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BRIEF REPORT

Pulmonary Arterial Hypertension Therapy May Be Safe and Effective in Patients With Systemic Sclerosis and Borderline Pulmonary Artery Pressure

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Objective. **Borderline pulmonary arterial hypertension (PAH), characterized by a marked exercise-induced increase in pulmonary artery pressure (PAP) with normal resting values, may precede overt PAH in systemic sclerosis (SSc). We undertook the present study to investigate whether PAH treatment is safe in these patients and might attenuate hemodynamic progression.**

Methods. **SSc patients with borderline PAH underwent right heart catheterization at baseline, after a 12-month observation period, and subsequently after 6 months of bosentan therapy. Changes in mean PAP at 50W during the observation period versus during therapy were compared.**

Results. **Ten patients completed the study. Mean PAP at rest, at 50W, and during maximal exercise increased significantly during the observation period (mean ± SD increases of 2.5 ± 3.0 mm Hg [$P = 0.03$], 4.0 ± 2.9 mm Hg [$P = 0.002$], and 6.8 ± 4.1 mm Hg [$P = 0.0005$], respectively) and tended to decrease during the treatment period (decreases of 2.5 ± 3.9 mm Hg [$P = 0.07$], 1.5 ± 4.5 mm Hg [$P = 0.32$], and 1.8 ± 7.0 mm Hg [$P = 0.43$], respectively). The changes during the observation period versus the therapy period were significantly different ($P = 0.03$ at rest, $P = 0.01$ at 50W [primary end point], and $P = 0.02$ during maximal exercise). The changes in resting pulmonary vascular resistance were also significantly different during the observation period (increase of 8 ± 25 dynes · seconds · cm^{-5}) versus during the therapy period (decrease of 45 ± 22 dynes · seconds · cm^{-5}) ($P < 0.0005$). Changes in resting pulmonary arterial wedge pressure were not significantly different between the observation period and the treatment period, despite the significant increase during the observation period (2.6 ± 2.5 mm Hg [$P = 0.01$]). No relevant adverse effects were reported.**

Conclusion. **In SSc patients with borderline abnormal pulmonary hemodynamics, resting and exercise PAP may increase significantly within 1 year of observation. Bosentan might be safe and effective to attenuate these changes. Randomized controlled trials are warranted to confirm the exploratory findings of this hypothesis-generating pilot study.**

Pulmonary arterial hypertension (PAH) is a progressive disease of the small pulmonary arteries which leads to decreased exercise capacity, right ventricular failure, and eventually, death. Resting mean pulmonary artery pressure (PAP) of 8–20 mm Hg is considered to be normal (1), and PAH is diagnosed when mean PAP is ≥25 mm Hg and pulmonary arterial wedge pressure (PAWP) is ≤15 mm Hg (2). Although exercise data are still not standardized, results of recent studies have suggested that a marked exercise-induced increase in PAP may indicate early pulmonary vasculopathy and represent an intermediate stage between normal PAP and PAH (3,4). In a British study, 19% of patients with

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systemic sclerosis (SSc; scleroderma) with an exercise-induced mean PAP increase of >30 mm Hg progressed to manifest PAH within 3 years (5). In accordance with this, our group showed that borderline elevation of resting PAP and a marked exercise-induced increase in PAP in SSc patients was associated with decreased exercise capacity (6). Apart from a few promising case reports (7), it is unclear whether scleroderma patients without overt PAH but with borderline abnormal pulmonary hemodynamics, characterized by a marked exercise-induced increase in PAP, would benefit from targeted PAH therapy.

Studies involving invasive followup of borderline PAH in scleroderma patients have not been reported to date. The goal of this exploratory pilot study was therefore to invasively monitor the natural course of this disease entity and to investigate the effects of bosentan on hemodynamics and exercise capacity in these patients. We hypothesized that pulmonary hemodynamics would deteriorate over time and that this could be attenuated by administration of a targeted PAH therapy such as bosentan.

PATIENTS AND METHODS

Patients in whom SSc was the only risk factor for PAH were enrolled in a screening program for PAH as described previously (6,8). All patients fulfilled the American College of Rheumatology criteria for SSc (9). SSc was classified according to the criteria proposed by LeRoy et al (10). Patients were excluded if they had known manifest PAH, symptomatic obstructive or restrictive pulmonary disease (prebronchodilator forced vital capacity in 1 second <65% of predicted), systolic or diastolic left ventricular failure (ejection fraction <50%, diastolic failure of more than a mild degree) (11), hemodynamically significant valvular disease, systemic arterial hypertension, or clinically relevant arthritis or myositis that might have substantially influenced the exercise tests. The study design and protocol were in compliance with the Helsinki Declaration and were approved by the local ethics committee. All patients provided written informed consent. Patients with a mean PAP of <25 mm Hg (and PAWP of ≤15 mm Hg) at rest and >30 mm Hg during exercise (concomitant cardiopulmonary exercise testing) at right-sided heart catheterization (RHC) were eligible for this pilot study. Six-minute walk test, pulmonary function testing, and laboratory tests including tests for N-terminal pro–brain natriuretic peptide (NT-proBNP) were performed within 24 hours of RHC.

After this baseline RHC there was a 12-month observation period, during which no changes in the hemodynamic medication were allowed. After this period, a second RHC was performed under the same conditions as the baseline assessment, and the described tests were repeated.

This was followed by a 6-month treatment period, in which patients received bosentan (62.5 mg twice daily for 1 month, then 125 mg twice daily for 5 months). After this, RHC and all other described examinations were repeated.

The end points of the study and the statistical tests

Table 1. Comparison of hemodynamic and pulmonary function parameters and exercise capacity in the 10 systemic sclerosis patients at baseline, after the observation period, and after the treatment period*

	Baseline	After observation period	After treatment period	*P*		
				Observation period	Treatment period	Observation vs. treatment
Mean PAP at rest, mm Hg	15.5 ± 3.2	18.0 ± 3.2	15.5 ± 3.1	0.03	0.07	0.03
Mean PAP at 50W, mm Hg	28.1 ± 5.5	32.1 ± 5.9	30.6 ± 6.4	0.002	0.32	0.01
Mean PAP at maximum exercise, mm Hg	34.5 ± 3.7	41.3 ± 3.2	39.5 ± 7.1	0.0005	0.43	0.02
PVR at rest, dynes · seconds · cm^{-5}	163 ± 67	171 ± 51	126 ± 38	0.32	<0.0005	<0.0005
PVR at 50W, dynes · seconds · cm^{-5}	137 ± 54	141 ± 52	116 ± 41	0.57	0.06	0.13
PVR at maximum exercise, dynes · seconds · cm^{-5}	127 ± 55	137 ± 47	102 ± 38	0.35	0.003	0.02
PAWP at rest, mm Hg	6.4 ± 2.2	9.0 ± 2.7	8.4 ± 2.5	0.01	0.63	0.12
PAWP at 50W, mm Hg	12.5 ± 4.9	16.3 ± 4.9	16.3 ± 6.0	0.002	1.0	0.14
PAWP at maximum exercise, mm Hg	17.7 ± 6.2	22.4 ± 6.6	25.3 ± 6.8	0.03	0.32	0.60
Cardiac output at rest, liters/minute	4.7 ± 0.9	4.2 ± 0.8	4.6 ± 0.7	0.04	0.15	0.05
Cardiac output at 50W, liters/minute	9.6 ± 2.0	9.1 ± 1.2	10.1 ± 1.7	0.36	0.09	0.16
Cardiac output at maximum exercise, liters/minute	11.5 ± 2.3	11.4 ± 2.1	12.2 ± 2.6	0.54	0.18	0.49
Peak V_{O_2} during exercise, ml/minute/kg	20.6 ± 2.9	19.5 ± 3.2	20.1 ± 3.1	0.13	0.21	0.08
6-minute walk, meters	464 ± 69	452 ± 54	459 ± 61	0.29	0.52	0.31
NT-proBNP, pg/ml	112 ± 73	123 ± 56	132 ± 79	0.56	0.75	0.93
DLCO, % predicted	78 ± 9	76 ± 11	76 ± 13	0.33	0.97	0.69
FVC, % predicted	90 ± 16	86 ± 16	85 ± 15	0.02	0.47	0.17
Weight, kg	70 ± 14	68 ± 11	68 ± 12	0.09	0.89	0.27
WHO classification, no. in class I/II/III	2/7/1	2/7/1	4/5/1	–	–	–
BDI at end of 6-minute walk	2.6 ± 1.5	2.4 ± 1.4	2.3 ± 1.6	0.63	0.82	0.74

* Except where indicated otherwise, values are the mean ± SD. PAP = pulmonary artery pressure; PVR = pulmonary vascular resistance; PAWP = pulmonary arterial wedge pressure; NT-proBNP = N-terminal pro–brain natriuretic peptide; DLCO = diffusing capacity for carbon monoxide; FVC = forced vital capacity; WHO = World Health Organization; BDI = Borg Dyspnea Index.

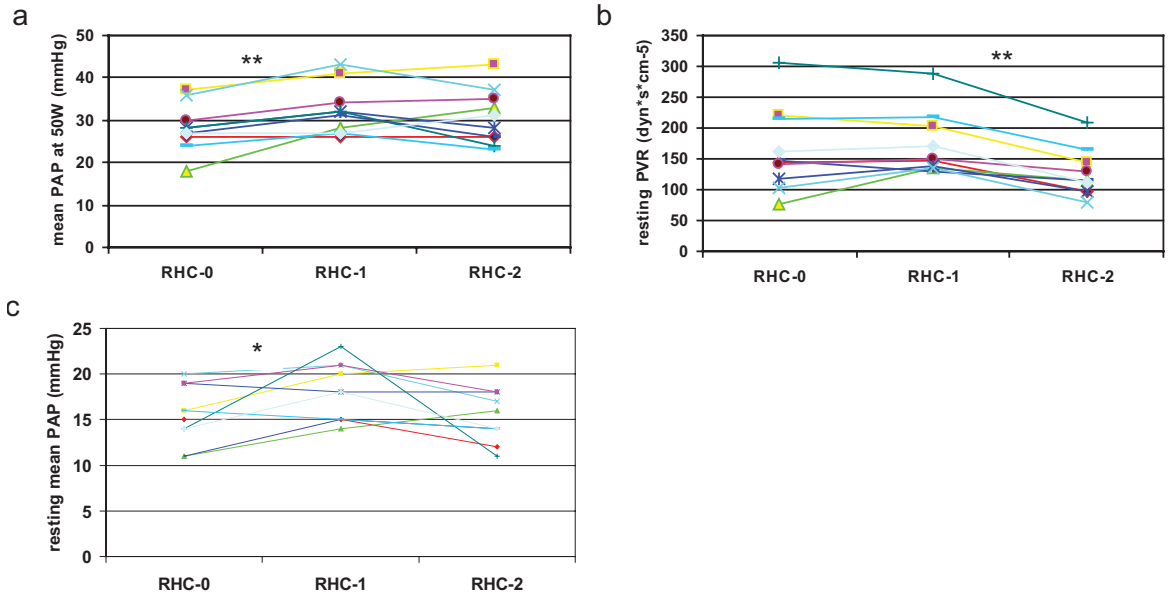

Figure 1. Individual changes in mean pulmonary arterial pressure (PAP) at 50W (**a**), resting pulmonary vascular resistance (PVR) (**b**), and resting mean PAP (**c**) during the observation period and the treatment period. RHC-0, -1, and -2 = right-sided heart catheterization at baseline, at the end of the 12-month observation period, and at the end of the 6-month bosentan treatment period, respectively. $* = P = 0.03$; $** = P \leq 0.002$.

were defined a priori and approved by the local ethics committee. The end points were based on the results of a previous exploratory study suggesting that mean PAP values at 50W and at rest, as well as pulmonary vascular resistance (PVR) values at rest, may be of clinical relevance in scleroderma patients with borderline PAP (6). The primary end point in the present study was the change in mean PAP at 50W during the course of the treatment period as compared to the observation period. Secondary end points included the change in resting and exercise PVR and the change in peak Vo_2 during the treatment period as compared to the observation period. The changes in these parameters were compared by 2-sided paired *t*-test. For the secondary end points as well as for resting mean PAP, PAWP, and 6-minute walk distance, the same analysis was used in an exploratory manner. Results were expressed as the mean ± SD.

RESULTS

Ten patients with SSc (6 with limited cutaneous SSc, 1 with diffuse cutaneous SSc, 3 with overlap; mean ± SD age 55.4 ± 8.9 years, mean ± SD disease duration 8.3 ± 9.8 years) were enrolled. During the observation and treatment periods, no adverse events or relevant side effects of bosentan were observed. No patient discontinued participation in the study prematurely. There were no protocol violations.

Changes in hemodynamics and exercise capacity during the observation and treatment periods are shown in Table 1. Mean PAP at 50W increased significantly during the observation period (mean ± SD +4.0 ± 2.9 mm Hg; $P = 0.002$) and was unchanged during the treatment period (−1.5 ± 4.5 mm Hg; $P = 0.32$). The changes during the treatment period versus the observation period (primary end point) were statistically different ($P = 0.01$) (Table 1 and Figure 1a).

Among the secondary end points, resting PVR tended to increase during the observation period (mean ± SD +8 ± 25 dynes · seconds · cm^{-5}; $P = 0.32$)

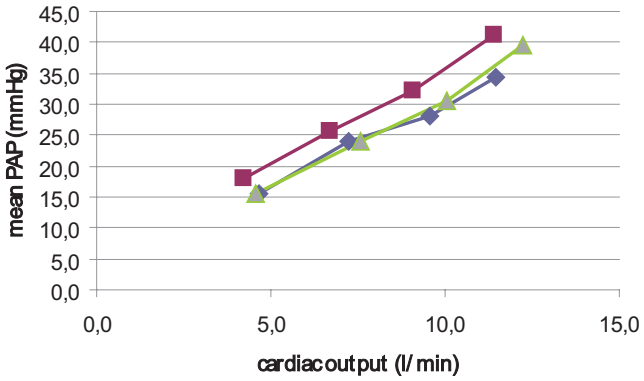

Figure 2. Pressure/flow diagram of mean pulmonary arterial pressure (PAP) versus cardiac output. Values are the mean at baseline (blue), at the end of the observation period (red), and at the end of the treatment period (green).

and decreased significantly during the treatment period (-45 ± 22 dynes · seconds · cm^{-5}; $P < 0.0005$) (Table 1 and Figure 1b). The changes between the 2 periods were highly significantly different ($P < 0.0005$), and PVR at the end of the treatment period was even significantly lower than at baseline ($P = 0.01$). The changes in PVR during maximal exercise followed the same pattern ($+10 \pm 35$ dynes · seconds · cm^{-5} versus -35 ± 26 dynes · seconds · cm^{-5}; $P = 0.02$). PVR at 50W also increased during the observation period and decreased during the treatment period ($+4 \pm 24$ dynes · seconds · cm^{-5} versus -25 ± 38 dynes · seconds · cm^{-5}); however, the difference in the changes between the 2 periods did not reach statistical significance ($P = 0.13$). There was a trend toward an improvement in peak VO_2 during the treatment period ($+0.6 \pm 1.2$ ml/minute/kg) as compared to the observation period (-1.1 ± 2.0 ml/minute/kg), but these changes were not significantly different ($P = 0.08$) (Table 1).

Among further parameters of interest, resting mean PAP increased during the observation period (mean ± SD $+2.5 \pm 3.0$ mm Hg; $P = 0.03$), and this was reversed during the treatment period (-2.5 ± 3.9 mm Hg; $P = 0.07$). The changes were significantly different between the 2 periods ($P = 0.03$) (Table 1 and Figure 1c). Similarly, mean PAP at maximal exercise level increased during the observation period ($+6.8 \pm 4.1$ mm Hg; $P = 0.0005$) and was unchanged during the treatment period (-1.8 ± 7.0 mm Hg; $P = 0.43$), and the changes during the 2 periods were significantly different ($P = 0.02$).

All patients had normal resting PAWP (defined as ≤15 mm Hg) at all 3 RHC examinations. During the observation period, PAWP increased significantly, both at rest and during exercise, and resting PAWP decreased slightly during the treatment period (Table 1). Six-minute walk distance showed a slight deterioration during the observation period (mean ± SD -12 ± 33m) and a slight increase during the treatment period ($+7 \pm 31$m); however, the difference in these changes was not significant ($P = 0.31$). Changes in pulmonary function test results, diffusing capacity for carbon monoxide, or NT-proBNP levels were not significantly different between the treatment and observation periods. The Borg Dyspnea Index at the end of the 6-minute walk test was stable throughout the study.

During the 12-month observation period, as mean PAP increased, cardiac output decreased (by ~0.5 liters/minute). After "correction" for the decrease in cardiac output, mean PAP values would have increased by 3–5 mm Hg instead of 2.5 mm Hg. After the 6-month treatment period, the mean PAP/cardiac output slope almost completely returned to baseline (Figure 2).

DISCUSSION

In this exploratory pilot study, we hypothesized that targeted PAH treatment might attenuate hemodynamic progression in SSc patients without manifest PAH but with borderline abnormal pulmonary hemodynamics. As a marker we used the previously accepted definition of exercise-induced PAH, indicated by an increase in PAP to >30 mm Hg. Based on published reports, such hemodynamic changes may be relatively common among SSc patients (4). To our knowledge, this is the first study to assess hemodynamic changes and to investigate the safety and potential effects of targeted PAH therapy in this group of patients, using invasive hemodynamic monitoring. The results suggested that at this early stage, the progression in resting and exercise hemodynamics toward PAH was attenuated and partially reversed by bosentan treatment. The clinical significance of the observed small absolute changes in hemodynamic parameters needs to be validated by long-term followup and with a prospective randomized approach in a sufficiently powered study.

The observation period results in our study showed that significant increases in mean PAP at rest and during exercise were observed within just 1 year. Four of the 10 patients had mean PAP values of 20–25 mm Hg at the end of the observation period, whereas the value was in this range in only 1 of the 10 at baseline. Our data suggest that, assuming a linear change over time, certain patients may experience relatively rapid progression from normal mean PAP values and develop PAH within a short period of time. These findings are supported by data from the French Scleroderma Registry, showing that ~55% of patients with scleroderma-associated PAH had developed PAH within 5 years after the diagnosis of SSc (after the first non–Raynaud's phenomenon symptom) (12). Data from a British scleroderma registry suggest that patients with a PAP of 20–25 mm Hg and those with a marked increase in exercise-induced PAP may be especially prone to rapid development of overt, and ultimately fatal, PAH (5).

Patients with significant diastolic dysfunction were excluded from enrollment in our study, and accordingly all patients had normal resting PAWP values (≤15 mm Hg) during all RHC investigations. During the observation period, PAWP increased slightly but significantly both at rest and during exercise, which may have contributed to the observed increase in mean PAP. This

increase in PAWP explains why the calculated PVR increase was minor and did not reach statistical significance, although cardiac output decreased significantly. It also suggests that both left ventricular diastolic function and pulmonary vasculopathy may have contributed to the increase in PAP. This notion is supported by previous studies showing that both mechanisms are common in SSc (13). However, the technical limitations of PAWP measurement during exercise and the absence of an international consensus on well-defined normal ranges of PAWP at given exercise levels make the analysis and interpretation of these data difficult. Therefore, given the small patient cohort in our study, interpretation of the role of PAWP remains speculative. Future investigation of the potential relevance of longitudinal changes in PAWP during rest and exercise in scleroderma patients may yield important information.

During the treatment period, exercise and resting mean PAP values were stabilized and PVR decreased. The number of patients with resting mean PAP between 20 and 25 mm Hg decreased: after 6 months of therapy, mean PAP remained in this range in only 1 of the 10 patients. The hemodynamic improvement may represent a reversal of pulmonary vessel wall proliferation and/or constriction. Both factors (proliferation and constriction) contribute to pulmonary vasculopathy. Long-term observation is warranted to determine whether bosentan reverses or just attenuates and delays early pulmonary vasculopathy in scleroderma.The bosentan treatment regimen in the study patients appeared to be safe, with no significant adverse effects.

Throughout the treatment period, transaminase levels were not significantly elevated (>3 times the upper limit of normal) in any of the patients. Eight of the 10 patients continued treatment after the end of the study (for a mean $\pm$ SD of 22 $\pm$ 5 months), without relevant side effects. Three patients had transitional peripheral edema during the first weeks of therapy. One patient developed low leukocyte counts during the study treatment period, but this was probably due to ongoing azathioprine therapy, and it improved after reduction of the azathioprine dosage. There were no signs of any drug interactions or significant changes in hemoglobin level during the study.

Exercise capacity, as assessed by peak V_{O_2} and 6-minute walk distance, did not change significantly during the observation period or the treatment period. The reason may be that the study was not sufficiently powered for this purpose. Furthermore, the absence of change in exercise capacity may reflect the minimal baseline impairment of the patients.

Some potential limitations of the present study must be considered. It is important to emphasize that the study was performed in patients with SSc, and the results may not apply to other subjects with exercise-induced PAH. The small number of study patients also precludes general conclusions. We performed a sequential comparison rather than a parallel-group comparison and used different lengths of time for the observation and the treatment periods, which may have introduced bias. This design was employed due to the limited number of patients and the time restrictions in this pilot trial. The advantage was the complete data set without any need for data imputation. Medication was given on an open-label basis, which also might have biased some results. However, while this may have occurred for exercise capacity measurements, it is unlikely to have influenced invasively measured hemodynamics. It is possible that vasodilatory properties of bosentan, rather than antiproliferative properties, contributed to the hemodynamic effects. However, this is a general issue with drugs that have vasodilatory properties. PAWP measurements during exercise may be inaccurate for technical reasons, which is a general limitation of studies assessing exercise hemodynamics.

In conclusion, resting and exercise PAP increased significantly within 1 year of followup in scleroderma patients without overt PAH but with borderline abnormal pulmonary hemodynamics. This increase was significantly attenuated by bosentan therapy. Randomized controlled trials, including assessment of potential changes in left ventricular function, are warranted to confirm the findings of this hypothesis-generating study.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Kovacs had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Kovacs, Aberer, Brodmann, Graninger, Hesse, Rubin, Olschewski.

Acquisition of data. Kovacs, Maier, Aberer, Brodmann, Graninger, Kqiku, Scheidl, Tröster, Hesse, Olschewski.

Analysis and interpretation of data. Kovacs, Maier, Kqiku, Rubin, Olschewski.

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Actelion Austria had no involvement in the design and conduct of the study or the interpretation of the results. Publication of this article was not contigent upon approval by Actelion Austria.

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