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Care of Patients With Pulmonary Hypertension

# Improved survival of Korean patients with idiopathic pulmonary arterial hypertension after the introduction of targeted therapies

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ABSTRACT

*Objectives:* We compared the survival of patients with idiopathic pulmonary arterial hypertension (IPAH), receiving conventional and targeted therapies.
*Background:* IPAH is an incurable disease with high mortality. To manage IPAH, several targeted therapies have been used in Korea.
*Methods:* We performed a retrospective study of 71 patients diagnosed with IPAH in a tertiary hospital between January 1994 and February 2013. Patients were classified into "conventional therapy group" (treated with conventional therapies and/or beraprost) and "targeted therapy group" (treated with targeted therapies other than beraprost).
*Results:* The median age of the patients was 33 years and 50 patients were female. The survival rate at 1, 3, 5, and 10 years was 80.1% 62.0%, 51.5%, and 26.8%, respectively. The survival rate in the targeted therapy group was greater than in the conventional therapy group ($p$-value = 0.026).
*Conclusions:* We believe targeted therapies would improve survival benefits in IPAH patients.


## Introduction

Idiopathic pulmonary arterial hypertension (IPAH) is a sporadic disease with no identifiable cause and family history. It is classified as Group 1.1 in the Nice classification.[1] The incidence of IPAH is between two and five cases per one million people and disease progression is fatal, resulting in a progressive rise in pulmonary vascular resistance (PVR) and right heart failure.[2] Median survival of patients with IPAH is 2.8 years without proper treatment.[3] Although several medical therapies have been tested, at present there is no cure for IPAH.

In the past, the principal treatments for pulmonary arterial hypertension (PAH) involved conventional approaches including oxygen supplementation, digoxin, diuretics and anticoagulation.[2] Oxygen supplementation can help to prevent hypoxic pulmonary vasoconstriction.[4] In patients with IPAH and right heart failure, the short term use of digoxin may produce an increase in cardiac output and a decrease in the blood norepinephrine level.[5] Diuretics are often used for the treatment of volume overload in right heart failure and anticoagulation has also been attempted for the management of PAH based on thrombotic arteriopathy.[6] Most conventional treatments are used to alleviate symptoms and improve quality of life.[7] In addition, although some studies suggest survival benefits of anticoagulation,[8,9] data regarding the survival outcomes of other conventional treatments are lacking and there has been no randomized controlled study to date of the survival benefits of conventional treatments.

Novel and targeted therapies are currently used for the treatment of PAH, such as prostanoids (e.g., epoprostenol, iloprost, treprostinil, and beraprost), endothelin receptor antagonists (e.g., bosentan, ambrisentan and macitentan), and phosphodiesterase type 5 inhibitors (e.g., sildenafil and tadalafil).[10,11] These therapies improve symptoms, hemodynamic parameters, and survival in patients with PAH, and the "Updated Evidence-Based Treatment Algorithm in Pulmonary Arterial Hypertension" recommends using these drugs for the management of PAH.[7]

There has been no universal guideline for the treatment of PAH before 2004. After the American College of Chest Physicians (ACCP)

*Abbreviations:* A, aorta; ACCP, American College of Chest Physicians; CI, cardiac index; CO, cardiac output; CT, computed tomography; $DL_{CO}$, Diffusing capacity; HIV, human immunodeficiency virus; IPAH, idiopathic pulmonary arterial hypertension; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PFT, pulmonary function test; PVR, pulmonary vascular resistance; RAP, right atrial pressure; REVEAL, Registry to EValuate Early And Long-term PAH disease management; RHC, right heart catheterization; TTE, transthoracic echocardiography; US, ultrasonography; WHO, World Health Organization.

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guidelines were released in 2004, they were adopted for the treatment of PAH patients in Korea. Among the novel and targeted drugs, beraprost, bosentan, ambrisentan, sildenafil, iloprost, and treprostinil have been approved in Korea. In 2009, Barst et al reported that beraprost treatment showed no hemodynamic benefits[7]; in another study conducted in 2003, the author demonstrated that an increase in exercise capacity was observed at 3 and 6 months, but was not persistent after 9 months.[12] Because conventional therapies such as oxygen supplementation, digoxin, diuretics and anticoagulation have limited therapeutic benefits on patients with PAH, beraprost has been used in the treatment of PAH in Korea before the advent of other targeted therapies. (Iloprost was used as a targeted therapeutic agent in a clinical trial in Korea in 2004.)

Although several studies from Asian countries have recently been published,[13,14] data on the survival benefits of targeted therapies to treat PAH have been based on retrospective and non-randomized studies mostly originating in Western countries.[15,16,17] Macitentan is another novel potent dual endothelin receptor antagonist that was recently developed by modifying the structure of bosentan.[11] To our knowledge, Pulido et al analyzed efficacy of macitentan and it was the only randomized control study on the survival benefits of targeted therapy.[18] The purpose of this study was to compare the survival of patients with IPAH, receiving conventional and targeted therapies in a tertiary hospital in Korea.

## Methods

### *Study subjects*

We performed a retrospective electronic review of patients diagnosed with PAH by a respirologist at the Asan Medical Center in Korea between January 1994 and February 2013. We diagnosed PAH based on right heart catheterization (RHC) and transthoracic echocardiography (TTE) findings. We diagnosed PAH as a mean pulmonary artery pressure (PAP) $>$ 25 mm Hg, with a pulmonary capillary wedge pressure (PCWP) $<$ 15 mm Hg and a PVR $>$ 3 Wood units at rest by RHC, or systolic PAP $>$ 40 mm Hg by TTE in patients without RHC.[2,19] After reviewing the medical history, autoantibodies, liver function test, human immunodeficiency virus (HIV) test, pulmonary function test (PFT), liver ultrasonography (US), chest computed tomography (CT), TTE, and ventilation/perfusion scan of the patients, we excluded PAH patients affected by drugs, connective tissue disease, HIV infection, portal hypertension, and congenital heart disease. Because IPAH patients with a positive vasoreactivity test show a slower disease progression and a better prognosis than patients with a negative vasoreactivity test,[20] we also excluded IPAH patients with vasoreactivity on RHC. Positive vasoreactivity is defined as a fall in mean PAP $\geq$ 10 mm Hg and a final mean PAP $<$ 40 mm Hg without a decrease in cardiac output (CO).

This study was approved by the Institutional Review Board of the Asan Medical Center. We did not seek informed consent from the patients because it was a retrospective study. We encoded the patient identification numbers to keep it confidential.

### *Study design*

We retrospectively divided IPAH patients with a negative vasoreactivity into either a “conventional therapy group” or “targeted therapy group” based on the targeted therapies for PAH. We excluded beraprost from the targeted therapies because it did not yield better results than the placebo and was licensed for use only in Korea and Japan.[21] Therefore, the conventional therapy group was composed of patients only receiving conventional therapies and/or beraprost, and the targeted therapy group was composed of patients receiving targeted therapies other than beraprost, regardless of the conventional therapies, within the first year after diagnosis.

### *Outcome measures*

We assessed the efficacy of drugs by comparing patient survival periods in the conventional and targeted therapy groups. We defined the survival period as the time from diagnosis to death, or last hospital follow-up day. We assessed the survival status by analyzing the electronic medical records of the Asan Medical Center or the national health insurance data of Korea. The survival rates were calculated by using the Kaplan–Meier method in all patients and in both subgroups.

### *Baseline data collection*

Baseline clinical and hemodynamic data were investigated in all patients and both subgroups. We collected information on patients with IPAH at initial diagnosis, including gender, age, body mass index, smoking history, time from onset of symptoms to diagnosis, symptoms at admission, dyspnea severity according to the World Health Organization (WHO) functional class, laboratory findings, PFT, TTE, RHC, chest CT, and treatment drugs.

One respirologist reviewed all medical records, checked hemodynamic variables, and measured the vessel diameter in chest CTs more than twice. Two professors in the respiratory division also rechecked all the data for accuracy. We assessed dyspnea severity according to the WHO functional class based on the records from professors or residents in charge, and excluded missing patient records or those with a low reliability. We also confirmed smoking history, time from onset of symptoms to diagnosis, and symptoms at admission.

### *Pulmonary function test*

Diffusing capacity ($DL_{CO}$) and a 6-min walk test were performed according to the guidelines of the American Thoracic Society.[22] The $DL_{CO}$ was measured by a single breath technique (Vmax™ ENCORE 22; CareFusion) and compared to those predicted based on patient age, race, sex, and height, according to reference equations of Park and the ECSC (European Community for Steel and Coal).[23,24]

### *Echocardiography*

We routinely performed TTE at the Asan Medical Center by using a Philips iE33 ultrasound system (Philips Medical system). Ejection fraction measurement was based on the collation of multiple methods by using the Quinones formula from the parasternal views, or the quantitative 2-dimensional biplane volumetric Simpson method from the 4- and 2-chamber views.[25,26] Left ventricular end diastolic diameter was measured using the 2-dimensional linear or M-mode method from the parasternal long-axis view or the apical 4-chamber view.[26,27] Right ventricular end diastolic diameter was measured from the parasternal long-axis view or the apical 4-chamber view.[27] Systolic PAP was estimated using a trans-tricuspid gradient measured by the Doppler method in multiple projections plus right atrial pressure (RAP) where the trans-tricuspid gradient was calculated from the modified Bernoulli equation ($4v^2$, $v$ = peak velocity of tricuspid regurgitation, m/second), and RAP was empirically estimated as 10 mm Hg.[28] Mean PAP was calculated from the equation: mean PAP = 0.61 $\times$ systolic PAP + 2 mm Hg.[29]

### *Right heart catheterization*

We routinely performed RHC in the medical intensive care unit. A 7.5 F sheath was placed in the jugular vein under local anesthesia