

N-terminal pro-BNP in sclerodermic patients on bosentan therapy for PAH

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Abstract Systemic sclerosis (SSc) is characterized by vascular dysfunction that may lead to pulmonary artery hypertension (PAH). The N-terminal pro-B type natriuretic peptide (NT-proBNP), a marker of cardiac failure, is a diagnostic marker of early PAH in patients with SSc without heart failure. Our aim was to determine whether NT-proBNP levels may be a useful tool to evaluate the response to bosentan therapy in patients with PAH secondary to SSc. Ten patients with symptomatic, severe PAH secondary to SSc, received bosentan, 62.5 mg twice a day for 4 weeks followed by 125 mg twice a day for 7 months. Ten patients with SSc without PAH served as controls for basal level of NT-proBNP. Blood samples were obtained before the beginning of the therapy and after 3 and 7 months of treatment. SSc patients with PAH had significantly higher serum levels of NT-proBNP than those without PAH, at baseline. After 3 and 7 months of therapy,

NT-proBNP concentration showed a progressive decrease, nearly approaching statistical difference at 7 months when compared to baseline levels ($P = 0.953$ and $P = 0.600$). Our results show that serum NT-proBNP levels may be a useful marker for the response to bosentan therapy in patients with PAH secondary to SSc.

Keywords NT-proBNP · PAH · Systemic sclerosis · Bosentan

Introduction

Systemic sclerosis (SSc) is a connective tissue disease characterized by vascular damage, immunological abnormalities and fibrosis of the skin and internal organs [1]. Vascular involvement, with generalized disturbance of microcirculation, may lead to pulmonary artery hypertension (PAH) [2]. PAH is a major complication of both limited and diffuse SSc. Established, severe PAH is difficult to treat and has a poor prognosis [2]. The N-terminal pro-B type natriuretic peptide (NT-proBNP) is a potential marker of cardiac failure [3]. Also in patients with primary pulmonary hypertension (PPH), NT-proBNP levels are increased and correlate with functional class [4]. In patients with SSc and PAH without clinical heart failure, NT-proBNP is a diagnostic marker of early PAH [5] and its levels are directly related to the severity of PAH and are highly predictive of survival [6]. Bosentan is an oral endothelin receptor antagonist used in the therapy of primary and secondary PAH [7]. The aim of the present study was to determine whether the measurement of NT-proBNP may be a useful tool for the evaluation of the response to bosentan treatment in patients with PAH secondary to SSc.

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Materials and methods

Patients

We enrolled 10 patients (9 females and 1 male, mean age 55 year, range 40–70) who had symptomatic, severe PAH associated with SSc (NYHA functional class III or IV) despite treatments including calcium channel blockers, anticoagulants, diuretics, cardiac glycosides or supplemental oxygen. Three patients were on stable oxygen supplementation started more than three months before the study. None of the patients was on sildenafil. These patients received 62.5 mg of bosentan tablets twice a day for 4 weeks, followed by 125 mg twice a day for 7 months. The inclusion criteria were a baseline 6 min walking test between 150 and 450 mt, a resting mean pulmonary artery pressure greater than 30 mmHg. As controls we enrolled 10 age, sex, disease duration and subtype matched SSc patients (9 females and 1 male, mean age 52 year, range 35–68) without PAH. All the participants to the study were from Northern Italy. Patients with heart failure and renal involvement were excluded from the study (patients characteristics are summarized in Table 1).

We collected blood samples before the beginning of the therapy with bosentan and after 3 and 7 months of continuous treatment. Blood was drawn from all the subjects after obtaining written or oral informed consent.

Assay of proBNP and cardiac troponin T

Serum NT-proBNP concentration was determined on Elecsys 2010 instrument (Roche Diagnostics, Basel, Switzerland). A value lower than 14.8 pmol/L was considered normal.

In all patients blood sampling for cardiac troponin T (cTnT) was performed with highly sensitive third generation quantitative test (electrochemiluminescence method ECLIA Roche Diagnostics) to exclude patients with false positive value of NT-pro-BNP due to heart failure or acute coronary artery disease [8].

Statistics

Statistical analysis was performed using StartDirect Statistical software (Starts Direct Inc, UK). Since NT-proBNP concentration presented a not-normal distribution, data were expressed as median values with minimum–maximum range and non-parametric tests were used for the analysis. More precisely the Mann–Whitney test was used to compare NT-proBNP concentrations at baseline between sclerodermic patients with and without PAH, whereas Wilcoxon signed ranks test was used to compare the concentrations after 3 and 7 months of therapy. *P* values < 0.05 were considered statistically significant.

Results

Sclerodermic patients with PAH had significantly higher levels of NT-proBNP than those without PAH (mean value: 23.4 pmol/L, min–max range 11.1–38 vs. 12.2, min–max range 2.5–23.7; *P* = 0.028 by Mann–Whitney test).

Considering the threshold values for normality (14.8 pmol/L) provided by the manufacturer of NT-proBNP assay kit, 9/10 sclerodermic patients with PAH had high concentrations of NT-proBNP, while 3/10 sclerodermic patients without PAH had high concentrations of NT-proBNP. In sclerodermic patients without PAH, the mean concentration of NT-proBNP remained stable during the study

Table 1 Characteristics of patients and controls

	SSc + PAH (<i>n</i> = 10)	SSc no PAH (<i>n</i> = 10)	<i>P</i>
Age (year)	55 (range 40–70)	52 (range 35–68)	NS
M:F	1:9	1:9	NS
Autoantibody profile	10/10 ANA 5/10 anticentromer 5/10 scl70	10/10 ANA 5/10 anticentromer 5/10 scl70	NS
Patients with atrial fibrillation	0	0	
Patients with systemic hypertension	1	2	
Patients with severe bowel involvement	1	0	
Patients with coronary artery disease	0	0	
Leg ulcers	3	0	
NYHA functional class	III = 7; IV = 3	I = 8; II = 2; III-IV = 0	
Serum creatinine, mean ± SD mmol/L (range)	80 ± 11 (57–101)	79 ± 12 (66–99)	NS
Basal Pro-Nt-BNP levels pmol/L	23.4	12.2	0.028

whereas in the patients with PAH the mean concentration was 26 pmol/L (range 4.45–144 pmol/L) after 3 months, and 15.7 pmol/L (range 6–79 pmol/L) after 7 months of therapy with bosentan. There was no significant difference in NT-proBNP concentration at 3 and 7 months of therapy compared with that at baseline ($P = 0.953$ and $P = 0.600$, respectively, by Wilcoxon signed ranks test), although a trend towards lower levels was observed after 7 months of treatment (Fig. 1). All patients had a cTnT value <0.01 .

Of the ten patients with PAH enrolled in this study, three died after the follow-up period: one of scleroderma renal crisis, one of sepsis and one of cardiac arrhythmias. PAH remained stable during all the treatment period, the 6 min walking test was unchanged after 7 months of treatment compared to baseline and no adjunctive therapy was necessary. During bosentan therapy the leg ulcerations related to SSc did not improve. However, the three patients did not show the appearance of new ulcers.

Discussion

In our study, basal serum NT-proBNP concentration was significantly higher in patients with SSc and PAH than in SSc patients without PAH. These results are in accordance with those of other authors [2, 5, 6], who have reported that NT-proBNP is a useful biologic marker of early PAH in SSc patients without heart failure and that its levels are correlated with the severity of PAH. Moreover the test seems to have a negative predictive value, suggesting that patients with low NT-proBNP levels are highly unlikely to have PAH.

This is the first report on NT-proBNP serum levels variation during therapy with oral dual endothelin ET(A)/ET(B) receptor antagonist in patients with PAH secondary to SSc.

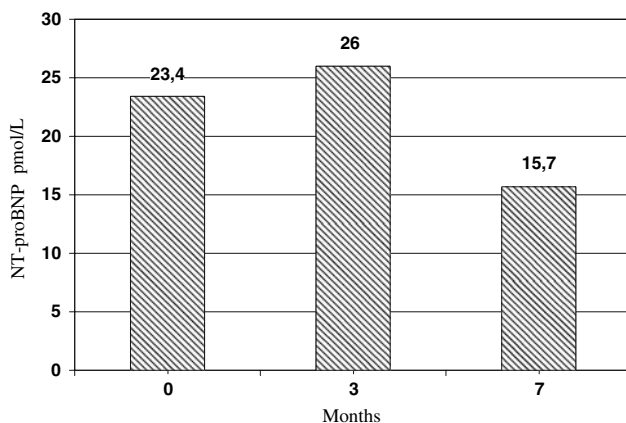


Fig. 1 Mean values of NT-proBNP in SSc with PAH on bosentan therapy at the beginning and after 3 and 7 months of bosentan therapy

We did not observe a statistically significant difference in NT-proBNP concentration after three and seven months of bosentan therapy and these findings may be related both to the low number of patients enrolled and to the duration of the study, since we observed a trends towards lower levels of NT-proBNP that nearly reached statistical difference compared to baseline levels, after seven months of therapy. Three patients without PAH had high NT-proBNP levels but no signs of heart cardiac failure: these patients are carefully monitored for the possibility that the high NT-proBNP levels may have a predictive value for the development of PAH.

Bosentan is clinically beneficial in patients with PAH secondary to SSc although pulmonary hemodynamics and pulmonary function tests seem to remain stable during the treatment [9]. These findings have been confirmed by other authors [10], who observed that in patients with connective tissue disease and PAH there is a progressive improvement in exercise capacity on bosentan therapy. However, pulmonary artery mean pressure remained unchanged. In a study conducted on 92 patients with SSc and PAH, the subjects receiving bosentan had a better survival rate compared to the group of patients not on bosentan therapy; in this last group pulmonary vascular resistance increased over a period of nine months while it remained stable in the group receiving bosentan [11]. Therefore it seems that patients with SSc and PAH experience an improvement in exercise capacity and walk distance during bosentan therapy although NT-proBNP levels and pulmonary vascular resistance remain stable. This behaviour seems different from that observed in patients with primary PAH who experience both a decrease in NT-proBNP concentration after 4 months of bosentan therapy [12] and an improvement in hemodynamic parameters when on bosentan therapy [13].

The identification of parameters able to evaluate the response to the treatment in subjects with PAH secondary to SSc is crucial and NT-proBNP was thought to be one such parameter. Indeed, our results confirm that NT-proBNP is a useful marker in discriminating SSc patients with PAH, and in monitoring the response to bosentan therapy after a long period of treatment. In our experience the 6 min walking test is not as useful as in patients with primary PAH or secondary to other connective tissue diseases since SSc patients may present with leg cutaneous ulcers and claudicatio that can invalidate the test. However, the 6 min walking test and the measurement of NT-proBNP at baseline and regularly after treatment initiation have been recently recommended, although these outcome measures lack some aspects of validation in PAH associated with connective tissue diseases [14].

Long-term follow-up in patients with PAH secondary to SSc is still necessary to understand the possible use of NT-proBNP as a prognostic marker for the response to therapy.

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