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A. BIRNHUBER ET AL.

Pirfenidone exacerbates Th2-driven vasculopathy in a mouse model of systemic sclerosis-associated interstitial lung disease

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Shareable abstract (@ERSpublications)
Pirfenidone worsens vascular and pulmonary dysfunction in a SSc-ILD mouse model due to its negative effects on primed endothelial cells and may lead to unfavourable effects in patients with underlying type 2 inflammation as seen in SSc-ILD https://bit.ly/3Jk821j

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Abstract

Background Systemic sclerosis (SSc) is an autoimmune disease characterised by severe vasculopathy and fibrosis of various organs including the lung. Targeted treatment options for SSc-associated interstitial lung disease (SSc-ILD) are scarce. We assessed the effects of pirfenidone in a mouse model of SSc-ILD.

Methods Pulmonary function, inflammation and collagen deposition in response to pirfenidone were assessed in Fra-2-overexpressing transgenic (Fra-2 TG) and bleomycin-treated mice. In Fra-2 TG mice, lung transcriptome was analysed after pirfenidone treatment. *In vitro*, pirfenidone effects on human eosinophil and endothelial cell function were analysed using flow cytometry-based assays and electric cell-substrate impedance measurements, respectively.

Results Pirfenidone treatment attenuated pulmonary remodelling in the bleomycin model, but aggravated pulmonary inflammation, fibrosis and vascular remodelling in Fra-2 TG mice. Pirfenidone increased interleukin (IL)-4 levels and eosinophil numbers in lung tissue of Fra-2 TG mice without directly affecting eosinophil activation and migration *in vitro*. A pronounced immune response with high levels of cytokines/chemokines and disturbed endothelial integrity with low vascular endothelial (VE)-cadherin levels was observed in pirfenidone-treated Fra-2 TG mice. In contrast, eosinophil and VE-cadherin levels were unchanged in bleomycin-treated mice and not influenced by pirfenidone. *In vitro*, pirfenidone exacerbated the IL-4 induced reduction of endothelial barrier resistance, leading to higher leukocyte transmigration.

Conclusion This study shows that antifibrotic properties of pirfenidone may be overruled by unwanted interactions with pre-injured endothelium in a setting of high T-helper type 2 inflammation in a model of SSc-ILD. Careful ILD patient phenotyping may be required to exploit benefits of pirfenidone while avoiding therapy failure and additional lung damage in some patients.