Bosentan in the treatment of refractory extremities ulcers in systemic sclerosis

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ABSTRACT

Introduction: Vasculopathy is a hallmark of systemic sclerosis (SSc) and may lead to complications such as ischemic ulcers, necrosis or amputation of fingers or lower limbs. Bosentan is a dual endothelin receptor antagonist currently used for prevention of digital ulcers in SSc. **Objective:** To evaluate the efficacy of bosentan in the treatment of recurrent and refractory extremity ulcers in patients with SSc. **Patients and methods:** An open and observational study was performed with three patients from the Rheumatology Division of UNIFESP aged 31, 58 and 61 years with diagnosis of SSc. All patients presented one or more active extremity ulcer refractory to conventional treatment. The first one (P1) presented one digital ulcer; P2 presented three ulcers on the right lower limb; and P3 presented an ulcer on the right digit, leg and heel, and on left maleolar region. Bosentan was prescribed in a dose regimen of 62.5 mg twice a day for 4 weeks, followed by 125 mg twice a day for additional 4 or 8 weeks. All patients were evaluated regarding the number and diameter of the ulcers in weeks 0, 4, and 8, and one of them in week 12 as well. **Results:** After the treatment with bosentan all patients presented complete resolution or reduction in the diameter of the ulcers. None of the patients presented a new ulcer. **Conclusion:** Bosentan was an effective treatment in refractory extremities ulcers and in the prevention of new ulcers in three SSc patients suggesting that this medication could be an option for patients with severe vascular involvement.

Keywords: systemic sclerosis, Raynaud´s phenomenon, ischemic ulcers, endothelin, bosentan.

INTRODUCTION

Systemic sclerosis (SSc) is a rheumatic autoimmune disease of unknown etiology, clinically characterized by a vasculopathy of the small and microcirculation as well as excessive deposition of collagen in the skin and internal organs affecting particularly the gastrointestinal tract, lungs, heart, and kidneys.[1] Vascular involvement is an early manifestation and represents a central event in the pathogenesis of the disease.[2] Functional abnormalities and structural alterations of the blood vessels, including alterations in the control of vascular tonus, endothelial lesion and disfunction, intimal proliferation of small arteries and arterioles, and diminution of the vessel's lumen, can be clinically expressed in many forms such as Raynaud's phenomenon, digital ischemia, sclerodermic renal crisis and pulmonary hypertension.[2-4]

Raynaud's phenomenon is the most frequent manifestation of SSc. It is characterized by transitory episodes of limb vasoconstriction, generally after contact with the cold or emotional stress, which triggers typical alterations in the colour of hands and/or feet. Due to the vascular abnormalities present in SSc, Raynaud's phenomenon episodes are usually more severe in these individuals and can lead to important complications like ischemic ulcers of the digits and lower limbs. Most times ulcers are recurring, extremely painful and disabling, and can evolve with secondary infection, gangrene and even amputation of extremities.[5] Many treatments are available for the prevention or healing of ischemic ulcers secondary to SSc, but most of them have little effectiveness.[6-7] The treatment of ischemic ulcers in patients with SSc involves nonmedicamentous measures, such as bandages and change

Received on 10/14/2008. Approved on 02/28/2009. We declare no conflict of interest.
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of habits (quit smoking, avoid exposure to the cold etc.), treatment of local infections and use of analgesics for pain control.[8] Vasoactive drugs such as calcium channel blockers (nifedipin), 5-phosphodiesterase inhibitors (sildenafil), and prostacyclin analogs intravenously (epoprostenol, alprostadil, and iloprost) have shown to be effective in some patients.[8-10] Prostacyclin analogs seem to be the most effective medicine, but they are still not much available and have the disadvantage of intravenous administration and necessity of hospitalization. Prostacyclin analogs with oral preparation did not show to be effective for treatment of Raynaud's phenomenon.[4,11]

In spite of being multifactorial, endothelin-1 (ET_1) has been more recently considered as an important factor in SSc's pathogenesis.[12] ET_1 is a potent vasoconstrictor produced mainly by endothelial cells, whose serum concentrations are increased in patients with SSc.[12-14] It is activated when connected to its receptors (ET_A and ET_B), expressed mainly by endothelial cells, smooth muscular cells and fibroblasts. Besides having a potent vasoconstrictive action, ET_1 also stimulates the proliferation of fibroblasts and smooth muscular cells.[14] Bosentan is an oral dual endothelin receptor antagonist used in the treatment of idiopathic pulmonary hypertension or secondary to autoimmune rheumatic diseases, including SSc.[15] More recent studies showed that the drug can also be beneficial for treatment of patients with ischemic ulcers secondary to SSc.[5,16-18] Two multicentric, placebo-controlled, double-blind studies (RAPIDS-1 and RAPIDS-2) were performed with a great number of patients to evaluate the effectiveness of bosentan in the treatment and prevention of acute ischemic ulcers in patients with SSc.[5,16] The RAPIDS-1 study showed that bosentan was effective in the prevention of new digital ulcers (mean 48% less than the placebo group). It was not demonstrated that bosentan reduced the period of healing of active ulcers (secondary endpoint). RAPIDS-2 was a study involving a larger number of patients that confirmed the findings of RAPIDS-1 regarding the prevention of new ulcers.

Due to the lack of studies about this therapeutic modality in our environment, we performed an open, observational study, for the evaluation of bosentan's effectiveness in a small group of SSc patients with recurring ulcers that are refractory to conventional treatments.

PATIENTS AND METHODS

Three patients from the Systemic Sclerosis Division of Rheumatology at Hospital São Paulo (UNIFESP) diagnosed with SSc according to the American College of Rheumatology (ACR)[19] criteria were included. All patients agreed to participate in the study and signed the Informed Consent Form, previously approved by the Ethics Committee of UNIFESP. They all presented complaints of important Raynaud's phenomenon, recurring ulcers and one or more active limb ulcers, which had not responded to the treatment with conventional drugs.

The clinical and demographic characteristics of the three patients are described in Table 1. Patient P1 presented a digital ulcer in the right hand (A); patient P2 presented three ulcers in the right lower limb (A, B, C); patient P3 presented ulcers in right digit (A), leg (B), and heel (C), and left malleolo (D) (Table 2). Patient P1, age 31, presented the diffuse cutaneous form of SSc overlapping with systemic lupus erythematosus for

Table 1
Clinical and demographic characteristics of the patients treated with bosentan

Characteristics	Patient 1	Patient 2	Patient 3
Age (years)	31	58	61
Gender	F	F	F
Time of diagnosis	9 years	12 years	6 years
Disease form (limited/diffuse)	Diffuse	Diffuse	Limited
Number of ulcers active at the beginning of the treatment	1	3	4
Antinuclear antibodies research (ANA)	Nuclear dense speckled 1/320	Nuclear fine speckled 1/320	Nuclear centromeric 1/1280
Anti-Scl 70	Negative	Positive	Negative
Periungueal capillaroscopy	Pattern SD	Pattern SD	Pattern SD
Cutaneous score of Rodnan	19	33	17
Other medication used for RP during treatment	Nifedipin Captopril	Nifedipin and Losartan	AAS

9 years, and also an extremely painful ulcer for approximately 8 weeks in the third digit of the right hand. The patient had already suffered previous amputation of the fourth digit and important loss of substance in the second right digit by ulcer. She was using: nifedipin 20 mg, 8/8h, and captopril 12,5 mg, 12/12h. Patient P2, age 58, had the diffuse cutaneous form of SSc for 12 years and had presented three ulcers in her lower right limb (pretibial and malleolar regions) for approximately 1 year. During this period she used: nifedipin 20 mg, 8/8h, losartan 100 mg/day, diltiazen 30 mg, 8/8h, pentoxifylline 400 mg, 12/12h, tramadol 50 mg, 8/8 h, intravenous xylocaine, besides local care (bandages in ulcers clinic), without any results. She kept using nifedipin 20 mg, 8/8h, in the 0 week. Patient P3, age 61, with the limited form of SSc for 6 years, presented an ulcer in the lateral region of the right leg and in the left malleolar region for approximately 1 year and an ulcer in the right second digit and heel for approximately 6 weeks. She had used: captopril 50 mg, 8/8h, nifedipin 20 mg, 6/6h, tramadol 50 mg, 8/8h, and AAS 100 mg/d, besides courses of antibiotics for the associated infection, also without any results. She did not tolerate the use of captopril or nifedipin due to hypotension.

TREATMENT AND EVALUATION PROTOCOL

Bosentan (kindly supplied by Actelion Pharmaceuticals do Brasil) was administered in the dosage of 62,5 mg VO two times/day for 4 weeks, followed by 125 mg two times/day for more 4 or 8 weeks. Other medications used by the patients were kept.

Patients were evaluated by the same researcher as to the number of ulcers and their diameter (in millimeters), in the 0, 4, and 8 weeks, and patient P3, who presented a more severe onset (four ulcers), was also evaluated after 12 weeks. In each evaluation, the patients were also questioned about the severity of Raynaud's phenomenon in the last week with visual analog scale of severity (grading from 0 to 10, where 0 means absence of Raynaud's phenomenon episodes, and 10 means the worst episodes experienced by the patient), and regarding the pain intensity of Raynaud's phenomenon with a visual analog pain scale (grading from 0 to 10, where 0 means no pain, and 10 means extreme pain).

During the study, transaminases was verified, before, and with 4 and 8 weeks of treatment, for monitoring the appearance of medicamentous hepatitis.

RESULTS

After the treatment with bosentan all patients presented healing or reduction in the diameter of the ulcers (Table 2). Patients P1 and P2 presented complete cicatrization of the ulcers, and patient P3 presented cicatrization of the two smaller ulcers and important reduction in the diameter of the larger ulcers (Figure 1). None of the patients presented new ulcers, or alteration in the transaminases levels before and after the treatment. After eight weeks of treatment, a heterogeneous behavior was observed regarding the visual analog scales of severity of Raynaud's phenomenon and pain intensity (Figure 2). Patient P3 presented an important improvement in the intensity of the pain and severity of Raynaud's phenomenon followed by a new worsening, due to a cyanosis in the second right pododactile, without ulceration.

DISCUSSION

Ischemic ulcers represent a severe and extremely disabling manifestation which affects up to 50% of the patients with SSc.[20] In the present study, we observed an improvement and fast cicatrization of ischemic ulcers in the three patients with SSc who used bosentan for 8 or 12 weeks. We highlight that all

Table 2
Evolution of the diameter (millimeters) of ulcers after treatment with bosentan in patients with systemic sclerosis

Time	Ulcers							
	P1	P2			P3			
	A	A	B	C	A	B	C	D
Day 0	9 x 7	15 x 8	10 x 5	21 x 14	9 x 4	45 x 30	15 x 15	10 x 10
Week 4	8 x 8	*	*	15 x 12	*	40 x 28	15 x 21	15 x 10
Week 8	*	*	*	*	*	40 x 25	17 x 20	12 x 12
Week 12	–	–	–	–	*	20 x 17	3 x 2	*

* Ulcers which healed entirely.

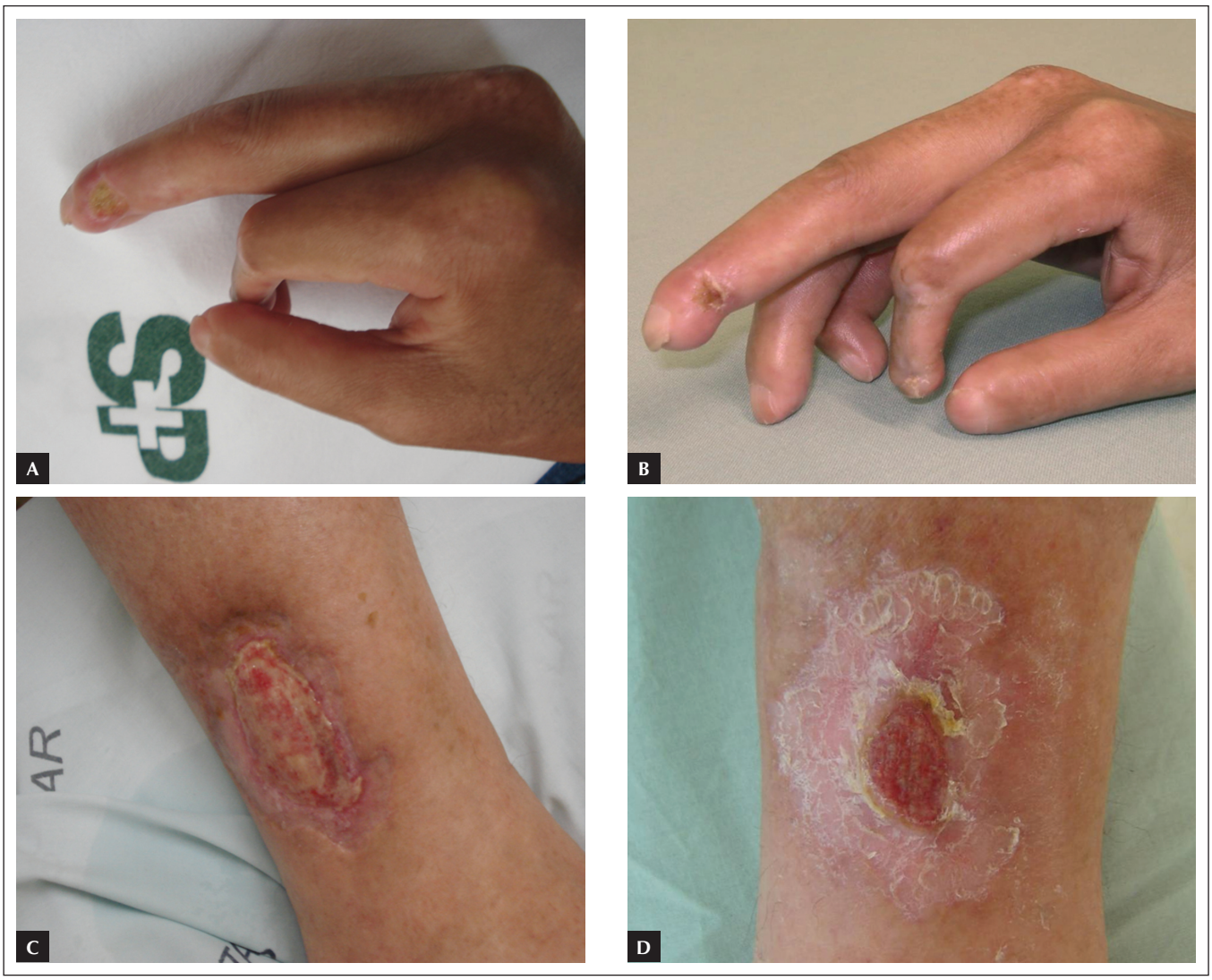

Figure 1. Digital ulcer of the right hand in patient P1 before treatment with bosentan (A) and after 4 weeks (B). Ulcer in right lower limb of patient P3 before treatment with bosentan (C) and after 12 weeks (D).

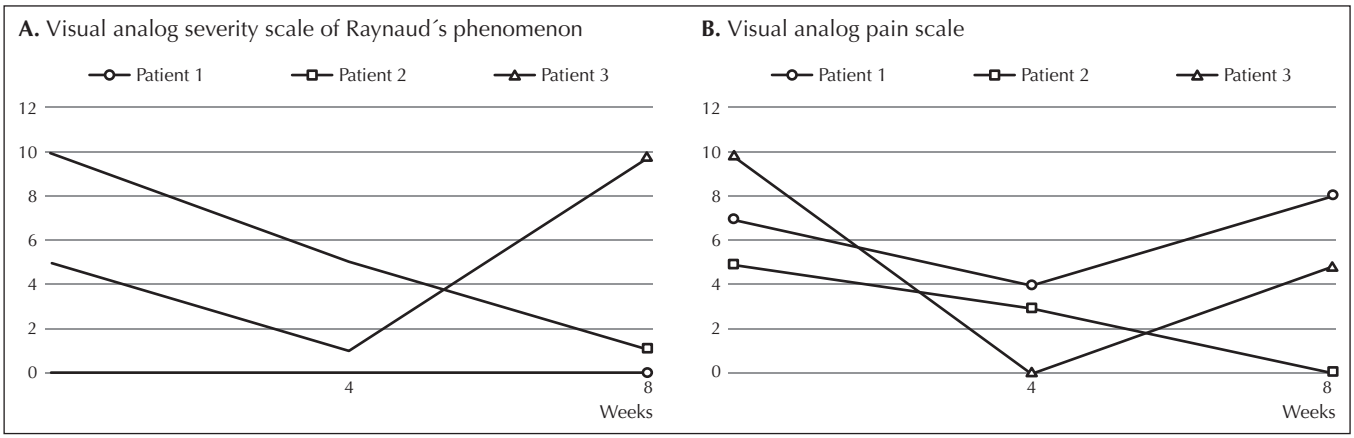

Figure 2. Evolution of the visual analog severity scale (A) of Raynaud's phenomenon and visual analog pain scale (B) during the follow-up of the three patients.

patients presented important peripheral vasculopathy – patient P1 presented a previous amputation of one digit, and patients P2 and P3 presented ulcers in lower limbs for approximately one year, all nonresponsive to treatment with calcium channel blockers, normally used as the first drug of choice in our service. Due to its ischemic characteristics, the ulcers secondary to SSc are usually extremely painful. We observed a significant improvement in the visual analog pain scale in two of the three patients evaluated.

Based on the results of the RAPIDS-1 and RAPIDS-2 studies, bosentan is a therapy approved in Europe for the reduction of the number of new ulcers in patients with SSc. Besides that, Peña-Lefebvre *et al.*[18] recently published a prospective study that evaluated the effectiveness and tolerability of bosentan in patients with SSc in the long term. There was a significant decrease in the number of new ulcers and a tendency to a decrease in the number of healed ulcers. Nevertheless, many questions regarding the role of bosentan in the treatment of ischemic ulcers have yet to be clarified, like which patients should be treated and at which moment. As the RAPIDS-1 and RAPIDS-2 studies showed that the treatment with bosentan is more preventive than curative, a questioning that emerges is if the drug should be used in patients with vasculopathy before becoming refractory, which would aim at decreasing severe complications such as gangrene and limb amputations. We should also remember that the cost of the medicine is high and it should be suggested only in selected cases.

Besides the vascular component, other factors associated with the presence of ulcers, mainly digital ulcers, are dermis fibrosis, dry and atrophic skin, micro traumas, and articular contractures.[6] These factors are implied in the poor response that some ulcers present facing therapies with vasodilators[8] and were also implied by Korn *et al*. as one of the possible factors which justify the negative results obtained in the cicatrization of digital ulcers in the RAPIDS-1 study.[5] The fact that the two patients with ulcers in the lower limbs presented a relatively fast cicatrization makes us believe that such ulcers present a greater predominance of the vascular component or suffer a minor influence of factors such as local traumas, presenting a more satisfactory response to a potent vasodilator like bosentan. Another factor that may have influenced the positive response obtained in our study is that the ulcers were clearly active at the beginning of the study, and healed or partially healed ulcers were not included in the evaluation. Studies with a larger number of patients presenting this type of ulcers are necessary to prove such hypothesis.

This study presents some limitations such as a small number of evaluated patients and the fact that it is a noncontrolled study of short duration and should be seen more as descriptive study. Nevertheless, SSc is a rare and extremely disabling disease, and the present observation of a clear reduction in the ulcer diameter or cicatrization ulcers in evaluated patients shows to be relevant.

In conclusion, the treatment with the endothelin receptor antagonist bosentan proved to be effective in the prevention of new ulcers in a short term and in the cicatrization of limb ulcers in three patients with SSc from our service. So, it is suggested that the drug could be a therapeutical option in patients with severe vasculopathy.

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