Pulmonary arterial hypertension (PAH) is a progressive intractable disease that is characterized by elevated pulmonary vascular resistance, right heart failure, and ultimately death, in the absence of treatment or lung transplantation. Targeted medical therapy has been established, and recent advances in the management of PAH have led to improvement in symptoms, exercise capacity, and prognosis for patients with PAH; however, the efficacy of medical therapy is not entirely satisfactory, as shown in the REVEAL registry, which documents a 5-year survival rate of 64.5% for patients with idiopathic PAH. The development of new drugs is expected to break the current stagnation in PAH treatment options.

A New Class of Drug for Pulmonary Arterial Hypertension – Can a Rho-Kinase Inhibitor Break the Stagnation in Treating It? –
Kazuya Miyagawa, MD, PhD; Noriaki Emoto, MD, PhD

At present, there are 3 established therapeutic targets: the endothelin pathway, the nitric oxide (NO)-cyclic guanosine mono-phosphate (cGMP) pathway, and the prostacyclin pathway. To target the respective pathways, endothelin-receptor antagonists (ERAs), phosphodiesterase-5 (PDE5) inhibitors, and prostacyclin analogs are currently available. Moreover, new classes of drugs are being developed for each of these pathways. Macitentan, a new ERA that has a high affinity for endothelin receptors and causes robust inhibition of the endothelin system, may be a first-line drug in the near future. A direct guanylate cyclase stimulator, riociguat, and selexipag, pulmonary arterial hypertension (PAH) is a progressive intractable disease that is characterized by elevated pulmonary vascular resistance, right heart failure, and ultimately death, in the absence of treatment or lung transplantation. Targeted medical therapy has been established, and recent advances in the management of PAH have led to improvement in symptoms, exercise capacity, and prognosis for patients with PAH; however, the efficacy of medical therapy is not entirely satisfactory, as shown in the REVEAL registry, which documents a 5-year survival rate of 64.5% for patients with idiopathic PAH. The development of new drugs is expected to break the current stagnation in PAH treatment options.

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an orally available, selective prostacyclin receptor agonist, are also promising drugs that target the NO-cGMP and prostacyclin pathways, respectively. These new drugs targeting established pathways have the potential to improve the prognosis of patients with PAH. However, these therapies do not address the mechanism of vascular remodeling and therefore, although they may improve symptoms and quality of life, do not reverse the underlying pathology. In order to overcome the intrinsic pathophysiology and reverse pulmonary arterial remodeling, a new treatment strategy targeting a novel pathway is required.

Rho-kinase (ROCK) is an effector of small GTPase RhoA, which is related to cytoskeleton dynamics and promotes vascular contraction. ROCK also plays an important role in a variety of cellular functions related to adhesion, migration, proliferation, and gene expression and is involved in the pathogenesis of cardiovascular diseases, including PAH. An intravenously administered ROCK inhibitor, fasudil, has already been used clinically to treat cerebral vasospasm after subarachnoid hemorrhage. In PAH, the ROCK pathway is thought to induce pulmonary vascular remodeling, which is characterized by constriction and obliteration of the pulmonary artery by hyperproliferation of pulmonary vessel cells and, furthermore, by inflammation and impaired cellular metabolism, (Figure) all of which converge in the pathogenesis of PAH. In animal models, fasudil ameliorates monocrotaline- and hypoxia-induced pulmonary vascular remodeling, and it may improve pulmonary hemodynamics in patients with PAH through the same mechanism. Thus, the ROCK pathway is a promising novel target for the treatment of PAH.

In this issue of the Journal, Fukumoto et al report a double-blind placebo-controlled clinical trial with an oral ROCK inhibitor, AT-877 (fasudil hydrochloride), for patients with PAH, and provide promising results for further trials. They demonstrate a higher prevalence of improved cardiac index in the AT-877 group and a tendency toward better hemodynamics in patients with higher concentrations of hydroxyfasudil. A new treatment strategy targeting a novel pathway is developing. In order to establish fasudil as an approved drug with robust data on safety and efficacy, larger and longer phase III trials will be needed. Because of the rarity of PAH, well-designed trials and appropriate endpoints will be required.14,15

In PAH, as is the case with other orphan diseases, recruiting a sufficient number of patients is an important and critical issue in the development of new treatments. To detect the clinical relevance of drug effects, a large population is needed. Clinical trial design is therefore another issue in developing new therapies for PAH. The placebo-controlled trial is considered to be the most powerful design, and, classically, the placebo-controlled monotherapy trial design was used in the development of PAH treatment in the absence of background therapy. However, because of the progressive nature of PAH and its poor prognosis, the classic trial designs are no longer feasible from an ethical point of view. Placebo-controlled add-on trials are reasonable but still challenging, because it is difficult to standardize background therapies. Setting endpoints in randomized controlled trials is also a prominent factor. The primary endpoint in a PAH trial must meet 3 criteria: (1) clinical relevance; (2) sensitivity to treatment effect; and (3) measurability and interpretability.13 In previous trials, the 6-min walk test (6MWT) was the most useful primary endpoint; however, in recent phase III trials, time to clinical worsening (TtCW) has been recommended as a primary endpoint. Clinical trials with TtCW as a primary endpoint tend to be longer than those using the 6MWT. Given these particular difficulties in designing PAH clinical trials, adaptive design, which allows modification of the trial design and early termination in case of inefficacy, can be considered for implementation of a novel treatment approach.14 With further clinical trials designed based on the results of their study, we believe that Fukumoto et al are on track to develop a promising new class of drug, the ROCK inhibitor, for PAH patients.

References