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Beraprost Therapy for Pulmonary Arterial Hypertension

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OBJECTIVES The purpose of this study was to assess the safety and efficacy of the oral prostacyclin analogue beraprost sodium during a 12-month double-blind, randomized, placebo-controlled trial in patients with pulmonary arterial hypertension (PAH).

BACKGROUND Pulmonary arterial hypertension is a progressive disease that ultimately causes right heart failure and death. Despite the risks from its delivery system, continuous intravenous epoprostenol remains the most efficacious treatment currently available.

METHODS A total of 116 patients with World Health Organization (WHO) functional class II or III primary pulmonary hypertension or PAH related to either collagen vascular diseases or congenital systemic to pulmonary shunts were enrolled. Patients were randomized to receive the maximal tolerated dose of beraprost sodium (median dose 120 μg four times a day) or placebo for 12 months. The primary end point was disease progression; i.e., death, transplantation, epoprostenol rescue, or >25% decrease in peak oxygen consumption (VO_2). Secondary end points included exercise capacity assessed by 6-min walk test and peak VO_2, Borg dyspnea score, hemodynamics, symptoms of PAH, and quality of life.

RESULTS Patients treated with beraprost exhibited less evidence of disease progression at six months ($p = 0.002$), but this effect was not evident at either shorter or longer follow-up intervals. Similarly, beraprost-treated patients had improved 6-min walk distance at 3 months by 22 m from baseline and at 6 months by 31 m ($p = 0.010$ and 0.016, respectively) compared with placebo, but not at either 9 or 12 months. Drug-related adverse events were common and were related to the disease and/or expected prostacyclin adverse events.

CONCLUSIONS These data suggest that beneficial effects may occur during early phases of treatment with beraprost in WHO functional class II or III patients but that this effect attenuates with time. (J Am Coll Cardiol 2003;41:2119–25) © 2003 by the American College of Cardiology Foundation

Despite recent therapeutic advances, pulmonary arterial hypertension (PAH) remains a life-threatening disorder (1–3). Continuous intravenous infusion of epoprostenol sodium (prostacyclin) improves exercise capacity, hemodynamics, and quality of life in patients with primary pulmonary hypertension (PPH) and in those with PAH related to collagen vascular diseases, congenital systemic to pulmonary shunts, or human immunodeficiency virus infection (4–12). In addition, improved survival with epoprostenol has been demonstrated in patients with severe PPH (4,5). Serious complications, however, are associated with the use of epoprostenol due in part to its short half-life (approximately 3 min) requiring a continuous intravenous infusion (4–7,12). Thus, alternative routes of delivery of prostacyclin are being investigated using stable prostacyclin analogues administered orally, subcutaneously, or by inhalation (13–19).

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Although beraprost sodium, a chemically stable and orally active prostacyclin analogue, has similar pharmacologic properties to epoprostenol, its half-life is significantly longer (20–26). Several uncontrolled studies in patients with PAH have reported improved exercise capacity, hemodynamics, and survival with chronic beraprost (13–15). Furthermore, a recently reported randomized, double-blind, placebo-controlled, multicenter study showed improved exercise endurance, i.e., 6-min walk distance, and symptoms after 12 weeks of beraprost treatment in World Health Organization (WHO) functional class II and III PAH patients (27),

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Abbreviations and Acronyms

PAH	= pulmonary arterial hypertension
PPH	= primary pulmonary hypertension
QID	= four times daily
VCO_2	= minute CO_2 output
V_E	= minute ventilation
V_E/VCO_2	= ventilatory equivalent for CO_2
VO_2	= oxygen consumption
WHO	= World Health Organization

i.e., treatment effect 25 m overall and 46 m in the subgroup of patients with PPH.

The current multicenter, double-blind, randomized, placebo-controlled study was designed to assess the effect of beraprost on disease progression over a 12-month treatment period in patients with WHO functional class II or III PAH, and to evaluate the effects of beraprost on exercise capacity, hemodynamics, signs and symptoms of PAH, and quality of life.

METHODS

Selection of patients. Patients eligible for this study were males or females over eight years of age with PAH in WHO functional classes II or III, including PPH, and PAH related to collagen vascular diseases or congenital systemic to pulmonary shunts, despite treatment with anticoagulant drugs, vasodilators (other than prostanoids or endothelin receptor antagonists), diuretics, cardiac glycosides, or supplemental oxygen. The inclusion criteria were a baseline peak oxygen consumption (VO_2) during exercise between 8 and 28 ml/kg/min determined during upright cycle ergometry (actual range for inclusion varied based on age and gender), a resting mean pulmonary artery pressure ≥25 mm Hg, with mean pulmonary capillary wedge pressure of ≤15 mm Hg and pulmonary vascular resistance >3 U. Patients were excluded if they had started or stopped any PAH therapy within one month before screening.

The study was conducted in accordance with Good Clinical Practices, the current version of the Declaration of Helsinki and with local institutional regulations. The local ethics review committee approved the protocol, and written informed consent was obtained from all patients.

Study design. The study was designed as a double-blind, randomized, placebo-controlled trial and was conducted in 10 centers in the U.S. All 116 patients were randomly assigned to receive one tablet (20 μg) of beraprost sodium or matching placebo (United Therapeutics Corporation, Research Triangle Park, North Carolina) four times daily (QID) with meals for the first two weeks, and the dose was increased by 20 μg or matching placebo QID with meals every two weeks, based on increasing signs, symptoms, and tolerability. The maximal dose allowed in the study was 200 μg QID. Side effects limiting dose increase were flushing, headache, jaw pain, and diarrhea. Patients were eligible for an open label continuation protocol with beraprost if they completed the month 12 visit or withdrew from the study because of a >25% decrease in peak VO_2 and were receiving placebo.

Outcome measures. Patients were evaluated at baseline and after 3, 6, 9, and 12 months of treatment with study drug. The primary efficacy measure was a combined end point of disease progression, defined as either the occurrence of death, transplantation, initiation of chronic intravenous epoprostenol or other chronic prostacyclin analogue therapy ("rescue therapy"), or a >25% decrease in peak VO_2 during exercise from baseline. The secondary measures of efficacy were the change from baseline to months 3, 6, 9, and 12 of exercise endurance (6-min walk distance), the Borg dyspnea score (a measure of perceived maximal breathlessness during the 6-min walk test on a scale of 0 to 10, with higher values indicating more severe dyspnea that is assessed immediately after completion of the 6-min walk test), exercise tolerance assessed by gas exchange (at rest and during exercise), signs and symptoms of PAH, and quality of life (global, physical, and emotional) as assessed by using the Minnesota Living with Heart Failure Questionnaire (28). Cardiopulmonary hemodynamics (at rest) were assessed at baseline and at the end of study assessment for patients who completed the study. Safety was assessed on the basis of recorded adverse events, laboratory measures, and electrocardiography.

Patients underwent cardiopulmonary testing on an upright cycle ergometer (to maximum tolerated exercise level). Gas exchange measurements were obtained throughout the baseline rest, exercise, and early recovery periods. With the patient in the upright position, while breathing room air through a low deadspace mask, minute ventilation, exhaled gas composition, systemic arterial blood pressure, and heart rate were continuously measured. The arterial pressures, heart rate, and gas exchange were recorded on a strip chart recorder and a computer. Peak VO_2, anaerobic threshold, peak O_2 pulse (VO_2/heart rate), and the aerobic response to the imposed work rate (VO_2/work rate) were determined. In addition, the ventilatory equivalent for CO_2 was determined (V_E/VCO_2, where V_E = minute ventilation and VCO_2 = minute CO_2 output). The peak VO_2 data were calculated from mean values from two separate cycle ergometry tests performed within seven days of each other at each assessment period. The cycle ergometry and 6-min walk tests were administered by a trained tester not involved in the patient's daily care and unaware of the patient's treatment assignment.

Statistical analysis. The data were retained and analyzed by the sponsor, United Therapeutics Corporation. The sample size was estimated under the assumptions of a two-sided alpha probability of 0.05, 80% power, and a relative reduction of 50% in disease progression in the beraprost group progression from a 50% incidence in the placebo group (i.e., 50% to 25% incidence from the placebo to beraprost treatment groups). Under these conditions, the study's 1:1 randomization required a sample size of 116 patients (58 per group).

Analysis was performed in the intent to treat population that included all patients who were randomized and received at least one dose of study drug. Data are presented as either medians or mean ± SEM. A value of $p < 0.05$ was considered statistically significant.

At the time of this study, the sponsor was also conducting a study of beraprost in patients with intermittent claudication. The claudication study was unblinded, and beraprost was shown to provide no benefit to patients with claudication, relative to placebo. Given the lack of efficacy and concerns of equipoise, a decision was made by the sponsor to terminate this study early to accelerate data review so as not to withhold other PAH therapies with proven efficacy. Because of the accelerated data review, changes from baseline to month 9 were used as the primary analysis for all efficacy measures. Patients may not have completed the study through the month 9 assessment for the following reasons: death, transplantation, clinical deterioration requiring rescue therapy, decrease of more than 25% from baseline in peak VO_2, withdrawal of consent, adverse event (other than that related to clinical deterioration of PAH), protocol violation, or lost to follow-up.

Patients who discontinued as a result of death, transplantation, rescue therapy owing to clinical deterioration, a decrease in peak VO_2 by more than 25% from baseline, or who were too critically ill to complete their final exercise assessment were analyzed as treatment failures. For the primary end point, these events were counted as disease progression events at the time of their discontinuation. For secondary efficacy end points, worst rank was assigned for nonparametric analyses, and a value corresponding to the worst relative change from baseline observed among all non-missing observations was assigned for parametric analyses.

Patients who discontinued or had missing assessments for any other reason, i.e., discontinuation due to withdrawal of consent, adverse event, protocol violation, or lost to follow-up, were censored at the time of discontinuation and were assigned a last rank carried forward value for nonparametric analyses of the efficacy end points.

The primary end point was compared between treatment groups using the Fisher exact test. Exercise capacity end points were compared between treatment groups using nonparametric analysis of covariance, adjusting for center, PAH etiology, and baseline peak VO_2, 6-min walk distance, Borg dyspnea score, and vasodilator use. Changes from baseline in hemodynamic parameters were compared between treatment groups using parametric analysis of covariance, adjusting for baseline value. For all efficacy end points, the effects of covariates on the treatment effect, i.e., treatment interactions, were further tested using logistic regression or parametric analysis of covariance. Covariates included disease etiology, age, gender, race, and WHO class, peak VO_2 during exercise, walk distance, Borg score, duration of disease, and vasodilator at baseline.

Table 1. Demographic Characteristics at Baseline

Characteristic	BPS (n = 60)	Placebo (n = 56)
Age (yrs)	42 ± 2	42 ± 2
Race		
White	73%	75%
Hispanic	10%	13%
African origin	7%	7%
Gender		
Female	87%	84%
PAH		
PPH	78%	70%
PAH–collagen vascular diseases	10%	11%
PAH–congenital systemic to pulmonary shunts	12%	20%
WHO		
Class II	55%	50%
Class III	45%	50%
Exercise		
Exercise endurance–6-min walk (m)	433 ± 11	445 ± 10
Exercise tolerance–peak VO_2 (ml/min)	955 ± 48	892 ± 40
Hemodynamics		
RAPm (mm Hg)	8.3 ± 0.7	8.8 ± 0.6
PAPm (mm Hg)	56 ± 2	55 ± 2
PCWPm (mm Hg)	9 ± 0.4	9 ± 0.5
CI (l/min/m^2)	2.7 ± 0.1	2.4 ± 0.1
PVRI (U·m^2)	21 ± 2	21 ± 2
SBP (mm Hg)	120 ± 2	119 ± 2
SvO_2 (%)	61 ± 2	64 ± 2
HR (beats/min)	78 ± 1	79 ± 2

Values are mean ± SEM.

BPS = beraprost sodium; CI = cardiac index; HR = heart rate; PAH = pulmonary arterial hypertension; PAPm = mean pulmonary artery pressure; PCWPm = mean pulmonary capillary wedge pressure; PPH = primary pulmonary hypertension; PVRI = pulmonary vascular resistance index; RAPm = mean right atrial pressure; SBP = systolic systemic arterial pressure; SvO_2 = mixed venous oxygen saturation; VO_2 = oxygen consumption; WHO = World Health Organization.

RESULTS

A total of 116 patients were included in this study: 60 received beraprost and 56 received placebo. The study was prematurely terminated by the sponsor to accelerate assessment of the study results. Fifty-six patients (93%) on beraprost and 52 patients (93%) on placebo were included in the 12-month evaluation; and 116 patients (100%) were included in the 9-month evaluation per protocol. At the end of 3, 6, 9, and 12 months, the mean dose of drug was 71 ± 3 μg (n = 60), 92 ± 4 μg (n = 57), 98 ± 6 μg (n = 49), and 107 ± 7 μg (n = 38), respectively, QID in the beraprost group, and 83 ± 4 μg (n = 53), 104 ± 4 μg (n = 47), 117 ± 4 μg (n = 43), and 122 ± 6 μg (n = 31), respectively, QID in the placebo group.

Baseline characteristics. The placebo and beraprost groups were well matched with respect to demographic and baseline characteristics. The groups did not differ significantly in PAH etiology, WHO class, peak VO_2 during exercise, 6-min walk distance, or severity of hemodynamics (Table 1).

Disease progression. Patients treated with beraprost exhibited less evidence of disease progression at six months ($p = 0.002$). This effect was not evident at either shorter or

Table 2. Cumulative Incidence of Disease Progression

	BPS	Placebo	p Value*
Month 3	0/60	3/56	0.109 (NS)
Death	0	0	
Rescue	0	2	
↓ VO_2	0	1	
Month 6	1/60	11/56	0.002
Death	0	2	
Rescue	1	6	
↓ VO_2	0	3	
Month 9	8/60	15/56	0.102 (NS)
Death	1	2	
Rescue	4	7	
↓ VO_2	3	6	
Month 12	10/56	15/52	0.254 (NS)
Death	1	2	
Rescue	5	7	
↓ VO_2	4	6	

*Fisher exact test.
BPS = beraprost sodium; VO_2 = oxygen consumption.

longer follow-up intervals, although each component of this end point occurred more frequently in the placebo group than in the beraprost group throughout the study (Table 2). Covariate analyses did not demonstrate any evidence of treatment interactions.

Exercise capacity. CYCLE ERGOMETRY (EXERCISE TOLERANCE). The peak VO_2 during exercise at baseline and the median change in peak VO_2 during exercise at 3, 6, 9, and 12 months for the beraprost group and the placebo group are shown in Table 3. Although the treatment effect did not reach statistical significance at any time point, the direction of change in the beraprost- versus placebo-treated patients was in favor of beraprost and supportive of both the disease progression data and the 6-min walk data. There was no evidence of any treatment interactions when the effects of covariates were assessed in the peak VO_2 analyses.

6-MIN WALK TEST (EXERCISE ENDURANCE). The median changes in distance walked in 6 min after 3, 6, 9, and 12 months in the beraprost group compared with the placebo group are shown in Figure 1. The beraprost group walked significantly further than the placebo group at month 3 and 6 ($p = 0.010$ and $p = 0.016$, respectively), but the difference in 6-min walk was not significant at either month 9 or 12 ($p = 0.098$ and 0.180, respectively). The median difference (Hodges-Lehmann estimate) in 6-min walk was 22, 31, 25, and 23 m at month 3, 6, 9, and 12, respectively. From analyses of the effects of covariates on the 6-min walk distance results, evidence of treatment interaction was remarkable in that patients with a shorter duration of PAH had a larger treatment effect at month 3 ($p = 0.012$), and patients who had higher baseline Borg scores had a larger treatment effect at month 9 ($p = 0.022$).

For both the peak VO_2 and 6-min walk data, the outcome within the beraprost-treated patients did not depend on the dose of beraprost with respect to the end points assessed in this study.

Signs and symptoms. Borg dyspnea score was not significantly improved at any time point (Fig. 2). Dyspnea-Fatigue Rating and composite Signs and Symptoms change score were similarly unaffected (data not shown).

WHO functional class. At baseline, 55% of the beraprost-treated patients and 50% of the placebo patients were class II, with 45% of the beraprost and 50% of the placebo patients class III. The majority of patients had no change in WHO class over the course of the study, and although there was no meaningful difference in the percentage of patients who improved on beraprost compared with placebo treatment during the 12-month study (Table 4), more of the placebo patients worsened over the duration of the study compared with the beraprost patients. Composite changes in WHO class were significantly different in the beraprost group at month 6 but not at other intervals.

Hemodynamics. The changes in hemodynamic measures from baseline to month 12 are shown in Table 5. No imputation was employed for missing data due to disease progression or other reason for premature discontinuation. The beraprost- and placebo-treated patients had small variations in hemodynamic parameters, and no statistically significant changes were detected.

Quality of life. Treatment with beraprost did not result in significant improvement relative to placebo in global, physical, or emotional indices of quality of life (data not shown).

Safety and tolerability. The most frequent adverse events in both treatment groups are shown in Table 6. Adverse events characteristic of prostanoid effects, such as headache, jaw pain, vasodilation (flushing), nausea, diarrhea, leg pain, and foot pain were more common in patients treated with beraprost. Palpitations were also significantly more common in the beraprost group. Two patients (3%) in the beraprost group (one before month 9 and one before month 12) withdrew prematurely from the study owing to nausea. No patients in the placebo group withdrew prematurely as a result of adverse events. No clinically meaningful adverse changes in hematologic or biochemical variables were seen in the beraprost group. Serious adverse events (fatal, life-threatening, or events requiring hospitalization) were more common in the placebo group (25% of patients) than in the beraprost group (18%) and were typical events (e.g., chest pain, syncope) for this population of patients.

Table 3. Peak VO_2 Changes from Baseline Through Month 12

	Beraprost	Placebo	Median Difference*	p Value†
Baseline	878 ml/min	777 ml/min	—	—
Month 3	−3.8 (n = 60)	−36.3 (n = 55)	35.4	0.125 (NS)
Month 6	−5.8 (n = 60)	−54.3 (n = 56)	39.6	0.204 (NS)
Month 9	−39.7 (n = 60)	−108 (n = 56)	57.0	0.160 (NS)
Month 12	−68.8 (n = 52)	−156 (n = 47)	66.0	0.084 (NS)

Median at baseline and median change from baseline. *Hodges-Lehmann estimate. †Nonparametric analysis of covariance, adjusted for center, etiology of pulmonary arterial hypertension, and baseline peak oxygen consumption (VO_2) 6-min walk distance, Borg dyspnea score, and vasodilator use.

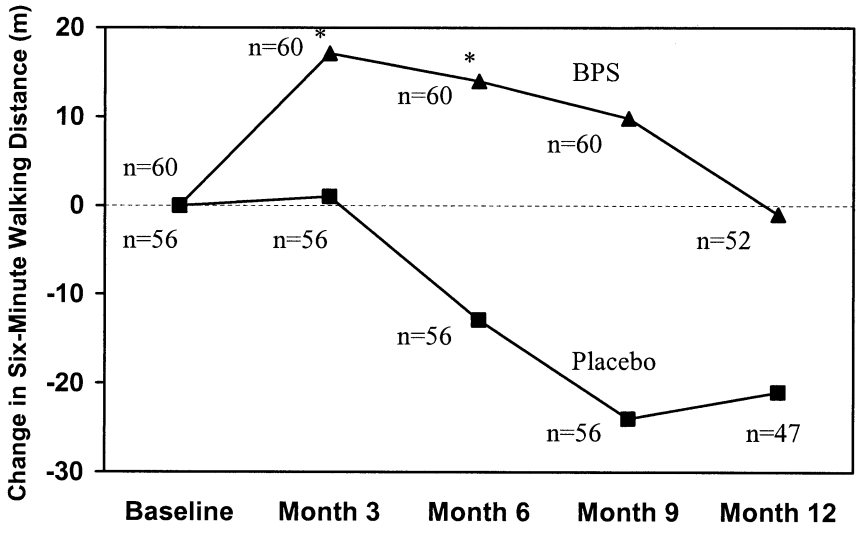

Figure 1. Median change in 6-min walking distance from baseline to months 3, 6, 9, and 12 in the placebo and beraprost sodium (BPS) groups; p = 0.010 at 3 months; p = 0.016 at 6 months; p = 0.098 at 9 months; and p = 0.180 at 12 months (adjusted for center, etiology, and baseline peak oxygen consumption, 6-min walk, Borg dyspnea score, and vasodilator use). Worst rank for all missing data.

DISCUSSION

This double-blind, placebo-controlled study is the longest controlled trial ever conducted in patients with PAH. Originally planned for 12 months, the study was terminated once all patients had completed 9 months of double-blind therapy to accelerate data review. Although terminated early, data were available for 93% of patients through 12 months of therapy. Patients treated with beraprost exhibited less evidence of disease progression at 6 months, but this effect was not evident at either shorter or longer follow-up intervals. Similarly, beraprost-treated patients had improved 6-min walk distances at 3 and 6 months compared with placebo, but not at either 9 or 12 months. The earlier time point data are consistent with the findings of the recently published Arterial Pulmonary Hypertension and Beraprost European Trial (ALPHABET) Study (27) which demonstrated that beraprost treatment for three months improved exercise capacity in patients with PAH, particularly PPH patients. However, unlike the ALPHABET Study, this study did not demonstrate a relationship between etiology (e.g., PPH vs. PAH related to other conditions) and effect on exercise, nor did this study confirm the symptomatic

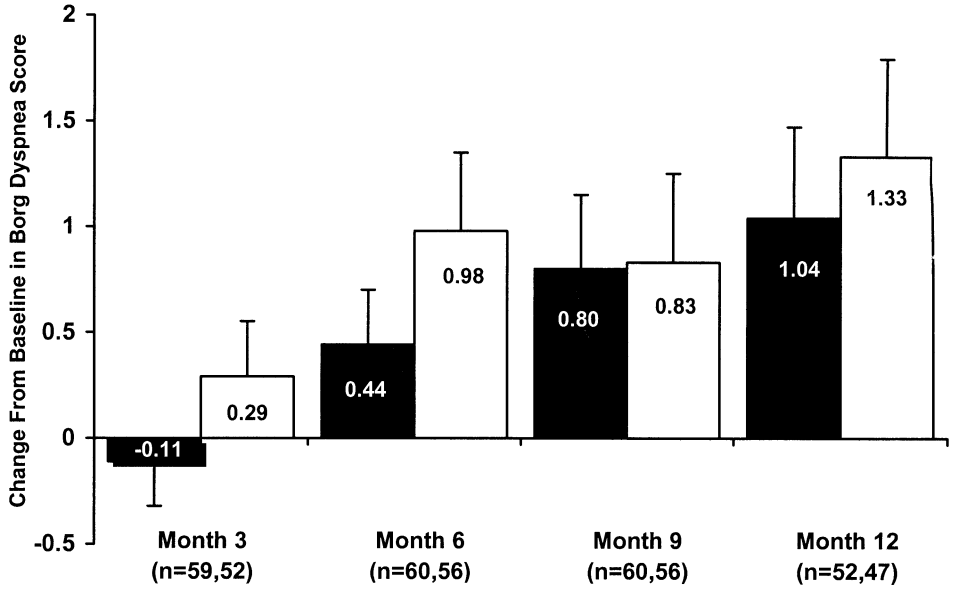

Figure 2. Mean change in Borg dyspnea score from baseline to months 3, 6, 9, and 12 in the placebo and beraprost sodium (BPS) groups; p = 0.24 at 3 months; p = 0.27 at 6 months; p = 0.92 at 9 months; and p = 0.75 at 12 months (analysis of covariance adjusted for center, etiology, and baseline peak oxygen consumption, 6-min walk distance, Borg dyspnea score, and vasodilator use). **Black bars** = BPS; **white bars** = placebo. **Number in the bars** = exact mean rates; **lines** = standard error of the mean.

Table 4. WHO Functional Class Changes (Percent) From Baseline Through Month 12

	Beraprost	Placebo	p Value*
Month 3			0.094 (NS)
Improved	10	11	
No change	88	73	
Worse	2	16	
Month 6			0.039
Improved	15	9	
No change	73	63	
Worse	12	29	
Month 9			0.804 (NS)
Improved	8	13	
No change	65	57	
Worse	27	30	
Month 12			0.155 (NS)
Improved	10	11	
No change	65	49	
Worse	25	40	

*Wilcoxon rank-sum test; drop-outs due to "disease progression" treated as "worse". WHO = World Health Organization.

improvement in Borg dyspnea score. It is possible that population differences explain these discordant findings as, e.g., patients in the ALPHABET Study had a lower mean baseline 6-min walk than patients in this study (approximately 370 m vs. approximately 440 m).

The results at early time points of this study are similar to the results of Bosentan Randomized Trial of Endothelin Antagonist Therapy (BREATHE)-1 (29) in which the orally active dual endothelin receptor antagonist bosentan (at the labeled dose of 125 μg twice daily) was compared with placebo over 16 weeks of therapy. As in the present study, patients treated with active drug exhibited similar improvement in 6-min walk (placebo-corrected mean difference of 35 m) and in the composite end point of "time to clinical worsening" (defined as either the occurrence of death, transplantation, initiation of chronic intravenous epoprostenol rescue therapy, or hospitalization for PAH, $p = 0.01$), but no significant improvement in Borg dyspnea score ($p = 0.42$).

The data in the present trial suggest that the early beneficial effects on disease progression and exercise characteristics that may be observed with beraprost attenuate with more prolonged exposure. It is possible that this waning of effect may relate to a number of factors, including: 1) inability to dose-escalate to maximal effects because of intolerance to common side effects such as nausea, headache, and/or dizziness; 2) lower potency of beraprost relative to epoprostenol or other prostacyclin analogues; or 3) a suboptimal dose regimen relative to the elimination half-life of beraprost (QID dosing with a half-life of only approximately 1 h).

An important observation from this trial is that longer controlled studies may be needed to evaluate the chronic effects of therapeutic agents currently being used to treat PAH (16,19,29) as well as for PAH therapies under clinical investigation. This is particularly important given that "surrogate" measures of efficacy, such as 6-min walk test over three to four months of therapy, comprise the standard historical evaluation that has been employed in clinical trials to date for investigational agents in PAH. Only epoprostenol therapy has improved a non-surrogate end point, i.e., survival (4). It is possible that some treatment modalities, such as chronic intravenous epoprostenol therapy, may produce sustained benefit (possibly via pulmonary vascular remodeling), whereas other therapies may yield only a small or transient benefit that rapidly wanes with time. Although even a short-term benefit may be desirable in patients with

Table 6. Most Frequent Adverse Events in the BPS and Placebo Groups

Event	BPS (n = 60)	Placebo (n = 56)	p Value
Headache	73%	57%	0.05
Jaw pain	57%	20%	<0.0001
Vasodilatation	57%	27%	0.001
Nausea	47%	34%	NS
Diarrhea	45%	27%	0.03
Dizziness	23%	30%	NS
Pharyngitis	22%	30%	NS
Abdominal pain	17%	20%	NS
Chest pain	17%	16%	NS
Asthenia	22%	7%	0.02
Other pain	27%	21%	NS
Leg pain	18%	7%	NS
Sinusitis	8%	18%	NS
Back pain	13%	11%	NS
Depression	13%	11%	NS
Peripheral edema	13%	9%	NS
Foot pain	13%	4%	NS
Palpitations	12%	0%	0.008
Syncope	5%	14%	NS

BPS = beraprost sodium.

Table 5. Hemodynamic Changes (Mean) From Baseline to Month 12

	BPS	Placebo	p Value*
RAPm (mm Hg)	+0 ± 1 (n = 38)	+1 ± 1 (n = 28)	0.992 (NS)
PAPm (mm Hg)	+1 ± 1 (n = 38)	+2 ± 2 (n = 28)	0.664 (NS)
CI (l/min/m^2)	+0.1 ± 0.1 (n = 35)	+0.1 ± 0.2 (n = 27)	0.875 (NS)
PVRI (mm Hg/l/min/m^2)	+1.1 ± 0.9 (n = 34)	+2.5 ± 0.9 (n = 27)	0.253 (NS)
SvO_2 (%)	+2 ± 3 (n = 36)	−3 ± 3 (n = 27)	0.424 (NS)
SBP (mm Hg)	+1 ± 3 (n = 37)	+5 ± 3 (n = 28)	0.360 (NS)
HR (beats/min)	+1 ± 1 (n = 38)	−1 ± 2 (n = 28)	0.623 (NS)

Values are mean ± SEM. *Analysis of covariance, adjusted for baseline value. Abbreviations as in Table 1.

advanced disease, considerations of risk, side effects, and expense must be addressed when assessing the clinical utility of various agents to treat PAH.

CONCLUSIONS

In patients with PAH, beraprost increased time to disease progression at six months, and improved exercise endurance compared with placebo at three and six months. However, these effects dissipated at 9 and 12 months of therapy and were not associated with detectable benefit in symptomatic status or quality of life as measured by standardized instruments, nor with hemodynamic improvement. Because of the potential convenience, relative safety, and economy of an oral prostacyclin analogue, the quest for an effective agent, particularly with an extended half-life, i.e., at least 4 h, remains a high priority. However, based on the data from this study, longer studies may be needed to evaluate overall risk:benefit considerations for many of the currently used therapeutic agents in the treatment of PAH; these long-term data are needed for safety as well as efficacy.

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