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BRIEF REPORT

Bosentan fosters microvascular de-remodelling in systemic sclerosis

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Abstract Bosentan, a dual endothelin receptor antagonist, may reduce blood pressure by blocking the vasoconstrictor effect of endothelin-1. In systemic sclerosis (SSc) nailfold videocapillaroscopy (NVC); allows diagnostic and follow-up of microvascular damage. Distinct NVC patterns have been identified for the evaluation of severity of SSc microvascular damage. The objective of this study is to evaluate the modification of the microvasculature under Bosentan therapy in SSc patients with pulmonary arterial hypertension (PAH). Nine patients with PAH related to SSc in New York Heart Association classes III–IV were treated with Bosentan 125 mg twice a day. NVC optical probe videocapillaroscopy equipped with 100× and 200× contact lenses and connected to image analyse software was performed before and after 12 months of Bosentan therapy to evaluate the modification of microvasculature. Nine PAH SSc patients treated with Iloprost were used as controls. Before Bosentan therapy, seven patients showed at NVC severe loss of capillaries with large avascular areas and vascular architectural disorganisation which are typically "late" SSc pattern. After 12 months of Bosentan, NVC pattern changed in seven patients from "late" into "active" SSc pattern. The disappearance of avascular areas and capillary haemorrhages was the most striking result. Two patients had an "active" SSc pattern, not modified by Bosentan treatment. These data show that Bosentan may improve NVC pattern in SSC and the presence of new capillaries suggests that it may favour angiogenesis. Bosentan may improve and stabilise the microvasculature in long-term treatment modulating the structural modifications detected by NVC.

Keywords Bosentan · Microvascular abnormalities · Nailfold videocapillaroscopy · Pulmonary arterial hypertension · Systemic sclerosis

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Introduction

Systemic sclerosis (SSc) is a multiorgan disease characterised by injury to vascular wall and extensive damage of the microvessels [1] with formation of megacapillaries and avascular areas. These modifications lead to a reduced blood flow to the tissue ischemia and eventually to digital ulcers [2]. Usually, microvascular changes are investigated with nailfold videocapillaroscopy (NVC) [2], which evaluates the severity of the SSc microvascular nailbed [3].

Overexpression of endothelin-1 (ET-1) is involved in the fibrotic and vasculopathic aspects of SSc as it has been shown to stimulate fibroblast and smooth muscle proliferation, bringing to pulmonary arterial hypertension and to vasculopathic manifestations of the disease, such as digital ulcers (DUs) [4]. Bosentan, a dual endothelin receptor antagonist, blocks ET-1 action and decreases permeability and remodelling of the pulmonary vessels, thus controlling pulmonary arterial hypertension (PAH) [5] and preventing new DUs formation [6]. The aim of our work was to evaluate prospectively, in SSc patients treated for PAH with Bosentan, the modifications of the nailfold microvasculature.

Materials and methods

Patients

Nine patients with diffuse SSc [7] and PAH (seven women and two men; mean age, 58.9±28.4; mean mRSS=18±4; medium number of DUs=5±2; medium value of pulmonary arterial pressure by right heart catheterization=33±2 mmHg) were treated for 12 months with Bosentan 125 mg twice a day (evaluated with NVC before and after 12 months of therapy). Nine SSc PAH patients (eight women and one man; mean age, 56.7±16.2; mean mRSS=20±3; medium number of DUs=5±3; medium value of pulmonary arterial pressure by right heart catheterization=30±3 mmHg) were treated with Iloprost infusion (mean dosage of 0.94±0.26 ng/Kg/min for 6 h/day once a month) and were used as control group [8].

Videocapillaroscopy

At baseline and after 12 months, NVC was performed as previously described [9] in order to evaluate the evolution of SSc NVC patterns. An optical probe videocapillaroscopy equipped with 100× and 200× contact lenses and connected to image analyse software (Videocap; DS MediGroup, Milan, Italy) was employed. The following parameters were considered [9]: presence of enlarged and giant capillaries, haemorrhages, loss of capillaries, disorganisation of the vascular array and ramified/bushy capillaries.

NVC pattern was classified in the "early", "active" and "late" NVC pattern [9]. A semiquantitative rating scale to score these changes was adopted, according to previous studies (0=no changes, 1=fewer than four alterations, 2=four to six alterations, 3=more than six alterations per millimetre) [9]. For each subject, the mean score for each of these parameters was obtained from the analysis of the second, third, fourth and fifth fingers of both hands, using the scoring system described [9].

Statistics

Data were analysed using SPSS 10.0 for Windows. Descriptive statistics were expressed as medium±1 standard deviation. Normal distribution of each examined parameter was verified by Kolmogorov–Smirnoff test. The statistical significance of the differences between means of two groups was evaluated by Student's *t* test for unpaired data. A *p* level of 0.05 or less was considered statistically significant.

Results

All patients were affected by PAH (NHYA III or IV class, medium value of pulmonary arterial pressure by right heart catheterization=32±2 mmHg).

In the Bosentan group, at baseline, seven patients had a "late" NVC pattern (few giant capillaries, severe loss of capillaries with large avascular areas, ramified capillaries and vascular architectural disorganisation) and two patients had an "active" SSc pattern. After 12 months, in seven patients, the "late" NVC pattern was reverted into an "active" pattern: frequent giant capillaries (more than 6 mm), haemorrhages, absence of avascular areas and disorganisations of the normal capillary array with ramified/bushy capillaries were clearly evident suggesting angiogenetic phenomena. The disappearance of avascular areas and the increase of megacapillaries and capillary haemorrhages was the most striking result. The pattern of the other two patients remained unchanged in the "active" pattern.

In the Iloprost group, three patients showed a "late" SSc pattern and six patients an "active" SSc pattern at baseline; no significant modifications of NVC parameters was observed after 12 months, as the NVC patterns were unchanged.

A semiquantitative analysis showed that enlarged and giant capillaries and haemorrhages were significantly increased at 12 months in patients treated with Bosentan versus Iloprost group ($p<0.00001$ for enlarged capillaries and $p<0.0001$ for haemorrhages). The statistical analysis on follow up parameters showed a significant reduction of loss

Table 1 Semiquantitative analysis of NVC at baseline and after 1 year of Bosentan therapy

Parameters	Bosentan			Iloprost		
	Baseline (mean±SD)	1 Year (mean±SD)	*p*	Baseline (mean±SD)	1 Year (mean±SD)	*p*
Enlarged capillaries	2.04±0.31	2.75±0.097	<0.00001	1.77±0.42	1.56±0.66	0.43
Megacapillaries	1.07±0.57	2.09±0.088	<0.0001	0.93±0.91	0.81±0.81	0.77
Haemorrages	0.7±0.46	1.53±0.1	<0.0001	0.38±0.51	0.27±0.46	0.64
Capillary loss	2.29±0.42	1.62±0.12	<0.001	1.71±0.48	1.87±0.47	0.48
Ramified capillaries	1.83±0.65	0.59±0.093	<0.0001	1.37±0.98	1.59±0.86	0.62
Capillary disorganisation	2.3±0.52	1.3±0.16	<0.0001	1.71±0.51	1.83±0.45	0.60

of capillaries ($p<0.001$), ramified capillaries ($p<0.0001$) and capillary disorganisation in patients treated with Bosentan versus Iloprost group ($p<0.0001$; Table 1). During the treatment, none of the patients developed new ulcers in the Bosentan group, while in the Iloprost group 3 patients developed a total of four ulcers.

Discussion

Our data suggest that Bosentan improves microcirculation with a process of microvascular de-remodelling already observed in the nailfold capillaries after the treatment with cyclophosphamide [10, 11]. The treatment with bosentan led to a shift from a late to an active pattern characterised by the disappearance of avascular areas. This event significantly improved the microcirculatory network and stabilised the microvasculature up to 1 year of treatment. These results suggest that Bosentan may modulate the structural microvascular modifications detected with NVC.

In our patients, after Bosentan treatment, new capillaries and microhaemorrhages were found and occurrence of further ischemic ulcers was not seen. This is in agreement with the evidence that Bosentan prevents the formation of new ulcers, in particular in those patients with severe digital ulcerations [6]. The limit of the study was that patients were followed up 12 months only and we do not know if the drug might have improved further the NVC pattern in a longer follow up.

In conclusion, our results even if obtained on a limited number of patients, indicate that Bosentan in SSc may help the de-remodelling process of the capillary microcirculation. Further studies on larger number of patients, in particular without PAH, are warranted to confirm our data and to get a correct profile of the drug capacity to restore the capillary network.

Disclosures None

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