Inhaled seralutinib exhibits potent efficacy in models of pulmonary arterial hypertension

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Shareable abstract (@ERSpublications)
Seralutinib is an inhaled, small-molecule kinase inhibitor that targets PDGFRα/β, CSF1R and c-KIT, and upregulates BMPR2 protein expression; these pathways play important roles in PAH. The efficacy of seralutinib is demonstrated in two animal models of PAH. https://bit.ly/3wObkEN

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Abstract

Background Signalling through platelet-derived growth factor receptor (PDGFR), colony-stimulating factor 1 receptor (CSF1R) and mast/stem cell growth factor receptor kit (c-KIT) plays a critical role in pulmonary arterial hypertension (PAH). We examined the preclinical efficacy of inhaled seralutinib, a unique small-molecule PDGFR/CSF1R/c-KIT kinase inhibitor in clinical development for PAH, in comparison to a proof-of-concept kinase inhibitor, imatinib.

Methods Seralutinib and imatinib potency and selectivity were compared. Inhaled seralutinib pharmacokinetics/pharmacodynamics were studied in healthy rats. Efficacy was evaluated in two rat models of PAH: SU5416/Hypoxia (SU5416/H) and monocrotaline pneumonectomy (MCTPN). Effects on inflammatory/cytokine signalling were examined. PDGFR, CSF1R and c-KIT immunohistochemistry in rat and human PAH lung samples and microRNA (miRNA) analysis in the SU5416/H model were performed.

Results Seralutinib potently inhibited PDGFRα/β, CSF1R and c-KIT. Inhaled seralutinib demonstrated dose-dependent inhibition of lung PDGFR and c-KIT signalling and increased bone morphogenetic protein receptor type 2 (BMPR2). Seralutinib improved cardiopulmonary haemodynamic parameters and reduced small pulmonary artery muscularisation and right ventricle hypertrophy in both models. In the SU5416/H model, seralutinib improved cardiopulmonary haemodynamic parameters, restored lung BMPR2 protein levels and decreased N-terminal pro-brain natriuretic peptide (NT-proBNP), more than imatinib. Quantitative immunohistochemistry in human lung PAH samples demonstrated increased PDGFR, CSF1R and c-KIT. miRNA analysis revealed candidates that could mediate seralutinib effects on BMPR2.

Conclusions Inhaled seralutinib was an effective treatment of severe PAH in two animal models, with improved cardiopulmonary haemodynamic parameters, a reduction in NT-proBNP, reverse remodelling of pulmonary vascular pathology and improvement in inflammatory biomarkers. Seralutinib showed greater efficacy compared to imatinib in a preclinical study.