Korean Circ J. 2018 Sep;48(9):854-856
https://doi.org/10.4070/kcj.2018.0156
pISSN 1738-5520·eISSN 1738-5555

kcj
Korean Circulation Journal

Editorial

Benefits from the Early Initiation of Macitentan for Pulmonary Arterial Hypertension

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▸ See the article "Hemodynamic and Histopathologic Benefits of Early Treatment with Macitentan in a Rat Model of Pulmonary Arterial Hypertension" in volume 48 on page 839.

Received: May 8, 2018
Accepted: May 31, 2018

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Conflict of Interest
The author has no financial conflicts of interest.

The contents of the report are the author's own views and do not necessarily reflect the views of the *Korean Circulation Journal*.

The term pulmonary arterial hypertension (PAH) describes a subpopulation of patients with pulmonary hypertension (PH) characterized hemodynamically by the presence of pre-capillary PH, defined as a mean pulmonary artery pressure ≥25 mmHg at rest, a pulmonary arterial wedge pressure (PAWP) ≤15 mmHg, and a pulmonary vascular resistance >3 wood units.[1] PAH encompasses a group of diseases characterized by remodeling of the small pulmonary arteries leading to a progressive increase in pulmonary vascular resistance (PVR), right ventricular failure and death.[2] Despite recent improvements of understanding of PAH, no current treatment cures this devastating condition.[3] The prognosis for patients with PAH remains poor with survival rates variously reported as 83% to 85% at 1 year and 58% to 67% at 3 years after diagnosis.[4] Since the introduction of pathogenesis of PAH and target therapies to PAH during past 30 years, the survival rate of PAH has been dramatically improved.[5] Several drugs have been introduced to improve survival and quality of life in the patients with PAH.[3] Especially, endothelin receptor antagonists (ERAs), phosphodiesterase type 5 (PDE-5) inhibitors, prostacyclin and prostacyclin analogs and guanylate cyclase (GC) stimulators are representative PAH drugs that have concrete evidences by big scaled studies. These drugs have developed in the concept that PAH is consequent to the imbalance between endogenous vasoconstrictors/mitogens, such as endothelin and thromboxane A2, and vasodilators/antimitotics, such as prostacyclin (prostaglandin I2, PGI2) and nitric oxide (NO). Macitentan is a new oral dual (ET-A and ET-B) ERA with improved tissue penetration.[6] In experimental models of PH, macitentan reduced mean pulmonary artery pressure and prevented right ventricular hypertrophy more effectively than other ERAs.[7] Importantly, the Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome (SERAPHIN) trial with macitentan is the first clinical trial demonstrating a long-term improvement in morbidity and mortality in PAH patients.[8] Therefore, current guidelines for PAH have consistently recommended macitentan to use as a first line maintenance therapy.

In this animal experimental study conducted by Kim et al.,[9] authors reported the hemodynamic and histopathologic benefits of macitentan. According to the study, these beneficial effects can be explained by two mechanisms. One is a potent ERA macitentan per se; another is the early initiation of treatment. PAH is known as a rapidly progressive disease, even at earlier stage and become irreversible beyond some stage of disease.[3] It is reason why PAH remains an incurable and eventually fatal disease even with increased physician

awareness and the relatively recent therapeutic developments. Although the concept that an early diagnosis and early therapeutic intervention are critical has been acknowledged, authors proved the benefits of the early initiation of macitentan by a well-designed protocol with monocrotaline-induced PAH rat model.[9] Accurate hemodynamic assessment using a Millar conductance pressure catheter and histopathologic back-up seems to be the main power of this study. Although SERAPHIN trial has shown clinical benefit of macitentan, hemodynamic or histopathologic changes on right ventricle (RV) could not be evaluated. RV usually compensate to the pressure overload by chamber dilatation. RV dilatation can subsequently be changed to dysfunction or failure when pressure overload is prolonged and severe. Thus, RV is a final victim and main prognosticator of PAH. In this study, hemodynamic, histopathologic and Doppler echocardiographic comparisons on the RV according to the therapeutic options seem to be relevant and appropriate. Thus, the results of this study can be applied to the interpretation of survival benefit in SERAPHIN trial. However, the combination of macitentan and sildenaphil in the study could not show additive or synergistic effects compared to the macitentan monotherapy.[9] The exact reasons should be answered by the subsequent experiments in near future. Despite the availability of several therapeutic options, the long-term prognosis for PAH treated in monotherapy remains unsatisfactory. An alternative approach is the combination therapy, using drugs targeting the different pathways implicated in PAH. Combination therapy appears promising for patients who are refractory to treatment or whose disease progression is not well controlled with monotherapy. The best combination regimen and the appropriate timing of combination in PAH remains debatable and further studies should be needed.

Although the monocrotaline-induced PAH in rat is not identical to human PAH, this animal disease model has been generally accepted by the most basic researchers in this field.[10] And the initiation of treatment 1 week after monocrotaline injection does not quite equally reflect an early treatment to the patients with PAH. However, this study gives us the valuable evidences such as the mechanisms of clinical benefits by macitentan shown in clinical trials and the importance of treatment initiation in early stage of PAH. We still have limited number of therapeutic options for PAH. Thus, researchers and clinicians should investigate more to understand the pathophysiologic and molecular mechanisms, and develop new pharmacologic therapies to inhibit the disease progression and improve survival.

REFERENCES

1. Hoeper MM, Bogaard HJ, Condliffe R, et al. Definitions and diagnosis of pulmonary hypertension. *J Am Coll Cardiol* 2013;62:D42-50.
PUBMED | CROSSREF
2. Chung WJ, Park YB, Jeon CH, et al. Baseline characteristics of the Korean Registry of Pulmonary Arterial Hypertension. *J Korean Med Sci* 2015;30:1429-38.
PUBMED | CROSSREF
3. Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary arterial hypertension. *N Engl J Med* 2004;351:1425-36.
PUBMED | CROSSREF
4. Benza RL, Miller DP, Barst RJ, Badesch DB, Frost AE, McGoon MD. An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the REVEAL Registry. *Chest* 2012;142:448-56.
PUBMED | CROSSREF
5. 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;122:156-63.
PUBMED | CROSSREF

https://doi.org/10.4070/kcj.2018.0156

6. Iglarz M, Binkert C, Morrison K, et al. Pharmacology of macitentan, an orally active tissue-targeting dual endothelin receptor antagonist. *J Pharmacol Exp Ther* 2008;327:736-45.
PUBMED | CROSSREF

7. Raja SG. Macitentan, a tissue-targeting endothelin receptor antagonist for the potential oral treatment of pulmonary arterial hypertension and idiopathic pulmonary fibrosis. *Curr Opin Investig Drugs* 2010;11:1066-73.
PUBMED

8. Pulido T, Adzerikho I, Channick RN, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med* 2013;369:809-18.
PUBMED | CROSSREF

9. Kim KH, Kim HK, Kim YJ, Chan SY, Sohn DW. Hemodynamic and histopathologic benefits of early treatment with macitentan in a rat model of pulmonary arterial hypertension. *Korean Circ J* 2018;48:839-53.
CROSSREF

10. Kim KC, Lee JC, Lee H, Cho MS, Choi SJ, Hong YM. Changes in caspase-3, B cell leukemia/lymphoma-2, interleukin-6, tumor necrosis factor-α and vascular endothelial growth factor gene expression after human umbilical cord blood derived mesenchymal stem cells transfusion in pulmonary hypertension rat models. *Korean Circ J* 2016;46:79-92.
PUBMED | CROSSREF