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Combining bosentan and sildenafil in pulmonary arterial hypertension patients failing monotherapy: real-world insights

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ABSTRACT Pulmonary arterial hypertension is a severe disease with a complex pathogenesis, for which combination therapy is an attractive option.

This study aimed to assess the impact of sequential combination therapy on both short-term responses and long-term outcomes in a real-world setting.

Patients with idiopathic/heritable pulmonary arterial hypertension, or pulmonary arterial hypertension associated with congenital heart disease or connective tissue disease and who were not meeting treatment goals on either first-line bosentan or sildenafil monotherapy, were given additional sildenafil or bosentan and assessed after 3–4 months. Double combination therapy significantly improved clinical and haemodynamic parameters, independent of aetiology or the order of drug administration. Significant improvements in functional class were observed in patients with idiopathic/heritable pulmonary arterial hypertension. The 1-, 3- and 5-year overall survival estimates were 91%, 69% and 59%, respectively. Patients with pulmonary arterial hypertension associated with connective tissue disease had significantly poorer survival rates compared to other aetiologies ($p<0.003$).

The favourable short-term haemodynamic results and good survival rates, observed in patients receiving both bosentan and sildenafil, supports the use of sequential combination therapy in patients failing on monotherapy in a real-world setting.

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Introduction

Pulmonary arterial hypertension (PAH) is a severe disease characterised by a progressive increase in pulmonary vascular resistance (PVR) that ultimately results in right heart failure and death [1]. While the pathogenesis of PAH is complex, three key mechanistic pathways: 1) the endothelin, 2) the nitric oxide, and 3) prostacyclin pathways, are known to be involved in the disease [1]. Therapies that target these pathways have contributed to improved survival in patients with PAH [2–4]; nevertheless, the disease remains a fatal condition.

Combining therapies is an attractive option for treating patients with PAH. Current recommendations advocate the use of targeted PAH monotherapy as a first-line approach and addition of a second or third agent (sequential combination) in patients who demonstrate an inadequate clinical response to treatment [2, 5]. For patients in the New York Heart Association (NYHA) functional class IV, initial combination therapy is also considered appropriate [5]. Until recently, data from randomised controlled trials supporting this approach have been limited; however, controlled data supporting the use of sequential combination therapy are increasing [6, 7], and in some cases include long-term data [8].

Despite limited long-term controlled data, the use of combination therapy has become part of the standard of care in many PAH centres. As such, registries have helped our understanding of this approach in the management of patients with PAH. Registry data show that combination therapy is widely used in the treatment of patients with PAH [9–13], and may play a role in the observed improved survival [10]. Furthermore, the results of two meta-analyses of placebo-controlled studies in PAH suggested an improved clinical outcome in patients treated with combination therapy, compared with the placebo-comparator arms [14, 15]. Despite these insights, many questions regarding combination therapy remain.

The objective of this retrospective analysis was to assess the short-term response of treating PAH patients with the endothelin receptor antagonist bosentan and the phosphodiesterase-5 inhibitor sildenafil, and to evaluate the impact of this combination on patients' long-term outcomes, in a real-world setting (COMBINATION Real-World Study).

Methods

This retrospective chart review was conducted in compliance with The Declaration of Helsinki. Patient data were anonymised and the patients provided written consent for their use.

Data from consecutive patients with PAH attending a national referral centre in Bologna, Italy, who received sequential combination therapy, were collected. The observation period was from October 2003 to December 2013.

Sequential combination therapy was indicated if treatment goals were not met at regular (3–4 months) clinical visits. The treatment goals were: 1) NYHA functional class I/II; 2) 6-min walking distance (6MWD) $\geqslant$500 m for patients aged $\leqslant$50 years or $\geqslant$380 m for patients aged >50 years; 3) cardiac index (CI) $\geqslant$2.5 L·min^{-1}·m^{-2}; and 4) right atrial pressure <10 mmHg. The goals were chosen based on the result of the predictors detected by Sitbon *et al.* [16] after 3 months of treatment with epoprostenol. We considered the 6MWD threshold of 380 m too low for younger patients and decided to increase arbitrarily the goal to 500 m for patients aged $\leqslant$50 years. These goals were applied since 2003 and have not changed over time. Adequate clinical response was defined when all goals were fulfilled. Right heart catheterisation was performed systematically 3–4 months after treatment initiation and when functional class and/or exercise capacity deteriorated on follow-up.

Combination therapy was, therefore, offered to patients not fulfilling their goals 3–4 months after treatment initiation, or to patients who did not maintain their treatment goals on follow-up despite an initial adequate clinical response.

Double combination therapy comprised of the addition of sildenafil in patients treated with first-line bosentan and the addition of bosentan in patients treated with first-line sildenafil. Triple combination therapy comprised of the addition of a prostanoid in patients treated with bosentan and sildenafil.

Patients

Consecutive patients (aged 12–82 years) with a diagnosis of idiopathic PAH/heritable PAH (IPAH/HPAH), PAH associated with congenital heart disease (PAH-CHD) or PAH associated with connective tissue disease (PAH-CTD), confirmed with right heart catheterisation, who were eligible for sequential double combination therapy (*i.e.* those who did not fulfil the above treatment goals) were included in the analysis. Patients with PAH associated with HIV infection or portal hypertension were excluded.

Treatment regimen

In patients, for whom sildenafil was added, the drug was initiated and maintained at a dose of 20 mg three times per day. For patients for whom bosentan was added, the initial dose was 62.5 mg two times per day, the dose was increased and maintained at 125 mg two times per day after 4 weeks.

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Assessments

Assessment of NYHA functional class, exercise capacity (*via* 6MWD) and cardiopulmonary haemodynamic parameters (*via* right heart catheterisation) was carried out at initiation/change in treatment, 3–4 months thereafter, and in case of clinical deterioration. NYHA functional class evaluation, 6MWD assessment and echocardiographic evaluation were also carried out every 3–4 months, with additional assessment by right heart catheterisation in case of signs of clinical deterioration.

All-cause mortality, non-elective hospitalisation for PAH and the need for triple combination therapy were all evaluated throughout the observation period; the latter was established if the goals for treatment were not met at any time point after the initiation of double combination therapy. Liver function was evaluated on a monthly basis.

Statistical analysis

Changes in NYHA functional class were assessed using the McNemar test, 6MWD and haemodynamic parameters were analysed using the non-parametric Wilcoxon–Mann–Whitney test. All data are expressed as the median (interquartile range). Survival and event-free survival were displayed using Kaplan–Meier plots and the difference between subgroups tested for significance using the log-rank test. Survival was evaluated from initiation of combination therapy, rather than from diagnosis of PAH, to avoid immortal time bias.

Results

Patient characteristics

Baseline characteristics of all 192 patients at the time of combination therapy initiation are described in table 1. Patients were predominantly IPAH/HPAH (n=102, 53%) with the remaining being PAH-CHD (n=61, 32%) and PAH-CTD (n=29, 15%). The mean duration of monotherapy prior to commencement of combination therapy was 16 months (5–39 months). During the observation period, 133 patients, initially treated with bosentan, received sildenafil as an additional therapy (sildenafil addition group), and 59 patients, initially treated with sildenafil, received bosentan as an additional therapy (bosentan addition group).

Short-term assessment of combination therapy

A total of 181 (94%) patients had a follow-up evaluation 3–4 months after initiation of double combination therapy. In the bosentan addition group, one patient was lost to follow-up, one patient died, and one patient withdrew due to hypotension. In the sildenafil addition group, five patients died and three declined right heart catheterisation.

Patients showed significant clinical and haemodynamic improvements after 3–4 months with the combination of bosentan and sildenafil (table 2). These symptomatic and haemodynamic improvements were independent of the order in which the drugs were administered (table S1) and were observed across the aetiology subgroups (table 2). The significant improvements in 6MWD (IPAH/HPAH and PAH-CHD p<0.001, PAH-CTD p=0.030), CI (IPAH/HPAH p<0.001, PAH-CHD p=0.003, PAH-CTD p=0.010), mean

TABLE 1 Baseline characteristics at initiation of combination therapy

	All patients	IPAH/HPAH	PAH-CHD	PAH-CTD
Patients n	181	102	61	29
Male %	40	48	38	17
Age at initiation of combination therapy years	50 (36–62)	50 (36–62)	45 (31–54)	66 (58–72)
Duration of monotherapy months	16 (5–39)	14 (4–35)	26 (8–51)	13 (6–27)
New York Heart Association functional class III/IV %	52	54	39	72
6-min walking distance m	425 (307–491)	441 (271–516)	428 (383–494)	360 (219–425)
Right atrial pressure mmHg	9 (7–13)	8 (7–12)	9 (7–12)	12 (7–16)
Mean pulmonary arterial pressure mmHg	62 (51–75)	59 (49–69)	78 (65–90)	50 (44–56)
Pulmonary wedge pressure mmHg	10 (8–12)	10 (8–12)	11 (9–12)	9 (6–12)
Mean systemic arterial pressure mmHg	85 (77–93)	85 (77–91)	82 (75–94)	89 (82–97)
Cardiac index $L \cdot min^{-1} \cdot m^{-2}$	2.2 (1.9–2.6)	2.3 (1.9–2.7)	2.1 (1.8–2.6)	2.1 (1.9–2.4)
Pulmonary vascular resistance WU	13 (10–18)	12 (9–16)	17 (13–27)	13 (8–14)
Systemic vascular resistance WU	20 (16–24)	18 (16–23)	21 (16–27)	20 (18–25)
Arterial oxygen saturation %	93 (90–96)	95 (92–97)	90 (84–95)	94 (92–97)
Pulmonary arterial oxygen saturation %	64 (57–69)	62 (56–67)	68 (61–73)	60 (51–64)

Data are presented as median (interquartile range) unless otherwise stated. PAH: pulmonary arterial hypertension; IPAH: idiopathic PAH; HPAH: heritable PAH; CHD: congenital heart disease; CTD: connective tissue disease.

TABLE 2 Symptomatic and haemodynamic parameters at baseline and after 3–4 months of combination therapy

	All patients n=192			IPAH/HPAH n=93			PAH-CHD n=60			PAH-CTD n=28		
	Baseline	3–4 months	p-value	Baseline	3–4 months	p-value	Baseline	3–4 months	p-value	Baseline	3–4 months	p-value
NYHA FC III/IV	49	35	<0.001	51	32	<0.001	38	28	0.146	71	64	0.687
6MWD m	428 (339–496)	465 (380–545)	<0.001	450 (302–531)	498 (376–570)	<0.001	431 (394–498)	456 (425–546)	<0.001	364 (214–426)	397 (310–434)	0.030
RAP mmHg	9 (7–12)	8 (6–11)	0.003	8 (6–11)	7 (6–10)	0.003	9 (7–12)	9 (7–11)	0.405	12 (7–16)	10 (6–15)	0.321
mPAP mmHg	62 (51–76)	57 (48–70)	<0.001	59 (49–69)	54 (46–63)	<0.001	78 (65–90)	73 (59–90)	<0.001	50 (43–56)	49 (42–54)	0.011
CI L·min^{-1}·m^{-2}	2.3 (1.9–2.6)	2.5 (2.2–2.9)	<0.001	2.3 (1.9–2.7)	2.7 (2.4–3.0)	<0.001	2.1 (1.8–2.6)	2.4 (2.1–2.9)	0.003	2.2 (1.9–2.5)	2.5 (2.0–2.8)	0.010
PVR WU	13 (10–18)	11 (8–15)	<0.001	12 (9–16)	10 (7–12)	<0.001	17 (13–27)	14 (9–21)	<0.001	13 (8–14)	9 (7–14)	0.003

Data are presented as % or median (interquartile range), unless otherwise stated. PAH: pulmonary arterial hypertension; IPAH: idiopathic pulmonary arterial hypertension; HPAH: heritable PAH; CHD: congenital heart disease; CTD: connective tissue disease; NYHA FC: New York Heart Association functional class; 6MWD: 6-min walking distance; RAP: right atrial pressure; mPAP: mean pulmonary arterial pressure; CI: cardiac index; PVR: pulmonary vascular resistance; WU: Wood units. The p-values were determined using a non-parametric Wilcoxon–Mann–Whitney test for all comparisons, except for NYHA that was evaluated by McNemar test.

pulmonary arterial pressure (IPAH/HPAH and PAH-CHD p<0.001, PAH CTD p=0.011) and PVR (IPAH/HPAH and PAH-CHD p<0.001, PAH-CTD p=0.003) were observed across all aetiologies. For NYHA functional class, improvements were statistically significant in the overall patient group (p<0.001). However, in the subgroup analysis, only the IPAH/HPAH group showed statistical significance (p<0.001); there was no statistically significant improvement observed in the PAH-CHD and PAH-CTD groups.

Survival and event-free survival in all patients

The mean duration of follow-up was 33 months (14–56 months). Kaplan–Meier estimates were 91%, 69% and 59% for the 1-, 3- and 5-year overall survival rates in the population (fig. 1a). The 1-, 3- and 5-year Kaplan–Meier estimates for hospitalisation-free survival were 79%, 46% and 32%, respectively (fig. 2), for triple combination therapy-free survival were 82%, 48% and 34%, respectively (fig. 3), and for hospitalisation and triple combination therapy-free survival were 72%, 35% and 18%, respectively (fig. 4). Over the course of the study there were a total of 66 deaths, with heart failure being the most common cause (table 3).

Survival and event-free survival according to aetiology

Survival estimates were similar between the PAH-CHD and IPAH/HPAH subgroups (p=0.268) and were significantly better in both subgroups when compared to PAH-CTD patients (p<0.001 and p=0.011, respectively) (fig. 1b). Kaplan–Meier survival curves describing event-free survival by aetiology are shown in figures S1–S3. For hospitalisation-free survival there were no significant differences between the

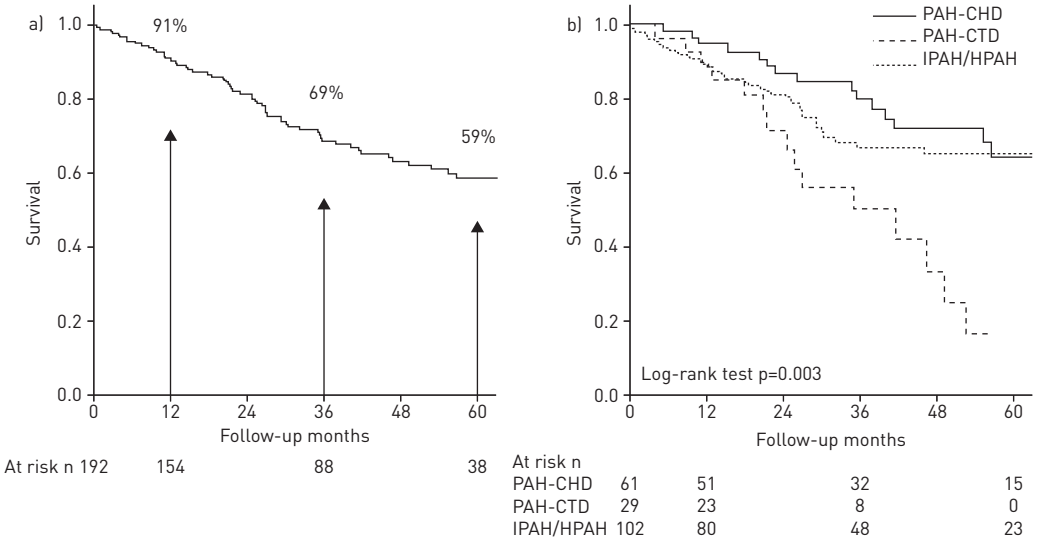

FIGURE 1 Overall survival. a) All-cause mortality and b) all-cause mortality by aetiology. PAH: pulmonary arterial hypertension; CHD: congenital heart disease; CTD: connective tissue disease; IPAH, idiopathic PAH; HPAH: heritable PAH. The percentages show the number of patients surviving.

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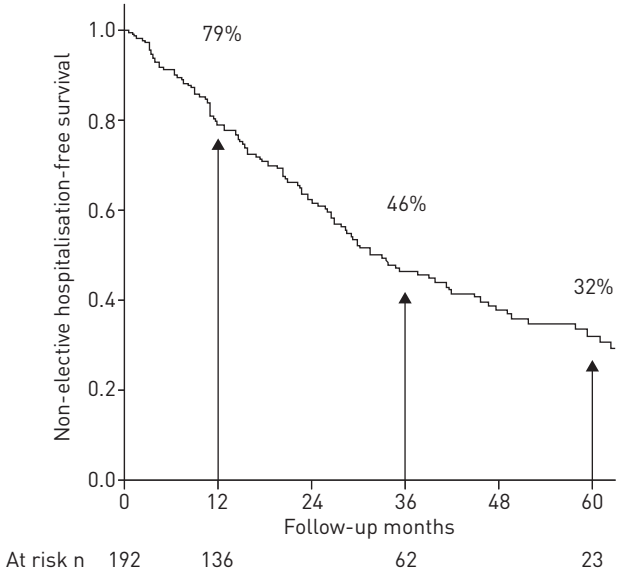

FIGURE 2 Non-elective hospitalisation-free survival for all-cause mortality. The percentages given are for patients alive and not requiring hospitalisation.

different aetiologies (fig. S1). Survival estimates of triple combination therapy-free survival showed significant improved outcomes for PAH-CHD patients when compared to IPAH/HPAH patients (p=0.003) and PAH-CTD patients (p<0.001), and for IPAH/HPAH patients compared to PAH-CTD patients (p=0.003). For hospitalisation and triple combination therapy-free survival, again the PAH-CHD patients showed better outcomes compared to IPAH/HPAH and PAH-CTD patients; however the differences were only significant for the latter comparison (p=0.339 and p=0.002, respectively). The IPAH/HPAH patients also displayed better hospitalisation and triple combination therapy-free survival compared to PAH-CTD patients; however the comparison was of borderline statistical significance (p=0.051). When grouped according to aetiology, heart failure was the most common cause of death within each group, with 17 out of 34, 11 out of 17 and 12 out of 15 deaths in the IPAH/HPAH, PAH-CHD and PAH-CTD groups, respectively (table 3).

Safety

Five patients experienced liver-function test elevations, bosentan addition group n=2 and sildenafil addition group n=3, and withdrew from their respective treatments after a median of 18 months (13–56 months). The two bosentan addition patients withdrew bosentan after 6 and 18 months, whilst the three sildenafil addition patients withdrew bosentan after 13, 56 and 81 months.

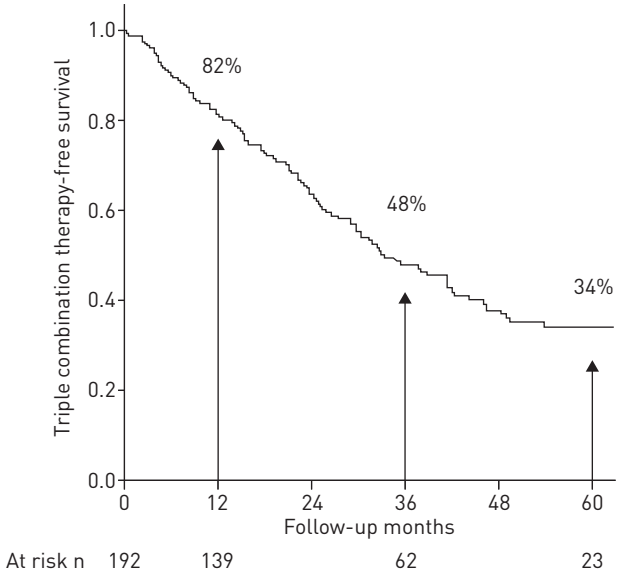

FIGURE 3 All-cause mortality and triple combination therapy-free survival. Percentages shown are for patients alive and not requiring triple combination therapy.

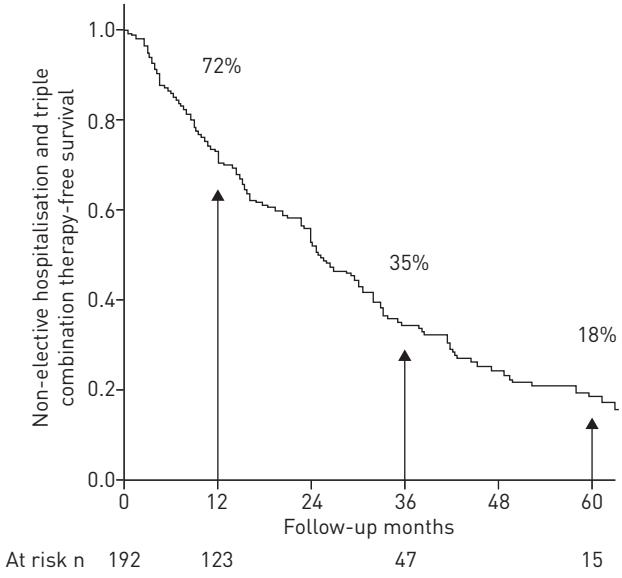

FIGURE 4 All-cause mortality for non-elective hospitalisation and triple combination therapy-free survival. Percentages shown are for patients alive and not requiring hospitalisation or triple combination therapy.

Discussion

In this retrospective analysis, significant improvements in NYHA functional class, exercise capacity and haemodynamic parameters were observed after 3–4 months of combination therapy with bosentan and sildenafil, in patients failing to meet treatment goals with either sildenafil or bosentan monotherapy. Long-term follow-up showed 5-year survival estimates of 59% in the overall population, with 5-year estimates for 1) hospitalisation-free survival, 2) triple combination therapy-free survival and 3) hospitalisation and triple combination therapy-free survival of 32%, 34% and 18%, respectively. The combination of bosentan and sildenafil was well tolerated; five patients withdrew from bosentan treatment due to liver enzyme elevations.

The short-term benefits of combining bosentan and sildenafil demonstrated in this study were observed regardless of the order in which the drugs were administered. In addition the benefits appeared to be consistent across all aetiological subgroups. Given that the strategy used to evaluate the need for treatment escalation reflects the recommendations from international treatment guidelines [2], and subsequent clinical practice, these results provide valuable information regarding the efficacy and safety of combining bosentan and sildenafil in PAH patients who display an inadequate response to monotherapy, in a real-world setting.

The 1-, 3- and 5-year overall survival rates of 91%, 69% and 59% seen in this study were comparable to those observed in the REVEAL (Registry to Evaluate Early And Long-term PAH Disease Management) registry (85%, 68% and 57%, respectively [17]) and the French registry (87%, 67% and not available,

TABLE 3 Cause of death

	All patients	IPAH/HPAH	PAH-CHD	PAH-CTD
Patients	192	102	61	29
Death	66	34	17	15
Heart failure	40	17	11	12
Sudden death	9	4	4	1
Haemoptysis	4	3	1	0
Respiratory failure	3	3	0	0
Infection	3	1	1	1
Other	3		0	
Neoplasia		1		
Myocardial infarction		1		
Renal failure				1
Unknown	4	4	0	0

Data are presented as n. PAH: pulmonary arterial hypertension; IPAH: idiopathic PAH; HPAH: heritable PAH; CHD: congenital heart disease; CTD: connective tissue disease.

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respectively [12]). However, our patient population included only patients not fulfilling specific treatment goals with monotherapy (either after 3–4 months of treatment initiation or on follow-up after an initial adequate clinical response) and may constitute a more compromised patient population as compared with the overall patient population included in registries. In addition, survival in our study was assessed from the beginning of combination therapy and not from the diagnosis of PAH, this may also unfavourably influence the comparison with registry data.

While overall survival estimates for patients treated with sequential combination therapy in this real-world setting seem encouraging, this outcome does not come without a cost. Event-free (*i.e.* no hospitalisation and/or triple combination therapy) survival rates were markedly lower than overall survival. This indicates that while patients may be living longer, the burden of PAH is still high and disease progression occurs, thus necessitating additional medication or admission to hospital. This highlights the need for further improvements in treatment, particularly since these longer-living but morbidity-prone patients would undoubtedly suffer additional complications that require hospitalisation, such as heart failure, haemoptysis, angina and arrhythmias. Indeed, for some patients, such as those with severe haemodynamic impairment, a more timely combination of therapies may be warranted [3].

In this study, all-cause mortality classified by aetiology showed that PAH-CTD patients, the smallest PAH subgroup, performed poorly relative to IPAH/HPAH and PAH-CHD patients. This was also apparent for hospitalisation-free, triple combination therapy-free, and hospitalisation and triple combination-free survival. This outcome is consistent with data from the REVEAL registry which has demonstrated that CTD is a significant predictor of mortality in the setting of PAH (hazard ratio 1.59, $p<0.001$) [13] and that PAH-CTD patients have significantly lower 7-year survival rates than IPAH patients (35% *versus* 57%; $p<0.001$) [17]. A similar trend was seen in the French registry; PAH-CTD patients had significantly worse survival at 3 years than IPAH or PAH-CHD patients ($p<0.05$) [12].

Interestingly, PAH-CHD patients who had an inadequate clinical response to initial monotherapy and received combination therapy had similar survival when compared to IPAH/HPAH patients requiring combination therapy. This suggests that when symptoms and haemodynamic parameters remain compromised in PAH-CHD patients, despite initial monotherapy, their inherent better survival compared to IPAH/HPAH patients is lost [18].

Our study is subject to a number of limitations. The data are not controlled and as such we cannot exclude the possibility of a favourable "placebo effect" on the outcome measures. Nevertheless, it is unlikely that such an effect would impact haemodynamic measurements, or outcome, suggesting that the observed improvements are indeed the result of a true effect. The patients, while not selected based on predefined criteria, are those who show an inadequate response to monotherapy and, therefore, may represent a specific subset with a progressive or resistant disease course. Even if the goals were based on the results of previous studies [16], they were not tailored according to factors such as aetiology, height and comorbidities. A larger proportion of patients received bosentan compared with sildenafil as first-line therapy; it is not clear if this may have influenced the results of this study.

The bosentan and sildenafil plasma levels were not assessed in the current study and, therefore, we cannot evaluate the potential influence of the reported pharmacokinetic interactions in normal individuals between the two drugs [19, 20] on our results.

Conclusion

Since this study is non-comparative, inferences cannot be made regarding the long-term outcome effect of the combination of bosentan and sildenafil based on the data presented here. Nevertheless, the short-term functional, exercise and haemodynamic results showed favourable effects across different PAH aetiologies, and the relatively good survival observed in IPAH and PAH-CHD patients failing monotherapy may support the possibility of a positive outcome effect. The findings of this study provide a valuable insight into real-world use of sequential combination therapy in patients with PAH.

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