CONNECTIVE TISSUE DISEASES

Undoing the damage caused by systemic sclerosis

Fibrosis of the skin and other organs underlies many of the severe manifestations of systemic sclerosis (SSc), and is a major contributor to the mortality and morbidity of the disease. Many patients with SSc present to their rheumatologist only after substantial tissue fibrosis has already occurred. Antifibrotic drugs for this disease should, therefore, aim to not only prevent the development of fibrosis, but also to induce regression of established thickening. In this context, a preclinical study of imatinib mesilate by Jörg Distler and colleagues shows that this tyrosine kinase inhibitor could be an effective treatment for patients with SSc.

Previous work by this group and others has demonstrated that imatinib prevents the development of inflammation-driven experimental fibrosis in various tissues. In a model of bleomycin-induced dermal fibrosis, for instance, treatment with imatinib prevented the development of fibrosis when started before the application of the profibrotic agent. This mouse model is representative of the early stages of SSc, during which fibrosis is driven by inflammatory processes. "In SSc, prominent inflammation is mainly restricted to the early stages of the disease, and rarely occurs in longstanding disease," explains Distler. "Models such as bleomycin-induced fibrosis mimic the early stages of SSc, but are less appropriate for representing the later stages of SSc." Distler's team set out to determine the efficacy of imatinib in preclinical models of established SSc that better reflect the clinical situation encountered by rheumatologists.

In the tight skin 1 genetic mouse model of SSc, in which the development of skin fibrosis is largely independent of inflammatory processes, imatinib almost completely prevented dermal thickening. The differentiation of resting fibroblasts into myofibroblasts—important effector cells in SSc fibrosis—was also largely prevented. The number of myofibroblasts in control mice was increased threefold compared with imatinib-treated mice, which had

normal numbers of these cells. Dermal thickness was at normal levels in imatinib-treated tight skin 1 mice, and hypodermal thickening was also greatly reduced in these mice compared with controls. In a separate experiment, the investigators used a modified model of bleomycin-induced fibrosis to illustrate the efficacy of imatinib in inducing the regression of established fibrosis. The researchers administered the profibrotic agent for a prolonged period that was continued during imatinib treatment, but imatinib nevertheless prevented further accumulation of extracellular matrix components. In fact, levels of dermal thickness following administration of imatinib were lower than pretreatment levels. Imatinib, therefore, not only stopped the progression of fibrosis but also induced the regression of pre-existing fibrosis.

Transforming growth factor β (TGF- β) and platelet-derived growth factor (PDGF) have important roles in fibroblast activation, and, therefore, in the accumulation of excess extracellular matrix proteins, in SSc. By blocking the tyrosine kinase activity of both Abelson kinase (c-Abl), an important downstream signaling molecule of TGF- β , and PDGF receptors, imatinib targets two major profibrotic pathways in SSc. These pathways are thought to be important in the development of fibrosis in the later,

noninflammatory stages of SSc. In these stages, tissue fibrosis is mediated by the persistent overproduction of extracellular matrix proteins rather than by the release of profibrotic mediators by inflammatory cells. The investigators hypothesize that imatinib probably induces the regression of established fibrosis by inhibiting *de novo* collagen synthesis, as opposed to stimulating matrix degradation.

Imatinib is already widely used as an oral treatment for various types of cancer. This study has now shown that it could be effective in SSc, a hypothesis that is supported by a report of its successful use in a small number of patients with nephrogenic systemic fibrosis. Together with the results of earlier trials, the present study shows that imatinib has promise for treating patients with SSc. Distler concludes that the findings "suggest that imatinib might induce the regression of established fibrosis and might also be a candidate for clinical trials in patients in the later, noninflammatory stages of SSc".

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