Pan-lysyl oxidase inhibitor PXS-5505 ameliorates multiple-organ fibrosis by inhibiting collagen crosslinks in rodent models of systemic sclerosis

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Abstract

Background/Purpose: Systemic sclerosis (SSc) is characterised by progressive multiple-organ fibrosis leading to morbidity and mortality. Lysyl oxidases play a vital role in the cross-linking of collagens and subsequent build-up of fibrosis in the extracellular matrix. As such, their inhibition provides a novel treatment paradigm for SSc. Experimental Approach: Lysyl oxidases are upregulated in preclinical models of fibrosis in skin, lung, heart, kidney and liver. A novel small molecule pan-lysyl oxidase inhibitor, PXS-5505, currently in clinical development for bone fibrosis treatment was evaluated in in vivo rodent models resembling the fibrotic conditions in SSc. Key Results: Both lysyl oxidase and lysyl oxidase-like 2 (LOXL2) expression was elevated in the skin and lung of SSc patients. Once-a-day oral application of PXS-5505 inhibited lysyl oxidase activity in the skin and LOXL2 activity in the lung. PXS-5505 exhibited anti-fibrotic effects in the SSc skin mouse model, reducing dermal thickness and α-smooth muscle actin compared to the disease controls. Similarly, in the bleomycin-induced mouse lung model, PXS-5505 reduced tissue fibrosis toward normal levels. The anti-fibrotic efficacy of PXS-5505 in the bleomycin exposed lungs was mediated by its ability to normalise collagen/elastin crosslink formation, a direct consequence of lysyl oxidase inhibition. PXS-5505 also reduced area of fibrosis in rodent models of the ischaemia-reperfusion heart, the unilateral ureteral obstruction kidney and the CCl4-induced fibrotic liver. Conclusion/Implication: PXS-5505 consistently demonstrates potent anti-fibrotic efficacy in multiple models of organ fibrosis relevant to the pathogenesis of SSc, suggesting that it may be efficacious as a novel approach for treating SSc.

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