, treatment was temporarily discontinued due to hepatic complications and three patients showed mild transitory raised liver enzymes. Other notable effects include two reports of anemia and six reports of non-anemic decreases in hemoglobin [22].

We found many adverse events but no new unidentified adverse reactions. Bosentan treatment resulted in an increase in aminotransferase in 17% of the patients and 14% permanently discontinued bosentan as a consequence of more than 8 times increase. The incidence of thrombocytopenia is also higher than previously reported, leading to treatment cessation in 6 (5.2%) of the cases. The increased incidence of elevated liver enzymes and thrombocytopenia in this and other studies reinforces the need for continuous monitoring of liver function and cell blood count with this treatment.

The major limitations of the present study are the small sample size and the fact that a significant proportion (11%) of the patients was lost to follow-up. In addition, the study was not designed to assess the effect of bosentan treatment on the dimensions of DUs and we did not assess new DUs but the total number of DUs.

CONCLUSION

The present data establish the long-term efficacy of bosentan in decreasing the overall number of DUs (present at baseline and/or new) in patients with SSc and improving patients' evaluation and quality of life. The beneficial effect of bosentan persisted throughout the study but was most evident in the first 6 months of treatment. Statistical analysis also showed a trend in slowing the microangiopathy evolution score from baseline to end of therapy. Further studies assessing the clinical usefulness of our data are needed to validate their application in routine use, preventive or early therapeutic strategies.

DECLARATIONS

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contributions

Laura Groseanu, Violeta Bojinca, Andra Balanescu, Ruxandra Ionescu contributed to the design of work. Laura Groseanu, Cristina Nita, Oana Naiman, Violeta Bojinca were responsible for literature search and manuscript preparation. Laura Groseanu performed a nailfold capillaroscopy for all the patients. Laura Groseanu, Cristina Nita, Violeta Bojinca, Andra Balanescu, Denisa Predeteanu, Andreea Borangiu, Florian Berghea, Ioana Saulescu, Diana Mazilu, Sanziana Daia-Iliescu, Mihai Abobului, Daniela Opris-Belinski, Cosmin Constantinescu contributed to data collection, literature search, manuscript preparation, and critical revision of manuscript for important intellectual content. Cristina Nita and Violeta Bojinca confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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