Macrophage activation induced by crizotinib exacerbates pulmonary arterial hypertension

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Introduction: Pulmonary arterial hypertension (PAH) is a lethal vasculopathy histologically associated with remodeling of distal pulmonary arteries and right ventricular failure that is drug-induced in approximately 10% of cases. Recently, PAH induced by chemotherapeutic agents such as receptor tyrosine kinase (RTK) inhibitors (e.g. dasatinib) has been described. Crizotinib is a new MET inhibitor increasingly used for the treatment of ALK-positive non-small cell lung carcinoma. Interestingly, crizotinib has been shown to induce endothelial cells (EC) dysfunction (e.g. inhibition of EC survival and angiogenesis) and is symptomatically associated with dyspnea and peripheral oedema in some patients, which are cardinal symptoms of PAH. We thus hypothesized that chronic administration of crizotinib exacerbates PAH.

Methods: Rats were randomly distributed between groups and all hemodynamic measurements were performed blinded to the condition. To induce PAH, rats were injected with 20mg/kg of Sugen and put in hypoxia (10% O_2) for 3 weeks. After the hypoxia period, rats already exhibited PAH symptoms. Daily oral administration of crizotinib (100mg/kg) or vehicle was performed during 2 weeks. Then, before sacrifice, all rats underwent a comprehensive pressure-volume evaluation by closed chest right heart catheterization. Finally, rats were sacrificed and tissues samples collected for histology measurements.

Results: We observed a significant increase in mortality rates in PAH rats treated with daily oral administration of crizotinib compared to rats treated with vehicle (n=6 per group, $p<0.05$). Furthermore, we demonstrated that crizotinib treatment was associated with worsening of hemodynamic parameters assessed by pressure-volume right heart catheterization in closed chest, please not that all measurements were performed blinded to the condition (n=6 per group, $p<0.05$). More specifically, crizotinib-treated rats exhibited increased right ventricular systolic pressure, mean pulmonary arterial pressure and pulmonary vasculature resistance, as well as decreased cardiac output and stroke volume compared to vehicle-treated rats (n=4 PAH+crizotinib, 6 PAH+vehicle, 5 PAH and 3 control rats; $p<0.05$). Histologically, crizotinib administration significantly increased pulmonary artery wall thickness ($p<0.05$). Finally, crizotinib increased macrophage accumulation and fibrosis within the lungs, as well as within the RV of PAH rats ($p<0.05$).

Conclusion: We documented for the first time that crizotinib treatment markedly increased vascular remodeling and macrophage activation with subsequent marked PAH exacerbation in Sugen-induced PAH rats. This study could have major clinical relevance in the management of patients treated with crizotinib.

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