Arsenic trioxide demonstrates efficacy in a mouse model of preclinical systemic sclerosis

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INTRODUCTION

Uncontrolled T-cell activation plays a key role in systemic sclerosis (SSc). Arsenic trioxide (ATO) has immunological effects and has demonstrated potential in preclinical SSc models. In this study, we assessed the efficacy of ATO in Fra2 transgenic ($Fra2^{TG}$) mice, which develop severe vascular remodeling of pulmonary arterioles and nonspecific interstitial pneumonia-like lung disease, closely resembling human SSc-associated pulmonary hypertension, therefore partially resembling to the SSc human disease.

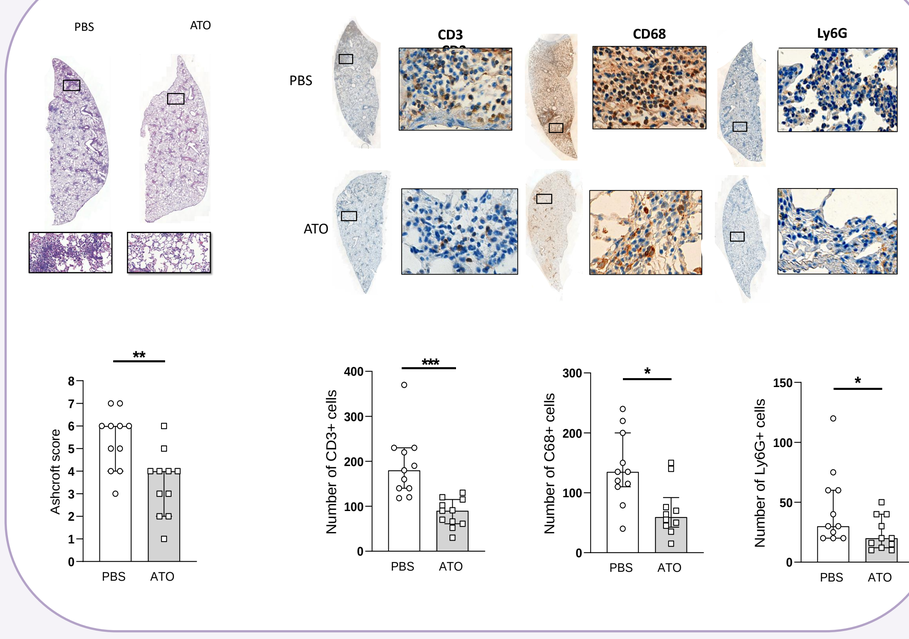
OBJECTIVE To investigate the efficacy of ATO, an immunomodulator drug, in reducing fibrosis features and vascular remodeling in Fra-2 transgenic mice

METHODS

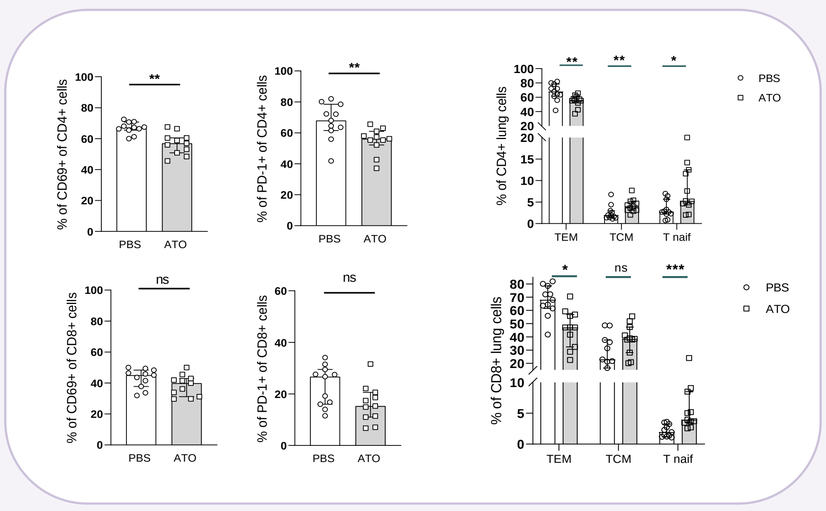
The efficacy of ATO in $Fra2^{TG}$ mice was evaluated through histological scoring and determination of cell infiltration. Fibrotic changes in the lungs were assessed by measuring collagen content biochemically, using second harmonic generation to measure fibrillar collagen, and imaging via computed tomography. Cardiovascular effects were determined by measuring right ventricular systolic pressure and vessel remodeling. The mechanism of action of ATO was then investigated by analyzing lung cell infiltrates using flow cytometry and bulk RNA with sequencing techniques.

RESULTS

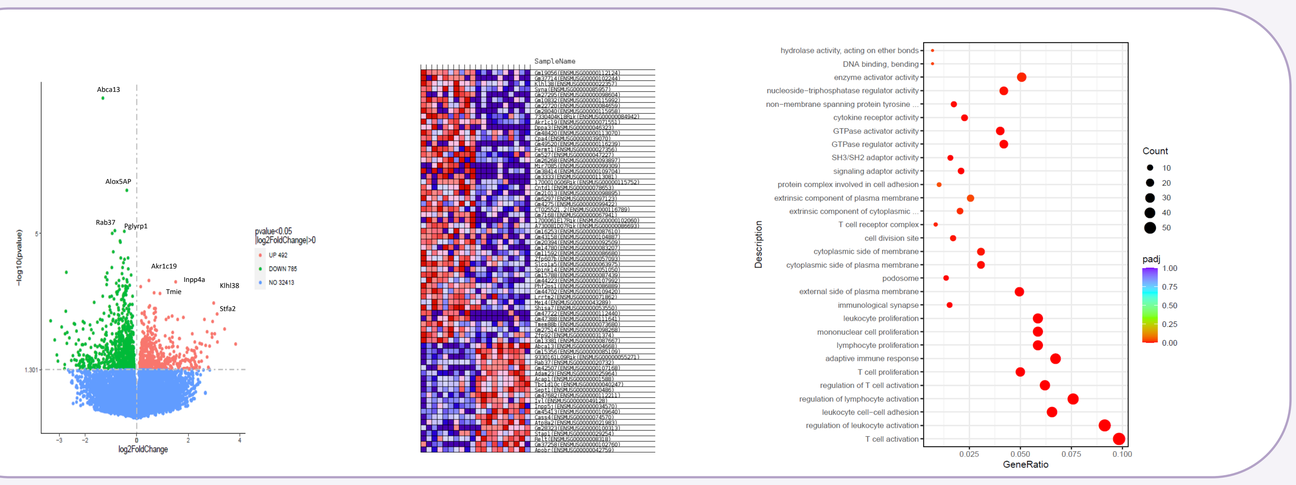
ATO alleviates Ashcroft histological score and inflammatory cell infiltration in the lung of Fra-2^{TG}



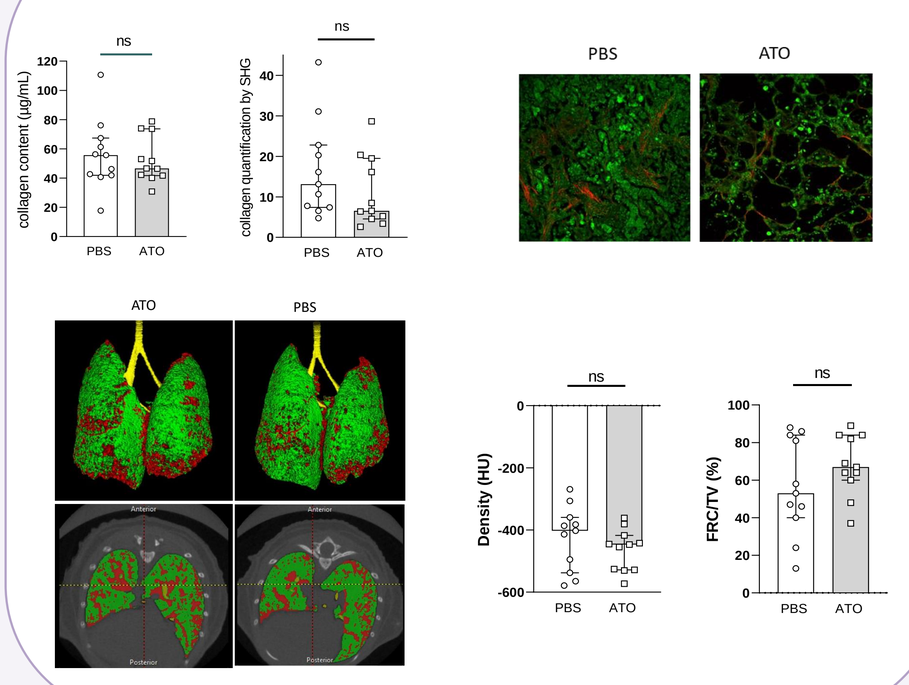
ATO decreases T-cell activation in $Fra2^{TG}$ lung cells



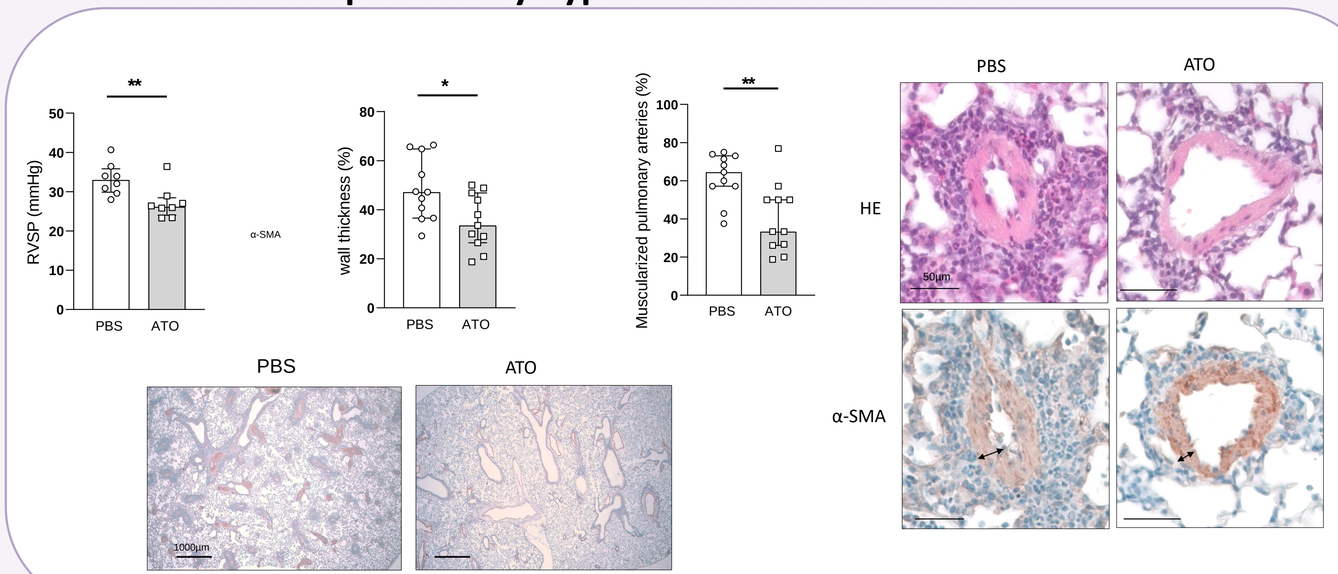
Downregulated genes expressed in ATO-treated lungs are associated with immune activity and inflammation



Investigations of fibrotic markers show a trend of reduction in various measurements of fibrosis



ATO alleviates pulmonary hypertension in $Fra2^{TG}$ mice



CONCLUSION

Our study provides compelling evidence of the positive effects of ATO treatment on lung function in a mouse model of SSc.
These effects were characterized by a significant reduction in inflammatory infiltration and strong improvements in vascular remodeling, although the impact on fibrotic features was incomplete.
We demonstrate that these benefits are mediated through positive immune improvements, particularly T-cell differentiation and activation.
Our findings represent a substantial advancement in understanding the complex interplay between inflammation-driven fibrosis and the pathophysiology of SSc.
The clinical translation of our results to patients will require further investigation in future follow-up studies.
Our results also pave the way for potential innovative therapies, especially in the early/inflammatory phase of SSc.

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