Clinical effect of ambrisentan in pulmonary hypertension
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Background: A development of the drugs used in pulmonary hypertension (PH) contributes a lot to its clinical improvement. An advent of new endothelin receptor blocker, ambrisentan, has further diversified selection of PH drugs. Purpose: The purpose of this study was to evaluate the efficacy and safety of ambrisentan on PH. Method: Ambrisentan was administered to 26 (50 ± 19 years old, 7 men, 19 women) patients with PH including 11 patients with chronic thromboembolic PH (CTEPH), 5 with Eisenmenger syndrome, 5 with connective tissue disease (CTD) PH and 3 with idiopathic pulmonary arterial hypertension. Ambrisentan was added to the other PH drugs in all the patients. The patients underwent right-side heart catheterization before and after the administration of ambrisentan with measurement of cardiac output (CO), mean right atrial pressure (mRA), mean pulmonary arterial pressure (mPA), pulmonary vascular resistance (PVR). Brain natriuretic peptide (BNP) was also determined. Results: After administration of ambrisentan (the average follow-up period was 168 ± 97 days), mPA (36 ± 9 vs 22 ± 6: p < 0.01) and mRA (11 ± 6 vs. 7 ± 4: p < 0.01) and CO (4.0 ± 1.5 vs. 4.8 ± 1.8: p < 0.05) improved significantly, but BNP, mRA nor heart rate did not. The most frequent adverse reactions was edema with 6 patients, 3 of which abandoned ambrisentan. Conclusions: Ambrisentan is useful for pulmonary hypertension even if added to other PH drugs.


Analysis of ET-1 system in mild and severe pulmonary arterial hypertension in mice
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Background: A recently developed mouse model for PAH combines hypoxia with a VEGF receptor blocker. Herein we aim to describe in detail this model. The TGFβ/Smad3 pathway is a pivotal factor regulating the transcription of the endothelin (ET-1) gene. Besides, interleukin-1β (IL-1β) increases expression of ET-1, and ETA receptor and reduces expression of ETB receptor. Methods and results: We placed 3-week old male SV129 mice under hypoxia (O2 = 10%) and treated them with a vascular endothelial growth factor receptor blocker (SU5416) (SU mice) (subcutaneous injection three times a week, 20 mg/kg) for 3 weeks. Compared to mice under hypoxia alone (H) and control mice (CTRL), these mice developed severe PAH, characterized by increased right ventricular systolic pressure measured in anesthetized mice by subxiphoid approach (SU: 37 ± 1.7: H: 29 ± 14.4: CTRL: 22.5 ± 1 mmHg), right ventricular hypertrophy (Fulton index: SU: 0.55 ± 0.042: H: 0.4 ± 0.04, CTRL: 0.31 ± 0.026) and muscularization of precapillary vessels together with proliferation of endothelial cells of small arterioles (PCNA positive on endothelial layer/arterial section = SU: 2.9 ± 0.25; H: 1 ± 0.13; CTRL: 0.7 ± 0.08), which lead to completely occluded arterioles by von Willebrand factor expressing cells. Increased ET-1 mRNA, ETA receptor mRNA, protein expression and immunostaining signals and reduced ETB receptor mRNA expression were observed in SU mice only. This was associated with an increased abundance of phosphorylated Smad3 and a 9-fold increase of IL-1β expression. TGF-β mRNA in H and SU mice was similar. Conclusion: In severe PAH, Smad3 by potentiating TGF-β and IL-1β might disturb the expression of the ET system and may represent therefore potential therapeutic targets.


Long-term advanced therapy with bosentan improves symptoms and the time to clinical worsening in the Japanese patients with inoperable chronic thromboembolic pulmonary hypertension
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Introduction: Chronic thromboembolic pulmonary hypertension (CTEPH) is a serious devastating disease. It is still a challenge to treat some patients who are not eligible for pulmonary endarterectomy. Short-term bosentan or PDE5 inhibitor was significantly improved in symptoms, hemodynamics and exercise capacity in such patients. However, the long-term beneficial effect of advanced pulmonary vasodilating drugs is little understood. Therefore, we investigated the long-term effect of advanced therapy in the patients with inoperable CTEPH retrospectively. Methods and results: All consecutive 7 Japanese patients (5 female, mean age 62.6 ± 6.9 years) treated with bosentan (125–250 mg) for symptomatic inoperable CTEPH were included. The time to clinical worsening (TCW) was examined (mean follow-up period 896 ± 564 days). WHO-FC was significantly improved from 3.1 ± 0.4 to 2.1 ± 0.4 (p < 0.01). Pulmonary vascular resistance was significantly decreased from 786.9 ± 300.0 to 352.2 ± 210.7 dyn cm−2 (p < 0.05). Mean pulmonary artery pressure and cardiac index were improved from 47.0 ± 7.6 to 43.3 ± 5.0 mmHg and from 2.18 ± 0.39 to 3.02 ± 0.74 l/min/m² (n = 3, follow-up 651–849 days). Six-minute walk distance was increased from 257.0 ± 151.0 to 369.8 ± 85.7 m (p = 0.06, n = 4, follow-up 651–931 days). Plasma BNP level was significantly decreased from 1160.0 ± 971.4 to 305.1 ± 285.9 pg/ml (p < 0.05). None of them were required hospitalization. Conclusions: Long-term advanced therapy with bosentan improves symptoms, hemodynamics and TCW in CTEPH patients. Advanced therapy is proposed as an essential treatment for the patients with inoperable CTEPH.