Eur Respir J 2007; 29: 469–475
DOI: 10.1183/09031936.00081706

Addition of sildenafil to bosentan monotherapy in pulmonary arterial hypertension

S.C. Mathai*, R.E. Girgis*, M.R. Fisher#, H.C. Champion¶, T. Housten-Harris*, A. Zaiman* and P.M. Hassoun*

ABSTRACT: Combination therapy has been recommended for the treatment of pulmonary arterial hypertension (PAH). However, there is scant information on combination therapy after failure of monotherapy, particularly in patients with scleroderma-associated PAH (PAH-SSD).

From a group of 82 consecutive patients with PAH who received initial bosentan monotherapy, a total of 13 idiopathic PAH (IPAH) and 12 PAH-SSD patients requiring additional therapy with sildenafil were studied. Sildenafil was added for clinical deterioration based upon symptoms, New York Heart Association (NYHA) classification or 6-min walk distance (6MWD). Clinical data and haemodynamics were collected at baseline. Assessments were made at 1–3-month intervals.

At baseline, there were no differences in demographics, NYHA classification, haemodynamics or 6MWD between the two groups. After initiation of bosentan, both groups experienced clinical improvement but ultimately deteriorated (median time to monotherapy failure 792 *versus* 458 days for IPAH and PAH-SSD patients, respectively). After addition of sildenafil, more IPAH patients tended to improve in NYHA class (five out of 13 *versus* two out of 12) and walked further (mean difference in 6MWD 47±77 m *versus* -7±40 m) compared with PAH-SSD patients.

In conclusion, addition of sildenafil after bosentan monotherapy failure improved New York Heart Association class and 6-min walk distance in idiopathic pulmonary arterial hypertension patients but failed to improve either parameter in scleroderma-associated pulmonary arterial hypertension patients. Additional studies are needed to assess the tolerability and efficacy of this combination in patients with scleroderma-associated pulmonary arterial hypertension.

KEYWORDS: Bosentan, combination therapy, pulmonary hypertension, scleroderma, sildenafil

Pulmonary arterial hypertension (PAH) is a progressive disease of the pulmonary vasculature that leads to right heart failure and death [1]. Pulmonary endothelial dysfunction characterised by impaired production of vasodilators and overexpression of vasoconstrictors has been implicated in the pathogenesis of the disease [2, 3]. Therefore, several novel therapies have been developed that target the prostacyclin (epoprostenol, treprostinil and iloprost), nitric oxide (sildenafil) or endothelin (bosentan) pathways.

Although the optimal long-term management for patients with PAH has yet to be defined, combination therapy with agents that target different pathways in the putative pathogenesis of the disease has been proposed in treatment algorithms [4–6]. The combination of two oral agents, such as bosentan and sildenafil, is particularly attractive given the ease of administration, differing mechanisms of action and tolerability. Several uncontrolled studies of the combination of these two agents in PAH have been reported [7, 8]. However, there are few data on the effect of combination therapy in patients with PAH associated with the scleroderma spectrum of diseases (PAH-SSD). Since patients with PAH-SSD tend to have a poorer response to available therapies compared with the idiopathic PAH (IPAH) population [9–13], combination therapy targeting multiple pathways may offer another option for these patients.

The present authors reviewed their experience with the addition of sildenafil to bosentan therapy in patients with both IPAH and PAH-SSD who had deteriorated clinically on bosentan monotherapy. It was hypothesised that the response to combination therapy might differ between these two groups of patients based upon

For editorial comments see page 432.

AFFILIATIONS
*Division of Pulmonary and Critical Care Medicine and,
¶Cardiology, Dept of Medicine, Johns Hopkins University, Baltimore, MD, and
#Division of Pulmonary and Critical Care Medicine, Dept of Medicine, Emory University, Atlanta, GA, USA.

CORRESPONDENCE
P.M. Hassoun
Johns Hopkins University
Division of Pulmonary and Critical Care Medicine
1830 East Monument Street
5th Floor
Baltimore
MD 21205
USA
Fax: 1 4109550036
E-mail: phassoun@jhmi.edu

Received:
June 22 2006
Accepted after revision:
October 22 2006

STATEMENT OF INTEREST
A statement of interest for R.E. Girgis can be found at www.erj.ersjournals.com/misc/statements.shtml

European Respiratory Journal
Print ISSN 0903-1936
Online ISSN 1399-3003

previously described phenotypic characteristics and differential responses to therapy [14].

METHODS

The institutional review board reviewed and approved the conduct of the present study. The Johns Hopkins Pulmonary Hypertension Program maintains a registry of all patients evaluated at the centre. A total of 82 consecutive patients were identified in the registry who had a diagnosis of IPAH, anorexigen-associated PAH or PAH-SSD and received bosentan as initial therapy between January 2002 and January 2006. For the present study, anorexigen-associated PAH patients were grouped with IPAH patients as there is no evidence that clinical or pathological differences exist between these two groups [15, 16].

The diagnosis of PAH was confirmed by right heart catheterisation revealing a mean pulmonary artery pressure (mP_{pa}) >25 mmHg, pulmonary capillary wedge pressure <15 mmHg and pulmonary vascular resistance (PVR) >3 Wood units. Other causes of pulmonary hypertension, such as significant chronic obstructive or interstitial disease, portal hypertension, severe obstructive sleep apnoea, chronic thromboembolic disease or patients with scleroderma with significant interstitial lung disease, were excluded [12, 17]. Interstitial lung disease was defined based upon a combination of pulmonary function tests and chest radiography as previously described elsewhere [12]. The diagnosis of scleroderma was based upon American College of Rheumatology criteria [18].

Bosentan therapy was prescribed at recommended doses according to the package insert (Tracleer®; Actelion Pharmaceuticals, South San Francisco, CA, USA). The patients were monitored clinically for treatment efficacy as determined by symptoms, New York Heart Association (NYHA) functional classification (FC), distance achieved on 6-min walk testing (6MWD) and repeat haemodynamic assessment where clinically indicated. If patients deteriorated in any of these parameters, they were offered additional therapy with sildenafil. Bosentan monotherapy failure was defined as: worsening of the symptoms of dyspnoea or fatigue, decline in NYHA FC by at least one class or in 6MWD by >30 m. A distance of 30 m was chosen as a minimal clinically important difference for the 6MWD in PAH as an estimated average treatment effect size found in recent clinical trials of novel therapies [11, 19–21]. In total, 25 patients who fulfilled these criteria were offered addition of sildenafil or *i.v.* or subcutaneous prostacyclin analogues to bosentan treatment. All 25 patients chose a trial of sildenafil over prostacyclin analogues. Prior to July 2005, sildenafil was started at a dose of 25 mg *t.i.d.*. Over the course of 2-3 weeks, the dose was increased to a goal of 50 mg *t.i.d.* as tolerated. If no clinical improvement was noted at this dose, sildenafil was further increased to a maximum of 100 mg *t.i.d.* as tolerated. After sildenafil received regulatory approval for use in PAH in July 2005, patients who were started on sildenafil therapy received 20 mg *t.i.d.*, according to the package insert (Revatio®; Pfizer, New York, NY, USA). Patients who had received higher doses prior to regulatory approval of sildenafil remained on the higher doses for the duration of the present study.

STATISTICAL ANALYSIS

The baseline NYHA FC and 6MWD obtained prior to initiation of bosentan therapy were compared with values obtained after 3 months of combination therapy with bosentan and sildenafil. The effects of the therapy were compared between values obtained at baseline and after 3 months of bosentan monotherapy (period 1), at bosentan monotherapy failure (period 2) and after 3 months on combination therapy (period 3). Continuous variables were compared using the t-test (unpaired for between-group analyses, *i.e.* IPAH *versus* PAH-SSD; paired for within-group analyses, *i.e.* IPAH or PAH-SSD) or the Wilcoxon rank-sum test where appropriate. Categorical variables were compared using the Chi-squared statistic. Time to bosentan failure was compared using Kaplan–Meier analysis. Data were reported as mean values with SD or SE as noted. A two-tailed p-value <0.05 was regarded as indicating a statistically significant difference between groups.

RESULTS

Patient demographics

Between January 2002 and January 2006, 82 PAH patients who had received initial therapy with bosentan were identified. A total of 25 patients (13 with IPAH and 12 with PAH-SSD) received additional therapy with sildenafil for clinical deterioration. At baseline, patients with IPAH tended to be older but there were no significant differences in demographic characteristics, NYHA FC, haemodynamic parameters, 6MWD or medication use between the groups (table 1).

Table 2 shows the baseline characteristics of the patients who remained on bosentan monotherapy. When compared with the IPAH patients who received combination therapy, the IPAH patients who remained on monotherapy were significantly younger (51±14 *versus* 60±8 yrs; p=0.04). Conversely,

TABLE 1 Baseline characteristics of patients

	IPAH	PAH-SSD	p-value
Subjects n	13	12	
Age yrs	60±8	52±13	0.06
Race white	10 (77)	8 (75)	NS
Sex female	12 (92)	12 (100)	NS
NYHA FC at diagnosis I/II *versus* III/IV	3/10	2/10	NS
6MWD m	270±147	318±76	NS
RAP mmHg	14±5	12±6	NS
mP_{pa} mmHg	57±12	53±10	NS
CI $L \cdot min^{-1} \cdot m^{-2}$	2.3±1.0	2.1±0.4	NS
PVR Wood unit	13±5	11±4	NS
P_{pcw} mmHg	12±3	12±3	NS
Warfarin use	9 (69)	6 (50)	NS
Calcium channel blocker use	1 (8)	3 (25)	NS
Digoxin use	2 (15)	1 (8)	NS

Data are presented as mean±SD or n (%), unless otherwise stated. IPAH: idiopathic pulmonary arterial hypertension (PAH); PAH-SSD: scleroderma-associated PAH; NYHA: New York Heart Association; FC: functional class; 6MWD: 6-min walk distance; RAP: right atrial pressure; mP_{pa}: mean pulmonary arterial pressure; CI: cardiac index; PVR: pulmonary vascular resistance; P_{pcw}: pulmonary capillary wedge pressure; NS: nonsignificant.

TABLE 2 Characteristics of patients remaining on bosentan monotherapy

	IPAH	PAH-SSD	p-value
Subjects n	29	28	
Age yrs	51±14	65±11	0.001
Race white	23 (79)	22 (79)	NS
Sex female	23 (79)	25 (89)	NS
NYHA FC at diagnosis I/II *versus* III/IV	8/21	11/28	NS
6MWD m	361±183	275±51	NS
RAP mmHg	9±6	12±5	NS
mP_{pa} mmHg	53±12	46±12	NS
CI L·min^{-1}·m^{-2}	2.2±0.5	2.2±0.6	NS
PVR Wood unit	11±5	9±4	NS
P_{pcw} mmHg	11±4	12±3	NS
Warfarin use	22 (76)	17 (62)	NS
Calcium channel blocker use	3 (10)	9 (32)	0.04
Digoxin use	3 (10)	2 (7)	NS

Data are presented as mean±SD or n (%), unless otherwise stated. IPAH: idiopathic pulmonary arterial hypertension (PAH); PAH-SSD: scleroderma-associated PAH; NYHA: New York Heart Association; FC: functional class; 6MWD: 6-min walk distance; RAP: right atrial pressure; mP_{pa}: mean pulmonary arterial pressure; CI: cardiac index; PVR: pulmonary vascular resistance; P_{pcw}: pulmonary capillary wedge pressure; NS: nonsignificant.

PAH-SSD patients in the monotherapy group were significantly older than the PAH-SSD combination group (65±11 *versus* 52±13 yrs; p=0.003). There were no differences in other demographic or clinical characteristics between groups but IPAH patients in the combination group had significantly higher baseline mean right atrial pressure (RAP) compared with the bosentan-only group (14±5 *versus* 9±6 mmHg; p=0.02).

Although there were no significant differences in the duration of the follow-up periods between groups in period 1 (110±31 days for IPAH *versus* 95±26 days for PAH-SSD patients) or period 3 (115±22 days IPAH *versus* 110±27 days PAH-SSD), there was a trend towards a significant difference in time to bosentan failure (period 2) by time-to-event analysis (proportion remaining on therapy at 1, 2 and 3 yrs: 77, 62 and 8% IPAH patients *versus* 58, 33 and 0% PAH-SSD patients, respectively; log-rank p=0.06).

Change in FC

NYHA FC at baseline, after period 1, period 2 and period 3 is shown in figures 1a and b. At baseline, there were no significant differences in the FC between the two groups. After initiation of bosentan, nine out of 13 IPAH and five out of 12 PAH-SSD patients improved by at least one FC. At bosentan failure, seven IPAH (six of whom had initially improved on bosentan) and six PAH-SSD (five of whom had initially improved on bosentan) patients deteriorated by at least one FC. Five out of 13 patients improved by at least one FC after addition of sildenafil to bosentan in the IPAH group, whereas two out of 12 patients improved in the PAH-SSD group (p=0.22). One subject deteriorated by one FC in the PAH-SSD group. None deteriorated in the IPAH group.

Change in 6MWD

The 6MWD at baseline, period 1, period 2 and period 3 is shown in figure 2. There were no significant differences between the 6MWD in the IPAH and PAH-SSD patients at baseline (262±139 *versus* 319±76 m, respectively; p=0.31), period 1 (337±166 *versus* 345±105 m; p=0.90) or period 2 (294±104 *versus* 233±163 m; p=0.28). There was a trend towards a difference in distance achieved between the IPAH and PAH-SSD groups after the addition of sildenafil to bosentan (340±141 *versus* 224±159 m; p=0.06), corresponding to a mean difference of 47±77 m in IPAH patients and -7±40 m in PAH-SSD patients (p=0.04 for difference in mean change in 6MWD between groups). Within groups, 6MWD significantly improved in the IPAH group at period 1 (262±139 *versus* 337±166 m; p=0.04), then declined by period 2 (294±104 m). However, this change in 6MWD was not significant (period 1 *versus* period 2; p=0.18). After 3 months of combination therapy, the mean 6MWD increased significantly

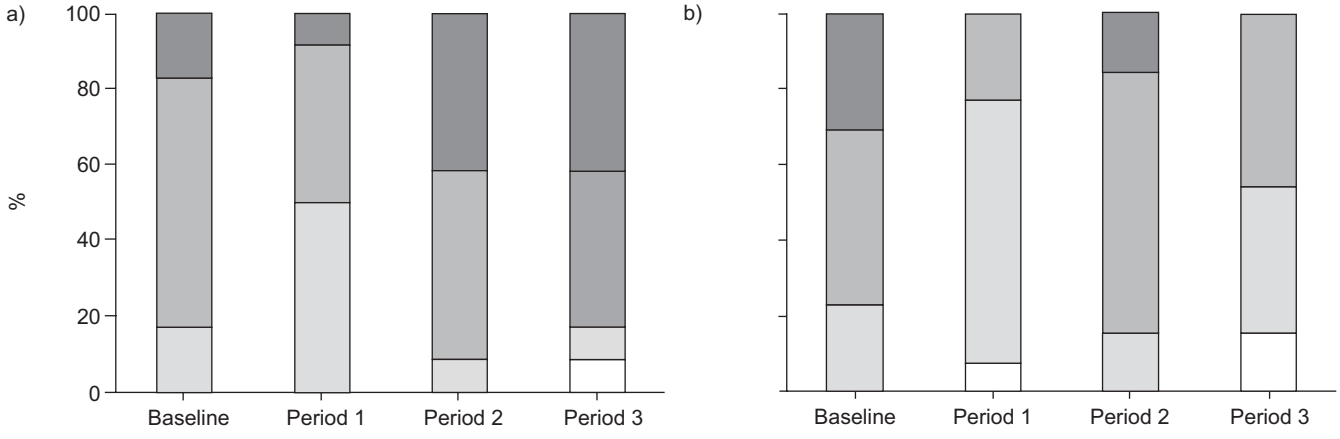

FIGURE 1. New York Heart Association functional class (NYHA FC) at baseline, after 3 months of bosentan monotherapy (period 1), at bosentan monotherapy failure (period 2) and after 3 months of combination therapy with bosentan and sildenafil (period 3) for a) scleroderma-associated PAH patients. b) idiopathic pulmonary arterial hypertension (PAH) patients. □: NYHA FC I; ▫: NYHA FC II; ▪: NYHA FC III; ■: NYHA FC IV.

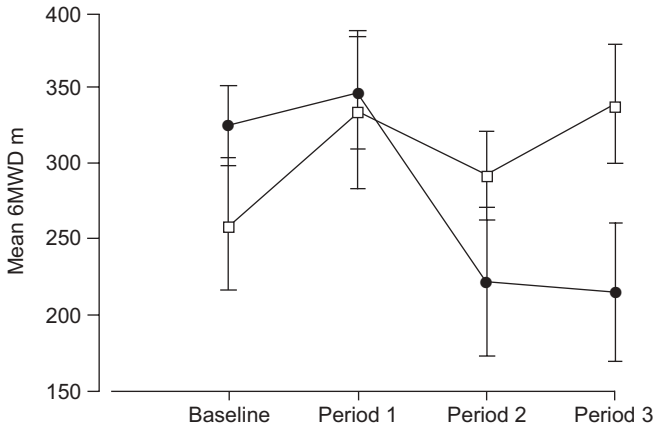

FIGURE 2. Mean 6-min walk distance (6MWD) at baseline, after 3 months of bosentan monotherapy (period 1), at bosentan monotherapy failure (period 2) and after 3 months of combination therapy with bosentan and sildenafil (period 3), for idiopathic pulmonary arterial hypertension (PAH) patients (□) and scleroderma-associated PAH patients (●). Error bars represent SE values.

(294±104 *versus* 340±141 m; p=0.05). In the PAH-SSD group, there was no significant improvement in 6MWD after initiation of bosentan. However, there was a significant decline in 6MWD at period 2 (345±105 *versus* 233±163 m; p=0.01). No change in 6MWD was observed after the addition of sildenafil to bosentan monotherapy. Overall, patients in the IPAH group improved significantly from diagnosis to combination therapy with bosentan and sildenafil (262±139 *versus* 340±141 m; p=0.04). The PAH-SSD group experienced a significant decline in 6MWD from diagnosis to combination therapy (319±76 *versus* 224±159 m; p=0.04).

Sildenafil dosage and side-effects

The average daily dose of sildenafil was significantly different between groups (98±65 mg·day^{-1} in the IPAH group *versus* 168±82 mg·day^{-1} in the PAH-SSD group; p=0.02). Two IPAH patients and one PAH-SSD patient started therapy after July 2005 (time of regulatory approval of sildenafil for PAH treatment) and thus received 20 mg *t.i.d.* (total dose 60 mg·day^{-1}). Several patients discontinued sildenafil owing to side-effects: one in the IPAH group after 4 months of 25 mg sildenafil *t.i.d.* (severe dyspepsia) and three in the PAH-SSD group. One patient had intractable headaches and discontinued sildenafil 25 mg *t.i.d.* after 3 months and two patients had liver function test (LFT) abnormalities that appeared after the addition of sildenafil to bosentan. Neither patient had prior LFT abnormalities on bosentan monotherapy. One of these patients discontinued sildenafil 75 mg *t.i.d.* after 5 months with subsequent resolution of the abnormalities; the other (sildenafil 50 mg *t.i.d.*) reduced the dose of bosentan to 62.5 mg *b.i.d.*, which normalised the LFTs.

Several patients required additional therapy for clinical deterioration after >3 months of combination therapy. Five out of the 12 PAH-SSD patients required additional therapy with either inhaled iloprost (n=4) or *i.v.* epoprostenol (n=1; mean time to additional therapy 123±52 days), whereas only one IPAH patient required additional therapy (continuous *i.v.* treprostinil after 118 days of combination therapy) for clinical worsening (p=0.05). Another patient in the PAH-SSD group required continuous *i.v.* dopamine for renal insufficiency and refractory right heart failure after >100 days on combination therapy. Four patients with PAH-SSD died during the study period from progressive right heart failure. One patient with IPAH died from gastrointestinal haemorrhage unrelated to pulmonary hypertension therapy.

DISCUSSION

The present study suggests that the response to combination therapy with bosentan and sildenafil after clinical failure of bosentan monotherapy may vary between patients with IPAH and PAH-SSD. It was found that while patients with IPAH experienced improvement in FC and 6MWD, patients with PAH-SSD did not. Two PAH-SSD patients developed LFT abnormalities after the addition of sildenafil; neither patient had previous liver function abnormalities on bosentan monotherapy. Additionally, more PAH-SSD patients required additional therapy with a prostanoid. Four patients in the PAH-SSD group died during the study period compared with only one patient in the IPAH group.

Improvement in IPAH patients on combination therapy after failure of bosentan monotherapy is consistent with a recent report by HOEPER *et al*. [7] on nine patients with IPAH. In that study, using a pre-defined treatment algorithm, IPAH patients who had failed on bosentan monotherapy received additional oral therapy with sildenafil and experienced a significant improvement in both 6MWD and peak oxygen uptake. Other studies and case reports of combination therapy have also shown improvements in FC, functional capacity and/or haemodynamics in IPAH patients [22–24]. The Bosentan Randomised trial of Endothelin Antagonist therapy for PAH (BREATHE-2), a randomised, double-blind, placebo-controlled study of the effects of the combination of bosentan and *i.v.* epoprostenol therapy, included patients with IPAH (n=27) and PAH related to connective tissue disease (PAH-SSD n=5, PAH-systemic lupus erythematosus (SLE) n=1) [25]. The BREATHE-2 study failed to find a significant difference between groups in PVR (the primary outcome), dyspnoea rating, FC or exercise tolerance. Interestingly, the authors suggest that inclusion of a larger proportion of patients with PAH-SSD in the treatment group (18 *versus* 9%) may have accounted for the failure to achieve the primary outcome, citing the poorer response to bosentan [11] and epoprostenol [26] in PAH-SSD patients noted in prior studies.

There are limited studies of combination therapy in PAH-SSD patients. In a follow-up study, HOEPER *et al.* [8] reported their experience with combination therapy in a cohort of 123 PAH patients. Over a 2-yr period, >40% of patients required combination therapy with bosentan and sildenafil. In total, >20% of the cohort required further addition of a prostanoid. Although 15 patients in the cohort were classified as having PAH related to connective tissue disease, whether this subset had PAH-SSD or another connective tissue disease and what proportion of this group required combination therapy is unclear.

Previous clinical investigations have also indicated differential response to therapy between IPAH and PAH-SSD patients. Continuous *i.v.* therapy with epoprostenol has been shown to

reduce mortality in IPAH patients but has no or only minimal long-term benefit in PAH-SSD [13, 26]. While ~7% of patients with IPAH have demonstrated a long-term response to oral calcium channel blocker therapy [10], only ~1% of PAH-SSD patients will experience a sustained benefit from this class of drugs [27]. This differential response to therapy has persisted with newer agents. Bosentan has been shown to improve FC and exercise capacity while delaying clinical worsening in short-term studies of IPAH patients [11, 28]. However, bosentan therapy only prevented decline in exercise capacity in the PAH-SSD group. The present authors' own experience with long-term bosentan treatment in PAH-SSD compared with IPAH patients also suggests that PAH-SSD patients do not exhibit a sustained clinical response and have worse survival rates [14, 29]. PAH-SSD patients in the present study failed bosentan monotherapy earlier than IPAH patients (median time to failure 458 *versus* 792 days, respectively). A recent study has suggested an improved survival in patients with bosentan monotherapy compared with historical controls treated with prostanoids [30]. However, nearly half of the patients in the historical cohort had clinically evident pulmonary fibrosis, compared with less than one-third of the bosentan cohort, which may account for the improved survival in the bosentan cohort. Furthermore, time to initiation of treatment was significantly longer in the historical controls compared with the bosentan cohort, which may have biased the survival analysis. Sildenafil has recently been shown to improve FC, exercise capacity and haemodynamics in patients with PAH including PAH associated with connective tissue disease [9]. However, PAH-SSD patients comprised a minority of the PAH associated with connective tissue disease cohort, with the majority of patients having SLE or other connective tissue disease. There are currently no studies reporting the long-term efficacy of sildenafil in PAH-SSD patients.

Several reasons for a diminished response to combination therapy in PAH-SSD may be contributing to this differential response to therapy compared with IPAH. First, it is possible that since the PAH-SSD patients deteriorated more on bosentan monotherapy than IPAH patients, the PAH-SSD group was less likely to respond to additional therapy, regardless of the medication chosen. Second, a drug-drug interaction between sildenafil and bosentan *via* the CYP3A4 enzyme can cause a significant reduction ($\leqslant$66%) in the plasma concentration of sildenafil [31]. The plasma concentration of sildenafil may be further reduced in patients with scleroderma due to gastrointestinal disease that may interfere with absorption, including oesophageal dysmotility [32], gastroparesis [33], small bowel malabsorption [34] and pancreatic insufficiency [35]. Thus, it is possible that despite the overall higher daily doses of sildenafil in the present group, therapeutic levels were not achieved in the plasma. Significant clinical improvement in the IPAH group despite these potential drug-drug interactions with combination therapy may support this hypothesis.

Alternatively, cardiac involvement may account for some of the differences in response to therapy. Previous studies have shown that left ventricular diastolic dysfunction occurs frequently in the scleroderma population and may increase the risk of death [36, 37]. The present authors have recently shown that the prevalence of diastolic dysfunction, as detected by echocardiography, was significantly higher in PAH-SSD patients compared with IPAH patients [14]. Myocardial fibrosis may also contribute to cardiac dysfunction, including right ventricular diastolic dysfunction and conduction abnormalities [38]. Large-vessel pulmonary vascular disease related to scleroderma may increase the effective load on the right ventricle through increased impedance and wave reflection. Although this increased pulsatile load on the right ventricle is present in other forms of pulmonary hypertension [39], it is possible that the pulmonary vascular stiffness in PAH-SSD results in greater impedance than in IPAH. This could potentially explain the poorer response to therapies that target the pulmonary microvasculature. Further, the increased impedance may lead to more rapid right ventricle failure in PAH-SSD despite similar pulmonary artery pressure and PVR in IPAH patients. Other factors that could contribute to divergent responses to therapy include underlying coronary vascular disease, which is common in SSD but rarely reported in IPAH [40], and associated subclinical interstitial lung disease [41].

Although generally well tolerated, the combination of bosentan and sildenafil may have potential toxicity. Two PAH-SSD patients who did not develop liver function abnormalities on bosentan monotherapy subsequently demonstrated elevation in transaminases after initiation of combination therapy, suggesting a possible drug-drug interaction. Prior studies in healthy volunteers have shown pharmacokinetic interactions between bosentan and sildenafil resulting in elevated plasma levels of bosentan in the presence of sildenafil along with reduction of the plasma levels of sildenafil [42]. Since the LFT abnormalities resolved with either reduction of the bosentan dose or cessation of sildenafil, it is possible that co-administration of sildenafil resulted in high plasma concentrations of bosentan that ultimately may have caused the hepatotoxicity. Additional pharmacokinetic studies are needed to define the mutual pharmacokinetic interactions between these medications.

There are several limitations to the present study. Since it is a retrospective study, it is susceptible to many potential biases. Inherent selection bias related to the retrospective design is further augmented by the inclusion of only patients who failed initial monotherapy with bosentan. However, when compared with the PAH group who remained on bosentan monotherapy, many demographic, clinical characteristics and haemodynamic parameters were similar. IPAH patients who failed bosentan monotherapy were older and had significantly higher RAP than the IPAH patients who remained on monotherapy. This suggests that these older patients with more advanced disease at baseline may not respond as well to monotherapy and ultimately require more aggressive therapy. PAH-SSD patients who failed bosentan therapy were significantly younger than those PAH-SSD patients who did not receive bosentan and sildenafil. Escalation of therapy in younger patients with PAH-SSD suggests that these patients may have a more aggressive disease than their older counterparts. The definition of bosentan monotherapy failure used in the present study has not been validated. However, the decision to escalate therapy in clinical practice is often based upon decline in symptoms, FC or functional capacity rather than serial invasive haemodynamic assessments. Further, although the minimal clinically important difference of 30 m for the 6MWD has not been

validated, a recent study by GILBERT *et al.* [43] found a similar value for the minimal clinically important difference in a population of PAH patients in the Sildenafil Use in Pulmonary Arterial Hypertension study [9].

In summary, in the present small cohort of patients who had failed initial monotherapy with bosentan, idiopathic pulmonary arterial hypertension patients experienced significant improvements in functional class and exercise capacity with the addition of sildenafil, whereas scleroderma-associated pulmonary arterial hypertension patients did not. Additional studies are required to define the basis for the inferior response in scleroderma-associated pulmonary arterial hypertension patients and to identify an optimal therapeutic strategy.

ACKNOWLEDGEMENTS

The authors would like to thank M.C. McCormack for her review of the present manuscript.

REFERENCES

1 Barst RJ, Rubin LJ, Long WA, *et al.* A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. *N Engl J Med* 1996; 334: 296–302.
2 Humbert M, Morrell NW, Archer SL, *et al.* Cellular and molecular pathobiology of pulmonary arterial hypertension. *J Am Coll Cardiol* 2004; 43: Suppl. S, 13S–24S.
3 Budhiraja R, Tuder RM, Hassoun PM. Endothelial dysfunction in pulmonary hypertension. *Circulation* 2004; 109: 159–165.
4 Galie N, Seeger W, Naeije R, Simonneau G, Rubin LJ. Comparative analysis of clinical trials and evidence-based treatment algorithm in pulmonary arterial hypertension. *J Am Coll Cardiol* 2004; 43: Suppl. S, 81S–88S.
5 Galie N, Torbicki A, Barst R, *et al.* Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. *Eur Heart J* 2004; 25: 2243–2278.
6 Badesch DB, Abman SH, Ahearn GS, *et al.* Medical therapy for pulmonary arterial hypertension: ACCP evidence-based clinical practice guidelines. *Chest* 2004; 126: Suppl. 1, 35S–62S.
7 Hoeper MM, Faulenbach C, Golpon H, Winkler J, Welte T, Niedermeyer J. Combination therapy with bosentan and sildenafil in idiopathic pulmonary arterial hypertension. *Eur Respir J* 2004; 24: 1007–1010.
8 Hoeper MM, Markevych I, Spiekerkoetter E, Welte T, Niedermeyer J. Goal-oriented treatment and combination therapy for pulmonary arterial hypertension. *Eur Respir J* 2005; 26: 858–863.
9 Galie N, Ghofrani HA, Torbicki A, *et al.* Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2005; 353: 2148–2157.
10 Sitbon O, Humbert M, Jais X, *et al.* Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. *Circulation* 2005; 111: 3105–3111.
11 Rubin LJ, Badesch DB, Barst RJ, *et al.* Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002; 346: 896–903.
12 Badesch DB, Tapson VF, McGoon MD, *et al.* Continuous intravenous epoprostenol for pulmonary hypertension due to the scleroderma spectrum of disease. A randomized, controlled trial. *Ann Intern Med* 2000; 132: 425–434.
13 Fagan KA, Badesch DB. Pulmonary hypertension associated with connective tissue disease. *Prog Cardiovasc Dis* 2002; 45: 225–234.
14 Fisher MR, Mathai SC, Champion HC, *et al.* Clinical differences between idiopathic and scleroderma-related pulmonary hypertension. *Arthritis Rheum* 2006; 54: 3043–3050.
15 Simonneau G, Fartoukh M, Sitbon O, Humbert M, Jagot JL, Herve P. Primary pulmonary hypertension associated with the use of fenfluramine derivatives. *Chest* 1998; 114: Suppl. 3, 195S–199S.
16 Tuder RM, Radisavljevic Z, Shroyer KR, Polak JM, Voelkel NF. Monoclonal endothelial cells in appetite suppressant-associated pulmonary hypertension. *Am J Respir Crit Care Med* 1998; 158: 1999–2001.
17 Barst RJ, McGoon M, Torbicki A, *et al.* Diagnosis and differential assessment of pulmonary arterial hypertension. *J Am Coll Cardiol* 2004; 43: Suppl. S, 40S–7S.
18 Subcommittee for scleroderma criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee, Preliminary criteria for the classification of systemic sclerosis (scleroderma). *Arthritis Rheum* 1980; 23: 581–590.
19 Simonneau G, Barst RJ, Galie N, *et al.* Continuous subcutaneous infusion of treprostinil, a prostacyclin analogue, in patients with pulmonary arterial hypertension: a double-blind, randomized, placebo-controlled trial. *Am J Respir Crit Care Med* 2002; 165: 800–804.
20 Oudiz RJ, Schilz RJ, Barst RJ, *et al.* Treprostinil, a prostacyclin analogue, in pulmonary arterial hypertension associated with connective tissue disease. *Chest* 2004; 126: 420–427.
21 Olschewski H, Simonneau G, Galie N, *et al.* Inhaled iloprost for severe pulmonary hypertension. *N Engl J Med* 2002; 347: 322–329.
22 Stiebellehner L, Petkov V, Vonbank K, *et al.* Long-term treatment with oral sildenafil in addition to continuous IV epoprostenol in patients with pulmonary arterial hypertension. *Chest* 2003; 123: 1293–1295.
23 Morice AH, Mulrennan S, Clark A. Combination therapy with bosentan and phosphodiesterase-5 inhibitor in pulmonary arterial hypertension. *Eur Respir J* 2005; 26: 180.
24 Gomberg-Maitland M, McLaughlin V, Gulati M, Rich S. Efficacy and safety of sildenafil added to treprostinil in pulmonary hypertension. *Am J Cardiol* 2005; 96: 1334–1336.
25 Humbert M, Barst RJ, Robbins IM, *et al.* Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2. *Eur Respir J* 2004; 24: 353–359.
26 Kuhn KP, Byrne DW, Arbogast PG, Doyle TP, Loyd JE, Robbins IM. Outcome in 91 consecutive patients with pulmonary arterial hypertension receiving epoprostenol. *Am J Respir Crit Care Med* 2003; 167: 580–586.
27 Sitbon O, Humbert M, Jais X, *et al.* Acute vasodilator responsiveness and long-term response to calcium channel blockers in different forms of pulmonary arterial hypertension. *Am J Respir Crit Care Med* 2004; 169: A210.
28 Channick RN, Simonneau G, Sitbon O, *et al.* Effects of the dual endothelin-receptor antagonist bosentan in patients

with pulmonary hypertension: a randomised placebo-controlled study. *Lancet* 2001; 358: 1119–1123.
29 Girgis RE, Mathai SC, Krishnan JA, Wigley FM, Hassoun PM. Long-term outcome of bosentan treatment in idiopathic pulmonary arterial hypertension and pulmonary arterial hypertension associated with the scleroderma spectrum of diseases. *J Heart Lung Transplant* 2005; 24: 1626–1631.
30 Williams MH, Das C, Handler CE, *et al.* Systemic sclerosis associated pulmonary hypertension: improved survival in the current era. *Heart* 2006; 92: 926–932.
31 Paul GA, Gibbs JS, Boobis AR, Abbas A, Wilkins MR. Bosentan decreases the plasma concentration of sildenafil when coprescribed in pulmonary hypertension. *Br J Clin Pharmacol* 2005; 60: 107–112.
32 Yarze JC. Esophageal dysmotility and its relation to systemic sclerosis variant. *Am J Gastroenterol* 1998; 93: 2630–2631.
33 Maddern GJ, Horowitz M, Jamieson GG, Chatterton BE, Collins PJ, Roberts-Thomson P. Abnormalities of esophageal and gastric emptying in progressive systemic sclerosis. *Gastroenterology* 1984; 87: 922–926.
34 Sjogren RW. Gastrointestinal features of scleroderma. *Curr Opin Rheumatol* 1996; 8: 569–575.
35 Pope JE, Seibold JR. International Conference on Systemic Sclerosis. *J Rheumatol* 1999; 26: 938–944.
36 Nakajima K, Taki J, Kawano M, *et al.* Diastolic dysfunction in patients with systemic sclerosis detected by gated myocardial perfusion SPECT: an early sign of cardiac involvement. *J Nucl Med* 2001; 42: 183–188.
37 Handa R, Gupta K, Malhotra A, *et al.* Cardiac involvement in limited systemic sclerosis: non-invasive assessment in asymptomatic patients. *Clin Rheumatol* 1999; 18: 136–139.
38 Fernandes F, Ramires FJ, Arteaga E, Ianni BM, Bonfa ES, Mady C. Cardiac remodeling in patients with systemic sclerosis with no signs or symptoms of heart failure: an endomyocardial biopsy study. *J Card Fail* 2003; 9: 311–317.
39 Castelain V, Herve P, Lecarpentier Y, Duroux P, Simonneau G, Chemla D. Pulmonary artery pulse pressure and wave reflection in chronic pulmonary thromboembolism and primary pulmonary hypertension. *J Am Coll Cardiol* 2001; 37: 1085–1092.
40 Kahan A, Devaux JY, Amor B, *et al.* Nifedipine and thallium-201 myocardial perfusion in progressive systemic sclerosis. *N Engl J Med* 1986; 314: 1397–1402.
41 Steen VD, Graham G, Conte C, Owens G, Medsger TA Jr. Isolated diffusing capacity reduction in systemic sclerosis. *Arthritis Rheum* 1992; 35: 765–770.
42 B Wittke, Burgess G, Ng T, Hoogkamer H, Dingemanse J., Mutual pharmacokinetic interactions between steady-state bosentan and sildenafil. *Proc Am Thorac Soc* 2005; 2: A200.
43 Gilbert C, Brown MC, Capelleri JC, *et al.* Establishing a minimally important difference in 6-minute walk distance and SF-36 among patients with pulmonary arterial hypertension. *Chest* 2005; 128: 365S.