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**Leflunomide prevents ROS-induced systemic fibrosis in mice<sup>☆</sup>**

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**ABSTRACT**

Systemic sclerosis (SSc) is a connective tissue disorder characterized by fibrosis of the skin and inner organs, vasculopathy and immunological abnormalities. Recent insights into the polarization of macrophages in scleroderma and into the implication of STAT6 and KLF4 in this process have prompted us to investigate the effects of the inhibition of STAT6 signaling pathway by leflunomide in mice. SSc was induced in BALB/c mice by daily subcutaneous injections of hypochlorous acid (HOCl) or bleomycin. Mice were treated (or not) every other day, for 4 or 6 weeks, by leflunomide. Skin and lung fibrosis as well as immunological features were studied. Mice exposed to HOCl developed a diffuse cutaneous SSc with pulmonary fibrosis and anti-DNA topoisomerase 1 auto-antibodies. STAT6 pathway was hyperactivated and KLF4 was overexpressed in the skin and the lungs of diseased mice. Their inhibition by leflunomide prevented skin and lung fibrosis. Moreover, the hyperproliferative and pro-oxidative phenotype of skin and lung fibroblasts was reversed by leflunomide. Beneficial immunological effects of leflunomide were associated with decreased activation

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