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Therapeutic potential of soluble guanylate cyclase agonists in pulmonary hypertension

Oleg V Evgenov*[1], Daniel S Kohane[2] and Warren M Zapol[1]

Address: [1]Department of Anesthesia and Critical Care, USA and [2]Department of Pediatrics, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Email: Oleg V Evgenov* - evgenov@etherdome.mgh.harvard.edu

* Corresponding author

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Pulmonary hypertension (PH) is usually characterized by excessive pulmonary vasoconstriction. Progression of PH is also associated with remodeling of the pulmonary vascular wall, localized thrombosis, and right heart hypertrophy and failure. Impaired bioavailability and/or responsiveness to endogenous NO and other vasodilators has been implicated in the pathogenesis of PH.

Pharmacological, NO-independent sGC agonists have been evaluated in several models of PH. Intravenous administration of the sGC stimulator BAY 41–2272 attenuates pulmonary vasoconstriction in ovine models of acute chemically-induced PH and persistent PH of the newborn. In rodent models of hypoxia- or monocrotaline-induced PH, oral treatment or intramuscular injections of BAY 41–2272 or oral administration of the sGC activator BAY 58–2667 attenuates the increase of right ventricular systolic pressure, right ventricular hypertrophy, and structural remodeling of the lung vasculature.

Targeted drug delivery to the lungs by inhalation results in high local bioavailability and a rapid onset of action at a reduced drug dose, and therefore avoids or reduces systemic side-effects. In sheep with acute PH, inhalation of the sGC agonists (BAY 41–2272, BAY 41–8543, or BAY 58–2667) encapsulated into dry-powder microparticles produces dose-dependent pulmonary vasodilation associated with increased transpulmonary cGMP release and improves arterial oxygenation without a significant reduction of systemic arterial pressure. Moreover, when vasodilator response to inhaled NO is impaired following oxidation of the prosthetic heme group of sGC by ODQ, both pulmonary vasodilation and transpulmonary cGMP release induced by inhaling BAY 58–2667 microparticles are greatly increased.

Taken together, these pre-clinical studies provide strong evidence that pharmacological agonists of sGC may provide a lung selective treatment modality for patients with PH particularly when endogenous NO-sGC-cGMP signaling is impaired.