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SHORT REPORT

Combination therapy with bosentan and sildenafil in idiopathic pulmonary arterial hypertension

M.M. Hoeper*, C. Faulenbach*, H. Golpon*, J. Winkler#, T. Welte*, J. Niedermeyer*

Combination therapy with bosentan and sildenafil in idiopathic pulmonary arterial hypertension. M.M. Hoeper, C. Faulenbach, H. Golpon, J. Winkler, T. Welte, J. Niedermeyer. ©ERS Journals Ltd 2004.

ABSTRACT: It has been proposed that targeted treatments should be combined for patients with idiopathic pulmonary arterial hypertension (IPAH) responding insufficiently to monotherapy.

This study followed the clinical course of nine patients with severe IPAH, in whom the endothelin receptor antagonist bosentan caused transient clinical improvement, eventually followed by a decline in exercise tolerance, who received adjunct treatment with the phospodiesterase-5-inhibitor sildenafil. Measurements included the 6-min walk distance (6MWD) and cardiopulmonary exercise testing (CPET).

The 6MWD at baseline was 346±66 m and improved to 403±80 m 3 months after introduction of bosentan treatment. However, this effect was not sustained and, after an interval of 11±5 months, the walk distance had declined to 277±80 m. At this point, sildenafil was added to bosentan. Three months later, the 6MWD had increased to 392±61 m and the patients remained stable throughout the median follow-up of 9 months (range 6–12). Measurement of the maximum oxygen uptake during CPET confirmed these results. The combination of bosentan and sildenafil was well tolerated by all patients.

These preliminary data suggest that combining bosentan and sildenafil may be safe and effective in patients with idiopathic pulmonary arterial hypertension.

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Idiopathic pulmonary arterial hypertension (IPAH), formerly called primary pulmonary hypertension (PPH), is a disease of unknown aetiology, characterised by progressive pulmonary vascular remodelling, ultimately leading to right heart failure and death [1, 2]. Without targeted treatment, IPAH carries a grave prognosis, with a median survival of 2.8 yrs after diagnosis [3].

In the last few years, a number of novel treatments for this devastating disease have been developed and are now in use. Intravenous epoprostenol has been shown in several studies to improve haemodynamics, exercise tolerance and survival [4–6]. To circumvent the risks, inconveniences and costs associated with continuous intravenous epoprostenol, stable prostacyclin analogues have been introduced that can be administered orally, subcutaneously or by inhalation [7]. In patients with IPAH, all these substances have been shown to improve exercise tolerance and haemodynamics in relatively short-term clinical studies [8–10], but the effects on long-term survival have not been thoroughly investigated.

Besides prostaglandins, novel substances with different mechanisms of action have been introduced in recent years. The dual endothelin receptor antagonist bosentan has been approved throughout the western world for treatment of pulmonary arterial hypertension (PAH) [11]. In addition, several case series and one small controlled study have suggested that phosphodiesterase-5-inhibitors, such as sildenafil, may have beneficial effects in PAH [12, 13].

Despite the fact that all of these substances have positive effects in IPAH, they do not provide a cure and, in many patients, the disease will eventually progress. The optimal management for patients who exhibit clinical deterioration despite targeted treatment is unclear. The introduction of intravenous epoprostenol is an option for patients in whom treatment with endothelin receptor antagonists, nonintravenous prostanoids or sildenafil fails. Another option is combination treatment [14]. A few uncontrolled clinical studies have suggested that combinations of aerosolised iloprost and sildenafil, as well as aerosolised iloprost and bosentan, are safe and effective in selected patients with progressive disease despite prostanoid treatment [15, 16]. Combining bosentan and sildenafil may also be an attractive choice, since both substances are orally available, act *via* different mechanisms and are usually well tolerated. This paper describes the clinical course of nine patients with severe and progressive IPAH who were treated with a combination of bosentan and sildenafil.

Patients and methods

Between January 2002 and December 2003, 58 patients received bosentan for treatment of IPAH at Hannover Medical School (Hannover, Germany). Bosentan was used either as first-line therapy or in addition to a prostanoid (*i.e.* inhaled iloprost, oral beraprost or intravenous iloprost). Treatment efficacy was monitored primarily by the 6-min walk distance (6MWD) and cardiopulmonary exercise testing (CPET), and was targeted to reach pre-defined goals

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based on prognostically relevant variables: a 6MWD >380 m [6] and a peak oxygen uptake measured during CPET >10.4 mL·min^{-1}·kg^{-1} [17]. Patients who did not reach these goals on two consecutive visits were offered additional treatment with sildenafil. There was no formal study protocol. All patients were informed about the fact that this approach was investigational, that long-term data on safety and efficacy of sildenafil in PAH were not available, that there were no experiences with the combination of bosentan and sildenafil, and about the alternative option to receive intravenous prostacyclin treatment.

Treatments and follow-up

All patients had an extensive diagnostic work-up to define the aetiology of pulmonary hypertension, including, but not limited to, ventilation-perfusion scanning, computed tomography of the chest, right heart catheterisation and pulmonary angiography, when indicated. Bosentan was considered first-line treatment for patients newly diagnosed with IPAH. After initiation of bosentan treatment, the patients were seen in the outpatient clinic in 3–4 monthly intervals. Follow-up examinations included regular 6MWD [18] and CPET [16]. Repeated right heart catheterisations were not part of the routine follow-up programme.

Bosentan treatment was started at a dose of 2×62.5 mg and the dose was increased to 2×125 mg after 4 weeks in all patients. Liver enzymes were monitored every 4 weeks. The dose of bosentan was not changed throughout the observation period.

Sildenafil was started at a dose of 3×25 mg (or 4×25 mg) and was increased after 4–12 weeks to 3×50 mg when the response to the initial dose was not sufficient (*i.e.* when the treatment goals as defined above where not reached).

Analysis

All values are given as mean±SD. Two baselines were set: the first one before bosentan was started and the second one before sildenafil was started. The treatment effects after 3 months were compared with the baseline values using paired t-tests (two-sided). A p-value <0.05 was considered statistically significant.

Results

Within the observation period, 2002–2003, nine out of 58 patients with IPAH, initially treated with bosentan or a combination of bosentan and a prostanoid, fulfilled the predefined criteria of clinical worsening as defined above. These patients suffered from severe and progressive pulmonary hypertension, and were in New York Heart Association (NYHA) functional class III or IV before treatment was started. All patients were nonresponders to acute vasodilator challenge. The baseline characteristics and haemodynamics of these patients are shown in table 1.

Functional classification

At baseline, eight patients were functional class (FC) III and one patient was FC IV. Three months after bosentan was started, two patients had improved to FC II and the patient who formerly was FC IV had improved to FC III. However, after a follow-up of 11±5 months, deterioration occurred in all patients and, before sildenafil was added to bosentan, seven patients were FC III and two patients were FC IV. After 3 months of treatment with bosentan and sildenafil, six patients were FC III and three patients were FC II. During the follow-up period of 6–12 months, two further patients improved from FC III to FC II (table 2).

Table 1. – Patients' baseline characteristics and haemodynamics

Age yrs	39±9
Sex female/male	7/2
NYHA class III/IV	8/1
6MWD m	337±73
Mean right atrial pressure mmHg	9±5
Mean pulmonary arterial pressure mmHg	62±12
Cardiac output L·min^{-1}	3.1±0.7
Cardiac index L·min^{-1}·m^{-2}	1.6±0.3
Pulmonary vascular resistance dynes·s·cm^{-5}	1549±440
Mixed venous oxygen saturation %	53±10

NYHA: New York Heart Association; 6MWD: 6-min walk distance. 1 mmHg=0.133 kPa.

Table 2. – Individual functional classes (New York Heart Association (NYHA)) and 6-min walk distance (6-MWD)

Patient no.	Baseline 1 before bosentan		3 months after introduction of bosentan		Baseline 2 before sildenafil		3 months after addition of sildenafil		6–12 months after addition of sildenafil	
	NYHA	6-MWD	NYHA	6-MWD	NYHA	6-MWD	NYHA	6-MWD	NYHA	6-MWD
1	III	393	II	478	III	297	III	363	III	373
2[#]	III	336	III	428	III	226	III	354	II	410
3	III	367	III	406	III	354	II	450	II	462
4	III	337	III	403	IV	132	II	414	II	382
5	III	420	II	497	III	371	III	421	II	481
6	III	328	III	406	III	353	III	425	III	425
7[¶]	III	330	III	343	III	303	III	335	III	345
8	IV	198	III	232	III	252	III	290	III	328
9	III	406	III	434	IV	203	II	480	II	450

[#]: receiving inhaled iloprost since 15 months before bosentan was started and iloprost was continued throughout the observation period; [¶]: bosentan replaced continuous intravenous iloprost that had been given for 2 yrs but had to be withdrawn after several episodes of life-threatening line sepsis, sildenafil was added 11 months after introduction of bosentan.

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Six-min walk distance

As shown in figure 1 and table 2, the 6MWD at baseline was 346±66 m. After introduction of bosentan treatment, the 6MWD improved by 57 m to 403±80 m (p=0.0003). However, this effect was not sustained and, after an interval of 11±5 months, the walk distance had declined to 277±80 m. At this point, sildenafil was added to bosentan. Three months later, the 6MWD had increased to 392±61 m (p=0.007) and the patients remained stable throughout the median follow-up of 9 months (range 6–12).

Cardiopulmonary exercise testing

Complete sets of data from CPET at all time points (baseline 1, three months after introduction of bosentan, baseline 2 and 3 months after the addition of sildenafil) were available from six patients. In these patients, the peak oxygen uptake ($V'O_2$,peak) was 9.9±1.9 mL·min^{-1}·kg^{-1} at baseline and increased to 12.3±1.9 mL·min^{-1}·kg^{-1} 3 months after introduction of bosentan (p=0.02). As with the walking distance, this effect was not sustained and, before introduction of sildenafil, $V'O_2$,peak had decreased to 10.4±2.3 mL·min^{-1}·kg^{-1}. Three months after sildenafil was added to bosentan, $V'O_2$,peak had increased to 13.8±1.5 mL·min^{-1}·kg^{-1} (p=0.006).

Side-effects

None of the patients in this case series died or experienced any drug-related serious adverse event. There were no abnormalities of liver enzymes before or after the introduction of bosentan, or after addition of sildenafil. All patients reported minor headache and flushing when sildenafil was added to bosentan, but these problems resolved within a few days without dose adjustments. The same was true with heartburn, reported by one patient after sildenafil was started. No patient described symptoms attributable to hypotension and there were no episodes of syncope during the observation period.

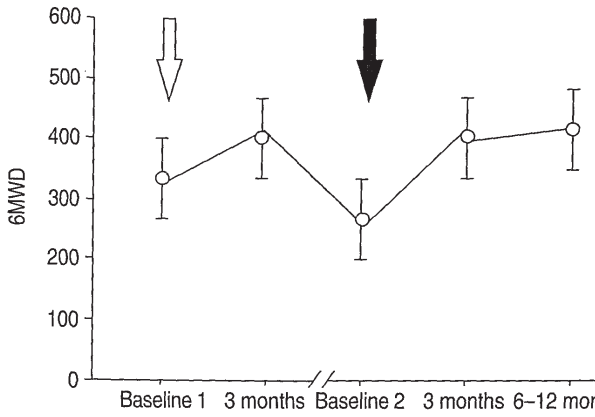

Fig. 1.–Six-min walk distance (6MWD) of nine patients with idiopathic pulmonary arterial hypertension at baseline 1 (before treatment with bosentan), 3 months after introduction of bosentan, baseline 2 (11±5 months later before addition of sildenafil), 3 months later and 6–12 months later. Open arrow: bosentan started; closed arrow sildenafil started.

Discussion

This case series may serve as a pilot trial showing that combining bosentan and sildenafil might be feasible in patients with IPAH. This combination was well tolerated by all patients and proved to be highly efficient. Of note, this patient population consisted of a "negatively" selected subgroup of young patients with very severe and rapidly progressive IPAH. Before targeted treatment was initiated, all patients were in functional class NYHA III or IV, and haemodynamic assessment confirmed the presence of advanced pulmonary hypertension with a mean pulmonary artery pressure of 62±12 mmHg, a cardiac index of 1.6±0.3 L·min^{-1}·m^{-2} and a pulmonary vascular resistance of 1,549±440 dynes·s·cm^{-5}. In accordance with current recommendations [7, 14], bosentan was started as first-line treatment, resulting in clinical improvement and increased exercise tolerance as determined by 6MWD and CPET. However, in contrast to the majority of patients receiving treatment with bosentan, this effect was not sustained. After an average period of close to 1 yr, the patients showed clinical deterioration and a marked decline in 6MWD, as well as in $V'O_2$,peak. It is the unfortunate clinical reality that, even with the novel targeted treatments available for PAH, a certain proportion of patients are going to deteriorate after initial improvement. Those patients are very likely to die from their underlying disease and they do require aggressive treatment. The most recent world conference on pulmonary hypertension recommended that prostacyclin treatment or, alternatively, combination treatment should be initiated in patients not responding sufficiently to treatment with endothelin receptor antagonists or nonintravenous prostanoids [14]. Since bosentan clearly had a beneficial effect in all of the patients in the current study, the authors decided to initiate combination treatment, reserving intravenous prostacyclin for treatment failures. For reasons discussed below, sildenafil was chosen as an add-on treatment. The combination of bosentan and sildenafil was surprisingly well tolerated by all patients and resulted in marked clinical improvement. The pre-defined treatment goals (6MWD >380 m and $V'O_2$,peak >10.4 mL·min^{-1}·kg^{-1}) were reached in six out of nine patients. The remaining patients were judged as sufficiently stable and showed a tendency towards further improvement during follow-up, so that introduction of intravenous prostacyclin was not deemed immediately necessary. It is noteworthy that none of the patients died during the observation period of 21±3 months, even though the expected 1-yr and 2-yr survival probabilities of these patients based on their baseline haemodynamics according to the formula of the National Institutes of Health were 0.64 and 0.51, respectively [3].

Obviously, this observational report has several inherent limitations: there was no control group, the patient population was small and the overall observation time was rather limited. In addition, treatment with bosentan and sildenafil was not part of a formal study protocol, and serial right heart catheter examinations were not performed and, therefore, haemodynamic follow-up data were not available. Although these data would be of value, it is the authors' practice to base most therapeutic decisions on the results of patient's self reporting (functional classification), clinical examination, 6MWT and CPET, and to reserve right heart catheterisation for open questions or for certain therapeutic decisions, such as listing for highly urgent lung transplantation.

Bosentan and sildenafil were combined rather than bosentan and a prostanoid for several reasons: at the time when combination treatment was initiated in the patients, bosentan was the only drug approved for treatment of IPAH

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in Germany (sildenafil, beraprost and treprostinil have not been approved in Germany, and aerosolised iloprost was officially introduced in January 2004); beraprost or treprostinil were not considered as first choices for combination treatment because the former drug has not been shown to exhibit long-term clinical efficacy [19] and the latter one commonly causes substantial infusion site pain [10]; compared to inhaled iloprost, sildenafil has the practical advantage of being orally administered rather than requiring six to nine inhalations daily; and in addition, although it has been shown that inhaled iloprost and sildenafil have synergistic effects [15, 20, 21], it was hypothesised that the combination of substances with different intracellular modes of action might be advantageous in the long run, although comparative studies are required to resolve this issue.

Economical considerations also contributed to the decision to combine bosentan and sildenafil. In Germany, the annual treatment costs for a single patient are ~€45,000 for bosentan, €70,000 for inhaled iloprost and €5,000–10,000 (depending on the dose) for sildenafil. Thus, the annual costs for combining bosentan and sildenafil are €50,000–55,000, compared to €75,000–80,000 for inhaled iloprost plus sildenafil and €115,000 for inhaled iloprost plus bosentan. In comparison, in Germany, the annual treatment costs for intravenous epoprostenol are €230,000 (at a dose of 25 $ng \cdot kg^{-1} \cdot min^{-1}$, which is a typical average dose in patients receiving epoprostenol for >1 yr [5, 6]) and those for intravenous iloprost are €180,000 (at a dose of 2 $ng \cdot kg^{-1} \cdot min^{-1}$, a typical average dose for intravenous iloprost [16]). Thus, when the clinical situation mandates combination treatment or the introduction of intravenous prostacyclin, the annual savings with the combination bosentan and sildenafil are >€100,000 for every patient, meaning that the approach in this study resulted in savings of >€1,000,000 just based on the nine patients described.

Despite these considerations, many open questions remain: it is unknown whether combination treatment is truly more efficient than single treatment (although theoretical reasoning clearly favours combination treatment, switching to sildenafil may have been equally effective as combining bosentan and sildenafil); it is unknown which combination regimens exert favourable long-term results (this will be difficult to answer as the number of potentially useful combinations is exponentially increasing with the introduction of novel treatments for PAH); and finally, so far, the combination of bosentan and sildenafil has only been used in patients with IPAH, and it is unknown whether these observations also apply to other forms of pulmonary hypertension.

In conclusion, the data presented here provide preliminary evidence that the combination of bosentan and sildenafil may be safe and effective in selected patients with idiopathic pulmonary arterial hypertension.

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