Macitentan Reverses Early Obstructive Pulmonary Vasculopathy in Rats: Early Intervention in Overcoming the Survivin-mediated Resistance to Apoptosis


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Objectives: We tested the hypothesis that a novel endothelin receptor antagonist macitentan reverses the early and/or late stages of occlusive pulmonary vascular disease in rats.

Methods: Rats with pulmonary arterial hypertension (PAH), which were produced by combined exposure to a vascular endothelial growth factor receptor inhibitor Sugen 5416 and hypobaric hypoxia for 3 weeks(SuHx), were assigned to receive macitentan (30 mg/kg, once daily by oral gavage) or vehicle during 3–5 weeks (early study, n=40) or during 5–8 weeks (late study, n=38) after Sugen injection. A baseline SuHx PAH rat group, sacrificed just before treatment initiation, was present in each study to evaluate the reversal of disease during treatment. A P-value of <0.05 was considered to be statistically significant.

Results: Compared with vehicle-treated PAH rats and baseline SuHx PAH rats, the macitentan-treated rats significantly showed decreases of the proportion of occlusive lesions in all small arteries (outer diameter: 15–50 μm) per lung section in the early study(baseline PAH rats: 33.8±4.4%, vehicle-treated PAH rats: 41.5±4.1% and macitentan-treated PAH rats: 17.9±2.8%), a finding consistent with the reversal of right ventricular systolic pressure(control rats: 19.4±1.4 mmHg, baseline PAH rats: 78.3±4.9 mmHg,vehicle-treated PAH rats: 79.5±6.4 mmHg and macitentan-treated PAH rats:50.3±5.0 mmHg), indices of right ventricular hypertrophy and medial wall thickness. Macitentan ameliorated but did not reverse the proportion of occlusive lesions in the late study. Although macitentan significantly decreased the proportion of Ki67 positive lesions in both studies, macitentan significantly increased the proportion of cleaved caspase 3 positive α smooth muscle actin (αSMA) cells in occlusive lesions and significantly decreased an anti-apoptotic molecule survivin protein and mRNA expression in lungs and the proportion of survivin positive αSMA cells in occlusive lesions in the early study but not in the late study.

Conclusions: Macitentan reversed early but not late obstructive pulmonary vascular disease in rats. This reversal was associated with the suppression of survivin-related resistance to apoptosis and proliferation of αSMA cells in occlusive lesions. These findings could be mechanistic basis for the efficacy of early treatment and give an insight into later appearance of resistance to treatment for this disorder.