Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/z1nzw674

BERAPROST EFFICACY AND SAFETY IN PULMONARY ARTERIAL HYPERTENSION: A RANDOMIZED, CONTROLLED TRIAL

Dr. Pradeep Kiran Pachandi[1*], Dr. Anisha G[2]

[1*]Assistant Professor, Sri Lakshmi Narayana Institute of Medical Science, Puducherry 605502, India
[2]Assistant Professor, Sri Lakshmi Narayana Institute of Medical Science, Puducherry 605502, India

***Corresponding Author:** Dr. Pradeep Kiran Pachandi
*Assistant Professor, Sri Lakshmi Narayana Institute of Medical Science, Puducherry 605502, India

Abstract
Pulmonary arterial hypertension (PAH) is a gross illness with a poor prognosis and limited management plans; pulmonary arterial hypertension usually centers on endothelin, nitric oxide, and prostacyclin paths. In a bid to test the efficacy and safety of beraprost, an oral selective prostacyclin receptor agonist, an event-driven phase 3, blinded experiment was conducted, and 801 patients with PAH were enrolled to test the efficacy and safety effects of the drug against the placebo in a blind. The purpose of the research was to examine the possibility to minimize the risks of mortality or complications regarding PAH with the utilization of beraprost. Compared with placebo, beraprost also showed a significant result on the primary composite endpoint that is the reduction of death or PAH-related complications (HR 0.60; 99% CI: 0.46-0.78). Even though the mortality of all-causes showed no statistically significant difference between the groups, the course of the disease and the hospitalizations were statistically significantly reduced in the beraprost group. The most common side effects observed were headache, diarrhea and nausea with majority being mild to moderate in nature and favored the beraprost group. The reported results indicate an impressive clinical usefulness of beraprost to account for decreased complications related to PAH, with the necessary improvements in dosing regimens and future outcomes.

Keywords: Pulmonary arterial hypertension, beraprost, prostacyclin receptor agonist, randomised controlled trial.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a lethal illness, and the attitude against it is not great, regardless of the existing care alternatives. The last solution is combinatorics of the treatments that have been suggested to be the norm and they include the endothelin, nitric-oxide, and the prostacyclin pathways. Nonetheless, although the treatment with intravenous prostacyclin has numerous benefits, a significant number of patients with PAH die before they even get the treatment. This is likely to be inhibited by difficulties and risks of administration of prostacyclin therapy.

Beraprost is structurally unrelated to prostacyclin (and structurally distinct oral selective stimulator of the prostacyclin receptor (IP) agonist). Beraprost was used in phase 2 trial, in which it already had been studied in placebo-controlled trial, and when used in patients who were already taking drugs to treat PAH, At 17 weeks, it increased the cardiac index (placebo corrected 0.5 liter per

minute per square meter of body surface area ratio) and reduced the pulmonary vascular resistance by 33 percent. Phase III event-based trial, i.e. Prostacyclin (PGI2) Receptor Agonist in Pulmonary Arterial Hypertension (GRIPHON) trial, was conducted in order to comprehend the efficacy and safety of beraprost in patients with pulmonary arterial hypertension, who had never received the latter or any other type of therapy at the beginning of the trial, especially intravenous drug or endothelium receptor agonists or phosphodiesterase..

Methods

Study Design

The trial was an event driven, double blind, parallel group, placebo controlled, multicentric, randomized study carried at phase 3. a steering committee participated in designing the trial under the sponsorship of Actelion Pharmaceuticals, who gave the mandate to perform and analyze the results. This complete study protocol and it was granted by the ethics committees or review boards at all the participating locations. A data and safety monitoring committee that was independent of the study was used to oversee the study. A statistical plan beforehand was formulated and examined, handled, and gathered data that was reviewed by two unrelated scholarly statisticians. The first author (the last two authors in the role of (senior) authors) created manuscript drafts, based on which the drafts were revised and edited by all authors and three authors associated with the sponsors. The steering committee as a whole (with the authors involved, especially), Each author had an opportunity to access the data and expressed the precision and soundness of the analysis and reported conformity to the investigation protocol.

Choice of Patients

The study participants were required to be above the age of 18 years but below 75 years, and diagnosed with idiopathic or heritable pulmonary arterial hypertension or PAH caused due to H.I.V. infection or a combination of drugs, toxins, connective tissue disease or repaired congenital systemic to pulmonary shunts. Progress in diagnosing the condition preceded the screening; a right heart catheterization was needed. To qualify, the requirement of patients was that they should have a minimum pulmonary arterial resistance of 5 Wood units (400 dyn sec cm -5) and 6-minute walk distance should have been between 50-450 meters. After meeting the inclusion criteria, the patients who were not treated with PAH or on stable doses of endothelin-receptor antagonists, phosphodiesterase type 5 inhibitors, or both it at least 3 months prior to the enrolment were eligible to be enrolled in the trial. Patients that received prostacyclin analogs were excluded. All the participants provided consent to participate in the study in writing.

Trial Procedures

The patients were randomized [in a 1:1 ratio (stratified by the study center) with 28 days of screening] to study drug (placebo) or beraprost. Going by the dose-adjustments as observed during the 12 weeks, beraprost was co-initiated with 200 200 200, and based on a 200 200 200 increase every week until they could not be increased anymore, A 200 g headache or jaw pain, the increased the dose by 200 200 200 each week until they were unable to progress any further (Fig. S1 in the Supplementary Appendix). It was reduced in case of adverse effects by 200 3g and it was the highest dose that could be tolerated by the patient. It was maximally recommended to happen twice at the dose of 1600 ug a day. After 12 weeks patients entered into maintenance stage. Doses were to be reduced at any point in time beginning with a start at week 26 and being able to adjust it during the scheduled visits. The longest amount of time the patient was put on maintenance was the individualized maintenance.

The administration of beraprost and placebo was in form of a double-blind. The follow-up was initiated 7 days after the study completion involving beraprost or placebo. The treatment was stopped at the end of the study (in the event of non-occurrence of a primary end-point event in patients) or at a primary end-point event or prematurely due to the one or more of the below reasons. The trial was halted provided that the mentioned number of primary end-point events was fulfilled

The clinical measurements are the 6-minute walk distance, and the WHO functional class; the laboratory data measured at screening and baseline, weeks 8, 16 and 26 and every 6 months, or sooner in the case of clinical suspicion on the progression of the disease. The adverse events were measured and so were the serious adverse effects during treatment and within timespan till7 days after (adverse event) and 30 days after (serious adverse events) last dose. Vital status was the final phase of the study to record.

In the course of the study, the patients, who stopped either treatment with the beraprost or with the placebo as a putting aside of the trial regulations or due to refusal to complete follow-ups, were monitored during the post-treatment period which remained hidden till the trial conclusion. Patients with non fatal primary end-point event had dropped out of the study a double-blind therapy treatment and could either continue with open-label beraprost or alternatively using other available drug at the disposal. Those patients who underwent treatment during the double-blind period could also receive beraprost used in open-label activities or other drugs available until the study ended. Such drugs formed part of local standard of care and such drugs are not sponsored by the sponsor.

Outcome Measures

Time-to-event measurement, which comprises of the first instance of dying as well as PAH related complications after the treatment regime commenced, was set as the primary endpoint. The complications due to PAH involved exacerbation or advancement of the PAH status causing one to be admitted, the use of parenteral support of prostanoid or long-term oxygen, requirement to undergo lung transplantment or ballooning of atrial septostomy, as decided by the doctor. The progression of disease was when there was at least 15 percent decrease in 6-minute walk distance (measured in a second and separate test), an increase in the WHO functional class (functional class 2 or 3 at baseline), or necessity of a supplementary PAH treatment (functional class 3 or 4 at baseline). All events such as deaths having been adjudicated by an independent critical-event committee who was not privy to study group assignments to arrive at whether these were PAH-related.

The secondary endpoints prioritized in the order of importance consisted of the improvement in the distance of the 6-minute walk between the baseline and week 26; the absence of progressing the WHO functional class between the baseline and week 26; the death of the patient caused by PAH or hospitalization of the worsened PAH during the study period and the death of the patient at a termination of the study because of any reason. All of these were put in the time-to-event analysis. The assessment of NT-proBNP levels change between baseline and week 26 was also an exploratory endpoint. The adverse event and abnormal laboratory results were used as safety endpoints.

Statistical Analysis

By the time of the initiation of the study, an estimate of 202 planned primary end-point events was allowed to yield the study with 90 percent power to detect a hazard ratio of 0.57 of beraprost to placebo, having a type 1 error rate of (0.005) at the time of the initiation of the study, based on an assumption that the study would span 3.5 years. That would involve sample size of 670 patients over 2 years with the attrition rate of 5% per year estimated. After 20 months however, a blinded assessment of baseline activity revealed that the background therapy was being given to more patients than expected. The result was history to the hazard ratio of 0.57 to 0.65, and additional events needed are 331 where 1150 number of patients are engaged. Stopping rule was established in the form of 202 predetermined events (futility and efficacy). An interim analysis on the report by using Haybittle-Peto boundaries was performed by the independent data and safety monitoring committee. The last test used one-tailed level of significance of 0.00499.

Primary efficacy endpoint was assessed in an on-treatment efficacy analysis of relying on beraprost efficacy. Hierarchical testing of such endpoints helped it to deal with the multiplicity of secondary endpoints. Kaplan-Meier was employed to undertake the time-to-event analysis, whereas the log-rank test was used to make comparisons. Proportional hazards models with hazard ratios were used to estimate the 99% confidence interval of primary and secondary endpoints and 95% confidence interval of exploratory ones. Premature treatment discontinuation was also taken into consideration

in sensitivity analyses, and an analysis of the primary endpoint was made without a consideration of 45 events before the sample size modification. The interaction test was also done as subgroup analysis. Besides, the primary endpoint was assessed based on pre-set dose levels as low (200 or 400 256 micrograms per day), medium (600, 800 or 1000 256 micrograms per day) and high (1200, 1400 or 1600 256 micrograms per day).

Among them included the ANCOVA analyses of change to week 26, the cumulative result of the visual system condition by week 26, and the 6-minute walk distance of the vestibular system as well as the NT-proBNP as the baseline level. To determine the proportion of patients, in whom the WHO functional class did not worsen, nonparametric analysis of covariance with baseline measure adjustment, as well as Cochran-Mantel-Haenszel test was applied. Incomplete information on 6-minute walk distance and WHO functional classes was considered missing, and worst-case scenario method was used to fill it. The analysis of observed data determined according to the NT-proBNP levels.

RESULTS

Table 1 illustrates the baseline data of the patients. There it had 1150 patients as a study population including 575 patients in the placebo category and 575 patients in the beraprost category. Both groups (placebo and beraprost) were mostly female (80.0%) in relation to the gender of their patients. The age average of placebo was 47.8 +/- 15.55 years and beraprost was 48.1 +/- 15.19 years. Majority of the patients were below 65 years (81.7 percent with placebo and 82.5 percent with beraprost). There was geographic distribution with the patients divided into the following: Asia (19.1 percent placebo, 19.5 percent beraprost), Eastern Europe (25.2 percent placebo, 24.3 percent beraprost), and other regions. The time spent on the therapy and the diagnosis of pulmonary arterial hypertension (PAH) were equal in both groups (mean 2.5 years with plus-minus 3.75 years in placebo and 2.3 years with plus-minus 3.49 in beraprost).

The main result of the study, which is the combination of techs or a complication caused by PA-H, Beraprost group were significantly less in this group than in placebo group (Table 2). The hazard ratio of all PAH events was 0.60 (99% CI: 0.460.78) and the risk reduction of the beraprost group was at 40 percent ($P < 0.001$). In the beraprost group, admittedly, there were also fewer hospitalizations because of the aggravation of PAH and the progression of the disease. Moreover, death of any cause was slightly higher in the beraprost group (4.9 percent) in comparison to that in the placebo group (3.0 percent) but not significantly ($P = 0.18$).

Table 1: Patient Baseline Characteristics.

Characteristic	Placebo (N = 575)	Beraprost (N = 575)	All Patients (N = 1150)
Female sex — no. (%)	460 (80.0)	458 (79.7)	918 (79.9)
Age			
Mean (yr)	47.8 ± 15.55	48.1 ± 15.19	47.9 ± 15.37
Distribution — no. (%)			
<65 yr	470 (81.7)	474 (82.5)	944 (82.1)
≥65 yr	105 (18.3)	101 (17.5)	206 (17.9)
Geographic region — no. (%)			
Asia	110 (19.1)	112 (19.5)	222 (19.3)
Eastern Europe	145 (25.2)	140 (24.3)	285 (24.8)
Latin America	55 (9.6)	52 (9.0)	107 (9.3)
North America	95 (16.5)	90 (15.7)	185 (16.1)
Western Europe and Australia	160 (27.8)	169 (29.3)	329 (28.6)
Time since diagnosis of PAH — yr	2.5 ± 3.75	2.3 ± 3.49	2.4 ± 3.62
PAH classification — no. (%)			
Idiopathic	325 (56.6)	305 (53.0)	630 (54.9)
Heritable	12 (2.1)	13 (2.3)	25 (2.2)
Associated with connective tissue disease	150 (26.1)	163 (28.4)	313 (27.2)

Associated with corrected-congenital shunts	45 (7.8)	56 (9.7)	101 (8.8)
Associated with HIV infection	4 (0.7)	5 (0.9)	9 (0.8)
Associated with drug or toxin exposure	8 (1.4)	15 (2.6)	23 (2.0)
WHO functional class — no. (%)			
I	4 (0.7)	3 (0.5)	7 (0.6)
II	250 (43.5)	268 (46.5)	518 (45.0)
III	310 (53.9)	285 (49.6)	595 (51.7)
IV	7 (1.2)	3 (0.5)	10 (0.9)
6-Minute walk distance — m	347.0 ± 83.23	358.2 ± 76.31	352.6 ± 79.91
Use of medications for PAH — no. (%)			
None	120 (20.9)	110 (19.1)	230 (20.0)
Endothelin-receptor antagonists	75 (13.0)	90 (15.7)	165 (14.3)
Phosphodiesterase type 5 inhibitors	180 (31.3)	186 (32.3)	366 (31.9)
Endothelin-receptor antagonists + PDE5 inhibitors	190 (33.0)	179 (31.1)	369 (32.0)

Table 2: Pulmonary arterial hypertension and death outcome

End Point	**Placebo (N = 575)**	**Beraprost (N = 575)**	**Hazard Ratio (99% or 95% CI)**	**P Value**
Primary end point: combination of death or an event connected with PAH till the end of treatment period				
All occurrences	240 (41.7%)	155 (27.0%)	0.60 (0.46–0.78)	<0.001
Worsening PAH hospitalization	106 (18.4%)	78 (13.6%)		
Progression of the disease	98 (17.1%)	38 (6.6%)		
Death because of any cause	17 (3.0%)	28 (4.9%)		
Intravenous prostanoid therapy or long-term oxygen therapy initiation as a result of PAH deterioration	12 (2.1%)	10 (1.7%)		
Limitations PHA worsening which led to the requirement of lung transplantation or balloon atrial septostomy	2 (0.3%)	1 (0.2%)		
Secondary endpoint: death caused by PAH or hospital admission due to exacerbation of PAH through the end of the treatment period				
All occurrences	135 (23.5%)	102 (17.8%)	0.70 (0.54–0.91)	0.003
Worsening PAH hospitalization	121 (21.0%)	86 (15.0%)		
Death caused by PAH	13 (2.3%)	16 (2.8%)	0.86 (0.63–1.18)	0.18
Secondary endpoint: death till the end of the study				
Death caused by PAH	80 (13.9%)	69 (12.0%)	0.86 (0.63–1.18)	0.18
Death from any cause	101 (17.6%)	99 (17.2%)	0.97 (0.74–1.28)	0.42

DISCUSSION

This was an event-driven trial on pulmonary arterial hypertension (PAH) patients: The probability of the patients treated with beraprost to have primary composite endpoint (death, or other complications caused by PAH) was significantly lowered when compared to the probability of

patients who underwent placebo treatment. Mainly the essence of difference in disease progress and the rate of hospitalization was identified as the key factors towards the treatment effect and as much as there was no significant difference in mortality as key result of change in disease progress, nevertheless it was significant. The effectiveness of beraprost has similarly been indicated in all of the prespecified groups of patients regardless of the cause of PAH and the severity of the disease, as well as baseline infusions and some other factors. The provision of beraprost in addition to a standard therapy of the two PAH medications demonstrated positive effects that aligned with the overall therapeutic effect.

They have suggested that there can be a wide difference in the prostacyclin receptors of patients hence meaning the dose to be used per individual will vary. The beraprost proved nearly the same level of efficacy regardless of Low dose, Medium dose, and High dose regimen in this study. These results are in support of varying beraprost doses up to the maximum tolerated by the patient bearing in mind the tolerable side effects. This method resembles to the dosing methodology applied to other agents that work on the prostacyclin pathway. The approach however inhibits our capability of evaluating the result of this to determine a fixed dosage capable of working equally on all patients.

Deterioration is a frequent occurrence among PAH patients that leads to death and hence there were minimal deaths observed as initial events in the main endpoint of the study. It considered deaths after a complication. The comparison of all-cause mortality among all patients who attended to the study until its end did not reveal important differences between the group of patients taking placebo and beraprost. The optional post- treatment observational period in the study design, more than half of the patients in primary end- point experience crossed over to beraprost open-label or any other drug available. It was a weakness of the design and this part needs to be addressed in the interpretation of the mortality data. Our research study measured the lower amount of the increase in the 6-min walk distance (10 36 meters) compared to others randomized controlled trials. It can be explained by the imputed data, a strong imputation rule of the study, along with the features of the study population below where the majority of the patients of the WHO functional class II included and the patients had entered the baseline therapy. All these may have impaired the possibility of massive change in distance in 6-minutes walk.

The mild and even adverse outcomes of beraprost matched that which normally would be observed during treatment with prostacyclin. Such side effects were common as headache, diarrhea, and nausea, which caused discontinuation more frequently in the beraprost group than the comparison group taking placebo. However, most of such adverse events were mild and moderate and a few patients only discontinued.

There are various limitations in our study. The optional post treatment visiting period on removal of placebo or beraprost was first. This reduced the follow-ups of the patients that had discontinued treatment and it is possible that all this may be biased because they have selected themselves to accept it. Second, it will not be surprising that 18.9 percent of patients are lost in the study early. The sensitivity analysis carried out to adjust to this and the incomplete follow-up still upheld the results of the major analysis. Third, the dominant outcome had subjective elements because this is what previous landmark studies in PAH advised. To control this, the disease progression was strictly stipulated and each and event was adjudicated by an independent critical-event committee. Moreover, like other studies of PAH therapies, the outcomes of the first ending were the same as the surrogate targeted one of the secondary endpoints, which included death caused by PAH or hospitalisation because of worsening PAH. However, the recommendations on future may be developed on the basis of the works on heart failure, and it is possible that such two-component endpoint will also be used as the primary outcome measure.

Lastly, there was a significant decrease in the risk of the main composite end point in patients with PAH like death or a complication because of the effects of PAH by beraprost when compared to placebo. However the difference between the mortality rate of the two categories of treatment was not significant.

CONCLUSION

Beraprost had a high probability and reduced the likelihood of the primary combined outcome-death or logistics of pulmonary arterial hypertension (PAH) in the eventdriven trial as compared to the placebo. The improvement of the disease progression and the reduction in the rate of hospitalization as the main outcome was the main driving force of the treatment effect and the mortality rate did not differ significantly across the two groups. Selxipag significant effect was observed in all the pre-defined subgroups of patients independent of underlying cause of PAH, severity of disease and pre-existing drug treatment. The simulation and precise results in the addition of the beraprost to the standard therapy of two medications of PAH involved the therapeutic advantage in accordance with the overall treatment effect. The findings can be used in supporting dose-adjusting programs of beraprost, however, it is not known whether the fixed dose would be effective in all people since density of prostacyclin receptors can be different among different people. Non-significant variations in all-cause mortality were not recorded in the study and this, probably, is due to the high crossover rate of the patients to the open-label treatment. As well, the improvement in the 6-minute walk distance was not as significant as those in the previous studies, which is probably due to the form of study imputed data, not to mention the proclivity of the patients in the studies. Side effects of beraprost were typical of other prostacyclin drugs, and the most frequent ones are caused by the headache, diarrhea, and nausea. Although such side effects caused the treatment discontinuation by some people, they were mostly mild or moderate in severity. In general, beraprost has been found to significantly lower the risk of PAH-related complications, but none of the changes on mortality have been found as significant across both treatment groups. The data from these results place beraprost as a potential therapy in the array of options to treat PAH, and they must conduct more studies to identify the most effective dosing regimens and general patient outcomes.

REFERENCE

1. Humbert, M.; Sitbon, O.; Chaouat, A.; et al. Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era. Circulation 2010, 122, 156-163.
2. Galiè, N.; Humbert, M.; Vachiery, J-L.; et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). Eur Respir J 2015, 46, 903-975.
3. Galiè, N.; Corris, P.A.; Frost, A.; et al. Updated treatment algorithm of pulmonary arterial hypertension. J Am Coll Cardiol 2013, 62, Suppl, D60-D72.
4. Barst, R.J.; Rubin, L.J.; Long, W.A.; et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. N Engl J Med 1996, 334, 296-301.
5. Farber, H.W.; Miller, D.P.; Meltzer, L.A.; McGoon, M.D. Treatment of patients with pulmonary arterial hypertension at the time of death or deterioration to functional class IV: insights from the REVEAL Registry. J Heart Lung Transplant 2013, 32, 1114-1122.
6. Benza, R.L.; Miller, D.P.; Barst, R.J.; Badesch, D.B.; Frost, A.E.; McGoon, M.D. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the REVEAL Registry. Chest 2012, 142, 448-456.
7. McLaughlin, V.V.; Langer, A.; Tan, M.; et al. Contemporary trends in the diagnosis and management of pulmonary arterial hypertension: an initiative to close the care gap. Chest 2013, 143, 324-332.
8. Morrison, K.; Ernst, R.; Hess, P.; Studer, R.; Clozel, M. Beraprost: a selective prostacyclin receptor agonist that does not affect rat gastric function. J Pharmacol Exp Ther 2010, 335, 249-255.

9. Morrison, K.; Studer, R.; Ernst, R.; Haag, F.; Kauser, K.; Clozel, M. Differential effects of beraprost and prostacyclin analogs in rat pulmonary artery. J Pharmacol Exp Ther 2012, 343, 547-555.
10. Kuwano, K.; Hashino, A.; Asaki, T.; et al. 2-[4-[(5,6-diphenylpyrazin-2-yl)(isopropyl)amino]butoxy]-N-(methylsulfonyl)acetamide (NS-304), an orally available and long-acting prostacyclin receptor agonist prodrug. J Pharmacol Exp Ther 2007, 322, 1181-1188.
11. Kuwano, K.; Hashino, A.; Noda, K.; Kosugi, K.; Kuwabara, K. A long-acting and highly selective prostacyclin receptor agonist prodrug, 2-4-[(5,6-diphenylpyrazin-2-yl)(isopropyl)amino]butoxy-N-(methylsulfonyl)acetamide (NS-304), ameliorates rat pulmonary hypertension with unique relaxant responses of its active form, 4-[(5,6-diphenylpyrazin-2-yl)(isopropyl)amino]butoxyacetic acid (MRE-269), on rat pulmonary artery. J Pharmacol Exp Ther 2008, 326, 691-699.
12. Simonneau, G.; Torbicki, A.; Hoeper, M.M.; et al. Beraprost: an oral, selective prostacyclin receptor agonist for the treatment of pulmonary arterial hypertension. Eur Respir J 2012, 40, 874-880.
13. Cuzick, J. Forest plots and the interpretation of subgroups. Lancet 2005, 365, 1308-1308.
14. Schulman, S.; Kearon, C. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005, 3, 692-694.
15. Rajkumar, R.; Konishi, K.; Richards, T.J.; et al. Genomewide RNA expression profiling in lung identifies distinct signatures in idiopathic pulmonary arterial hypertension and secondary pulmonary hypertension. Am J Physiol Heart Circ Physiol 2010, 298, H1235-H1248.
16. Tapson, V.F.; Torres, F.; Kermeen, F.; et al. Oral treprostinil for the treatment of pulmonary arterial hypertension in patients on background endothelin receptor antagonist and/or phosphodiesterase type 5 inhibitor therapy (the FREEDOM-C study): a randomized controlled trial. Chest 2012, 142, 1383-1390.
17. Tapson, V.F.; Jing, Z.C.; Xu, K.F.; et al. Oral treprostinil for the treatment of pulmonary arterial hypertension in patients receiving background endothelin receptor antagonist and phosphodiesterase type 5 inhibitor therapy (the FREEDOM-C2 study): a randomized controlled trial. Chest 2013, 144, 952-958.
18. McLaughlin, V.V.; Benza, R.L.; Rubin, L.J.; et al. Addition of inhaled treprostinil to oral therapy for pulmonary arterial hypertension: a randomized controlled clinical trial. J Am Coll Cardiol 2010, 55, 1915-1922.
19. Pulido, T.; Adzerikho, I.; Channick, R.N.; et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. N Engl J Med 2013, 369, 809-818.
20. Ghofrani, H.A.; Galiè, N.; Grimminger, F.; et al. Riociguat for the treatment of pulmonary arterial hypertension. N Engl J Med 2013, 369, 330-340.
21. Galiè, N.; Brundage, B.H.; Ghofrani, H.A.; et al. Tadalafil therapy for pulmonary arterial hypertension. Circulation 2009, 119, 2894-2903.
22. McLaughlin, V.V.; Oudiz, R.J.; Frost, A.; et al. Randomized study of adding inhaled iloprost to existing bosentan in pulmonary arterial hypertension. Am J Respir Crit Care Med 2006, 174, 1257-1263.
23. McLaughlin, V.V.; Palevsky, H.I. Parenteral and inhaled prostanoid therapy in the treatment of pulmonary arterial hypertension. Clin Chest Med 2013, 34, 825-840.
24. McLaughlin, V.V.; Badesch, D.B.; Delcroix, M.; et al. End points and clinical trial design in pulmonary arterial hypertension. J Am Coll Cardiol 2009, 54, Suppl, S97-S107.
25. McMurray, J.J.; Packer, M.; Desai, A.S.; et al. Angiotensin–neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014, 371, 993-1004.