Novel Oral Prostacyclin Analog With Thromboxane Synthase Inhibitory Activity for Management of Pulmonary Arterial Hypertension

Quang-Kim Tran, MD, PhD; Hiroshi Watanabe, MD, PhD

Pulmonary arterial hypertension (PAH) is a disease characterized by extensive remodeling of the small pulmonary arteries, resulting in increased elevated pulmonary arterial pressure and right ventricular heart failure. PAH is fatal if not treated, with only 34% survival rate after 5 years.¹ Pathobiologically, PAH is the result of a combination of many factors.² Simplistically, abnormal proliferation of endothelial cells is an important mechanism, which leads to increased arginase activity and downregulation of prostacyclin (PGI₂) synthase in lung tissues, and subsequent reduction in the production of the vasodilators nitric oxide (NO) and PGI₂.³⁻⁵ Endothelial hyperproliferation also increases the production of endothelin-1 (ET-1), one of the most potent vasoconstrictors. ET-1 overexpression in turn reduces the production of NO and PGI₂. These changes are associated with many other interrelated pathological changes, including vasoconstriction, hyper-

proliferation of vascular smooth muscle cells and fibroblasts, vascular wall hypertrophy, inflammation, platelet aggregation, and thrombosis, all contributing to the remodeling of the pulmonary vasculature in PAH (Figure).

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Based on these key features, currently approved therapies for PAH include phosphodiesterase 5 inhibitors (PDE-5I), endothelin-receptor antagonists (ERA) and PGI₂ derivatives (Figure). PDE-5Is prevent cyclic GMP breakdown and therefore enhance the vasodilatory effect of NO, ameliorating the effect of reduced NO production. ERAs prevent ET-1 interacting with its receptors, thereby alleviating the effects of excessive ET-1 in PAH patients. PGI₂ derivatives increase the levels of PGI₂, thereby alleviating the vasoconstriction caused by

Figure. Key pathophysiologic pathways of pulmonary arterial hypertension (PAH) and therapeutic targets. ET, endothelin; NO, nitric oxide; PGI₂, prostacyclin; TBXA₂, thromboxane A₂; VSMC, vascular smooth muscle cells. See text for explanation.

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Department of Physiology and Pharmacology, Des Moines University College of Osteopathic Medicine, Des Moines, IA (Q.-K.T.), USA;

Department of Clinical Pharmacology & Therapeutics, Hamamatsu University School of Medicine, Higashi-ku, Hamamatsu (H.W.), Japan

Mailing address: Quang-Kim Tran, MD, PhD, Department of Physiology & Pharmacology, Des Moines University College of Osteopathic Medicine, 3200 Grand Avenue, Des Moines, IA 50312, USA. E-mail: kim.tran@dmu.edu or Hiroshi Watanabe, MD, PhD, Department of Clinical Pharmacology & Therapeutics, Hamamatsu University School of Medicine, Handayama 1-20-1, Higashi-ku, Hamamatsu 431-3192, Japan. E-mail: hwat@hama-med.ac.jp

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reduced concentrations of PGI₂ in PAH patients. Generally, PDE-5Is and ERAs improve symptoms and survival;^{6,7} however, as the disease progresses, PGI₂ derivatives are required, and there is evidence that disease progression and survival are improved by timely PGI₂ usage.^{8,9} Nonetheless, there are serious limitations to currently approved PGI₂ derivatives,¹⁰ a major one being the instability of these drugs because of their metabolism by 15-hydroxyprostaglandin dehydrogenase, leading to short half-lives. As a result, they require inconvenient modes of administration, including subcutaneous or intravenous injection, or frequent sessions of inhalation, which greatly affects patient compliance.

In this issue of the Journal, Nakamura et al report on their testing of the effects of oral administration of ONO-1301, a PGI₂ analog with inhibitory effects on thromboxane synthase, in rats with monocrotaline-induced PAH.¹¹ ONO-1301 is a new compound with PGI₂ activity (related to a carboxylic acid and lipid-soluble functional group that activate the PGI₂ receptor), but is biologically stable because of the absence of prostanoid structures, including a 5-member ring and allylic alcohol.¹² These characteristics give it a longer half-life of 5.6h, compared with 6min for intravenous epoprostenol or 4h for subcutaneous treprostinil. The compound also inhibits thromboxane synthase activity because of the presence of a 3-pyridine radical and a carboxylic acid. This inhibitory activity would add therapeutic benefit to PGI₂ agonism, because it would not only further reduce vasoconstriction, but also help prevent thrombosis, an important pathophysiological feature of PAH (Figure). Subcutaneous ONO-1301 has been shown to reduce right ventricular pressure and pulmonary arterial medial wall thickness and improve survival in monocrotaline-induced PAH rats.¹²

Nakamura et al observed that following 16–24 days of twice-daily oral ONO-1301 administration, right ventricular pressure and medial pulmonary artery wall thickness were reduced using either a “preventive” or a “treatment” paradigm in the rat model of monocrotaline-induced PAH.¹¹ ONO-1301 plasma levels were similar after a single oral or subcutaneous dose over the course of 24h. In addition, plasma cAMP rapidly increased after oral administration and remained elevated for up to 6h. Thromboxane synthase inhibition was demonstrated by decreases in urinary 11-dehydrothromboxane B₂, a thromboxane A₂ metabolite. Interestingly, an antibody against hepatic growth factor (HGF) appeared to negate the effects of ONO-1301 on survival, which corroborates previous observations that HGF improves survival of PAH rats via amelioration of pulmonary hemodynamics,¹³ and suggests an interesting possibility that reduction in HGF production may be a factor in the pathogenesis of PAH. Detailed mechanisms of this putative involvement are yet to be defined.

Importantly, Nakamura et al observed that survival rates were not different among PAH rats under similar durations of monotherapy with oral ONO-1301, PDE-5I, sildenafil, or ERA, bosentan. An oral formulation of the PGI₂ derivative, treprostinil, has recently been intensively investigated as single therapy in multicenter clinical trials of PAH patients (FREEDOM-M)¹⁴ or as combined therapy on the background PDE-5I and/or ERA therapy (FREEDOM-C2).¹⁵ Those trials have demonstrated that although monotherapy with oral treprostinil improved exercise capacity, with the dosing regimens tested it does not appear to have additional benefit to PDE-5I or ERA in the combination regimens. Although ONO-1301 has yet to be tested on human subjects, with its additional inhibitory effect on thromboxane synthase activity, it will be very interesting to investi-

gate if ONO-1301 has additional effects on the hemodynamics and survival of PAH subjects when used in combination with PDE-5I and/or ERA therapy.

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