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Review

Treatment of idiopathic/hereditary pulmonary arterial hypertension

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ABSTRACT

Treatment of pulmonary hypertension has progressed by recently developed pulmonary arterial hypertension-targeted drugs. However, long-term survival of the patients with idiopathic/heritable pulmonary arterial hypertension is still suboptimal. To improve the outcomes, treatment goals of pulmonary hypertension were proposed at the 5th World Symposium on Pulmonary Hypertension held at Nice, France in 2013; parameters were obtained from cardiopulmonary exercise test, blood tests, echocardiography, and magnetic resonance imaging. In particular, parameters evaluating right ventricular function have been highlighted because survival of the patients with pulmonary arterial hypertension is closely related to right ventricular function. However, treatment specifically targeted to improve right ventricular function in pulmonary hypertension is not yet established. In this setting, we need to maintain or improve right ventricular function with available vasodilators. In this review, we focus on the following two points: (1) Why can pulmonary arterial hypertension-targeted drugs improve right ventricular function without an apparent decrease in pulmonary artery pressure? (2) Are proposed goals sufficient to improve long-term prognosis of the patients? Further, we will discuss what would be the appropriate goal in treating patients with pulmonary arterial hypertension.

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Introduction

Treatment of pulmonary arterial hypertension (PAH) has dramatically advanced by development of PAH-targeted drugs during the past two decades. At present, drugs targeting three pathways that are critical for pathogenesis and progression of PAH are available; namely, prostacyclin analogs that supply the deficient endogenous prostacyclin, endothelin receptor antagonists that inhibit the up-regulated endothelin pathway, and phosphodiesterase-5 inhibitors that compensate the down-regulated nitric oxide pathway. As a result, survival rates reported in recent registries have improved [1–3] (Fig. 1). In this review, we will focus on idiopathic/hereditary PAH (I/HPAH) especially when discussing patient survival because prognosis varies in other forms

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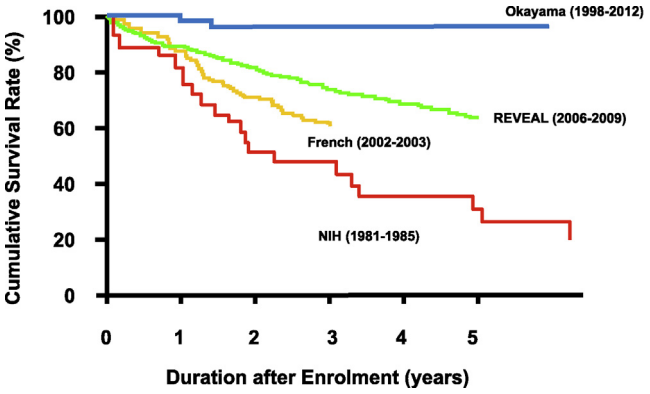

Fig. 1. Kaplan–Meier survival estimates in patients with idiopathic/heritable pulmonary arterial hypertension from reported registries. Red line indicates survival curve from NIH registry [1]. Orange line indicates survival curve from French registry [2]. Green line indicates survival curve from REVEAL registry [3]. Blue line indicates survival curve from Okayama Medical Center [41]. Although cumulative survival of the patients in registry studies has been improving over time, survival rate of the patients at Okayama Medical Center is outstanding. Cited and modified from Refs. [1–3,41].

of PAH in relation to coexisting disorders. In the US National Institutes of Health (NIH) registry conducted during 1981–1985 [1], the 1-, 3-, and 5-year survival rates were 68%, 48%, and 30%, respectively. The outcome was improved in the French registry conducted during 2002–2003 [2] where the 1- and 3-year survival rates were 83% and 58%, respectively. It was further improved in the REVEAL registry conducted during 2006–2009 [3], with 1-, 3-, and 5-year survival rates of 91%, 74%, and 65%, respectively. The treatment algorithm for PAH was updated at the 4th World Symposium on Pulmonary Hypertension (WSPH) held in Dana Point, CA, USA [4]. Worldwide recognition of this evidence-based algorithm may have contributed to the improvement in patient survival. However, PAH remains fatal considering the fact that survival curves show an ongoing decrease over years in the reported registries [2,3]. To improve the long-term survival of the patients with I/HPAH, it is necessary to identify appropriate objective treatment goals for I/HPAH.

Prognostic factors of I/HPAH

It is essential to clarify clinically relevant prognostic factors to identify treatment goals. At the time of the 4th WSPH, the results of the NIH registry provided the only available data [1]. It revealed that the relevant prognostic factors were functional class and hemodynamics. Thus, the goal in treating PAH was set to improve and maintain the patients' functional class at the 4th WSPH [4]. Other recent studies have provided additional prognostic factors besides the functional class and hemodynamic parameters; parameters were obtained from cardiopulmonary exercise test, blood tests, echocardiography, and magnetic resonance imaging as listed in Table 1 [1,5–15]. Among them, parameters representing right ventricular function have come to be emphasized as prognostic indicators at baseline and treatment targets.

Since the leading cause of death in I/HPAH is right ventricular failure [1], it has been recognized that the existence of right ventricular failure would worsen the prognosis of the patients. This recognition was reflected in a previously proposed treatment goal. Although PAH-targeted drugs can decrease pulmonary vascular resistance (PVR) in patients with I/HPAH to some extent (Table 2, [16–22]), none of the drugs are reported to be able to decrease pulmonary artery pressure (PAP) sufficiently. In that case, it is convincing that the patients' prognosis depends on better adaptation of the right ventricle to excessively increased afterload [23].

Table 1
Prognostic predictors in patients with idiopathic/heritable pulmonary arterial hypertension.

Parameter	Values predicting poor survival	Reference
Exercise capacity		
NYHA functional class	III or IV	[1,5,6]
6MWD	<165–307 m	[5,7–9]
Peak VO_2	<10.6–11.6 ml/kg	[8,10]
Hemodynamics		
RAP	>10–20 mmHg	[1,5,9,11]
mean PAP	–	[1]
CI	<2.5 l/min/m^2	[1,6,9]
PVR	>32 Wood units	[5,11]
S_VO_2	<65%	[6]
Biomarkers		
BNP	>50 pg/ml	[5]
NT-proBNP	>1400–1800 ng/l	[6,11]
UA	>6.4 mg/dl (female) >8.9 mg/dl (male)	[10,12]
Respiratory function		
% predicted DLCO	<80%	[1,5]
Echocardiographic measurements		
Right atrial area	–	[13]
Pericardial effusion	Presence	[13]
TAPSE	<1.8 cm	[14]
Magnetic resonance imaging measurements		
SVI	<25 ml/m^2	[15]
RVEDVI	>84 ml/m^2	[15]
LVEDVI	<40 ml/m^2	[15]

NYHA, New York Heart Association functional class; 6MWD, 6-min walk distance; Peak VO_2, peak oxygen consumption; RAP, right atrial pressure; PAP, pulmonary artery pressure; CI, cardiac index; PVR, pulmonary vascular resistance; SvO_2, mixed venous oxygen saturation; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal pro–B-type natriuretic peptide; UA, uric acid; DLCO, carbon monoxide diffusing capacity; TAPSE, tricuspid annular plane systolic excursion; SVI, stroke volume index; RVEDVI, right ventricular end-diastolic volume index; LVEDVI, left ventricular end-diastolic volume index.

Treatment goal recommended in the 5th WSPH

It was timely and meaningful to discuss treatment goals at the 5th WSPH held at Nice, France in 2013. As the committee mentioned, the focus of pulmonary hypertension specialists has shifted from short-term functional changes to improvements in long-term outcomes [24]. The focus of the discussion at the 5th WSPH was to set higher the "bar" of treatment goals. The recommended treatment goals included the following: modified New York Heart Association functional class I or II, 6-min walk distance ≥380–440 m, cardiopulmonary exercise test–measured peak oxygen consumption >15 ml/min/kg, and ventilatory equivalent for carbon dioxide <45 l/min/l/min, B-type natriuretic peptide (BNP) level toward "normal," echocardiography and/or cardiac magnetic resonance imaging demonstrating normal/near-normal right ventricular size and function, and hemodynamics showing normalization of right ventricular function with right atrial pressure <8 mmHg and cardiac index >2.5–3.0 l/min/m^2 [24]. Since right ventricular function came to be considered among prognostic indicators at baseline, maintaining right ventricular function was emphasized as the treatment goal. Then, how can we maintain or improve right ventricular function in PAH?

Established medications to treat chronic left heart failure with decreased ejection fraction, such as angiotensin-converting enzyme inhibitors and beta-blockers, have no evidence to ameliorate right heart failure of I/HPAH. Moreover, Provencher et al. [25] reported that beta-blockers were associated with significant worsening in exercise capacity and pulmonary hemodynamics in patients with moderate to severe PAH. The evidence in