Systemic sclerosis (SSc) is a connective tissue disease of inner organs and skin. Its cutaneous manifestations are called scleroderma but the terms “systemic sclerosis” and “scleroderma” are sometimes used interchangeably (Fett, 2013). The American College of Rheumatology and the European League against Rheumatism have recently issued a consensus statement for the classification of SSc (van den Hoogen et al., 2013), but the classification of this condition has not been universally accepted (Nihtyanova et al., 2014).

SSc has a prevalence of up to 1 in 1000 people, apparently depending on ethnicity, and it predominantly affects women, mostly in the third to fifth decade of their lives (D’Amico et al., 2013). It is a debilitating and often fatal condition for which no approved disease-modifying treatment exists (Ho et al., 2014; Nihtyanova et al., 2014). Therefore, a recent article in the Journal of Pharmacology and Experimental Therapeutics (Haak et al., 2014) is a sign of hope; the clinically available symptomatic and palliative treatments have been reviewed elsewhere (Bournia et al., 2009).

SSc is characterized by progressive fibrosis not only of the skin but also of multiple inner organs, including the lungs, heart, kidney, and gastrointestinal tract (Ho et al., 2014). Although fibrosis of the skin causes sometimes severe functional impairment, it is the fibrosis of the inner organs that ultimately leads to fatal outcomes. The pathogenesis of SSc remains to be defined in detail, but it involves chronic tissue injury, endoplasmic reticulum stress, endothelial dysfunction, pericyte activation, and aberrant T cell–driven autimmunity. Eventually, the final common pathway is the activation of fibroblasts, their transition to myofibroblasts, and excessive extracellular matrix deposition (Denton et al., 2006; Wynn and Ramalingam, 2012).

The recent work of Haak et al. (2014) is based on the concept that gene transcription induced by serum response factor is a critical driver of myofibroblast activation by nearly all factors leading to fibrosis. Such serum response factor–regulated gene expression involves Rho-GTPase–stimulated nuclear localization of its transcription coactivator myocardin-related transcription factor (MRTF). In support of this concept, Haak et al. (2014) demonstrate spontaneous activation of an MRTF-regulated gene transcription program in dermal fibroblasts from SSc patients. More importantly, they have identified a small molecule, CCG-203971 [N-(4-chlorophenyl)-1-[[3,5-bis(trifluoromethyl)phenyl]formamido]oxy]-N-(4-chlorophenyl)propanamide], an improved analog of CCG-1423 [2-[[3,5-bis(trifluoromethyl)phenyl]formamido(oxy)]-N-(4-chlorophenyl)propanamide] (Fig. 1), that blocks MRTF nuclear localization by interfering with the microtubule-associated mono-oxygenase, calponin and LIM domain–containing 2 (MICAL-2)–mediated regulation of intranuclear actin polymerization. In in vitro studies, CCG-203971 inhibited the enhanced proliferation of SSc-derived dermal fibroblasts but not that of normal fibroblasts. It also reversed the myofibroblast phenotype of transforming growth factor–β–stimulated normal dermal fibroblasts and the spontaneous activation of SSc-derived fibroblasts with a potency of about 3 μM; in this assay, CCG-203971 was about 100-fold more potent than pirfenidone (Fig. 1; Schaefer et al., 2011), a drug currently in phase II studies for the treatment of SSc patients. Furthermore, CCG-203971 prevented the development of bleomycin-induced skin thickening and collagen deposition in mice in vivo.

It is a long journey from nonclinical findings like those of Haak et al. (2014) to a safe and effective treatment of SSc and other fibrotic conditions. Given the plethora of chemokines, hormones, and growth and paracrine factors implied in fibrosis development (Denton et al., 2006; Wynn and Ramalingam, 2012), it is

This Commentary is in reference to “Targeting the Myofibroblast Genetic Switch: Inhibitors of Myocardin-Related Transcription Factor/Serum Response Factor–Regulated Gene Transcription Prevent Fibrosis in a Murine Model of Skin Injury,” found in J Pharmacol Exp Ther 2014, 349:480–486. dx.doi.org/10.1124/jpet.114.213520comm.

ABBREVIATIONS: CCG-1423, 2-[[3,5-bis(trifluoromethyl)phenyl]formamido]oxy]-N-(4-chlorophenyl)propanamide; CCG-203971, N-(4-chlorophenyl)-1-[[3-(furan-2-yl)phenyl]carbonyl]piperidine-3-carboxamide; IPF, idiopathic pulmonary fibrosis; MRTF, myocardin-related transcription factor; SSc, systemic sclerosis.
A unique set of mediators is involved in each of these fibrotic pathologies, such as arterial hypertension (Goldsmith et al., 1999; Sakamoto et al., 2009; Kusunoki et al., 2012). These effects were not explained by their blood pressure–lowering capacity; at least for some members of this drug class, beneficial effects in fibrosis animal models may involve additional mechanisms, such as partial agonism at peroxisome proliferator–activated receptor-\(\gamma\) (Kusunoki et al., 2012). However, none of the angiotensin II receptor antagonists have been conclusively studied in SSc or IPF.

Pirfenidone is an agent with an unclear molecular target but with efficacy in different animal models of fibrosis (Schaefer et al., 2011). Clinical studies of pirfenidone in patients with IPF have initially yielded inconsistent results (Potts and Yogaratnam, 2013), which has led to regulatory approval in Europe but not the United States for this indication; however, very recently another positive phase III study with pirfenidone was reported (King et al., 2014). Currently, pirfenidone is undergoing phase II studies in patients with SSc (www.clinicaltrials.gov).

Nintedanib (Fig. 1), a tyrosine kinase inhibitor targeting multiple pathways of fibrosis, has shown promising efficacy in human lung fibroblasts and two mouse models of IPF (Wollin et al., 2014). Nintedanib has demonstrated promising improvement in the decline in lung function in a 12-month phase II trial (Richeldi et al., 2011). Very recently, two phase III (INPULSIS) studies confirmed consistent clinical efficacy in slowing disease progression in IPF patients (Richeldi et al., 2014); data in SSc patients are not available. Whether efficacy in IPF is predictive of beneficial effects in SSc is unknown. Given their desperate situation, patients with SSc urgently await clinical data for the disease with pirfenidone, nintedanib, MRTF inhibitors, and other compounds.

References

Previous studies have established that the activation of fibroblasts and their transition to myofibroblasts, often detected as increased expression of \(\alpha\)-smooth muscle actin, involves the T cell–derived cytokines interleukin-4 and interleukin-13, and also growth factors such as transforming growth factor-\(\beta\) and connective tissue growth factor as well as hormones and paracrine factors, including angiotensin II, endothelin, lysophosphatidic acid, or thrombin (Denton et al., 2006; Wynn and Ramalingam, 2012). Accordingly, numerous molecular targets are currently under investigation for a potential treatment of fibrotic conditions; they have recently been reviewed (McMahan and Wigley, 2014), but it may be some time before most of these become available for clinical investigation.

Therefore, it may be useful to look at the compounds with proven effects in other fibrotic conditions that already are or will soon be clinically available. Given the role of angiotensin II in fibrosis development (Denton et al., 2006; Wynn and Ramalingam, 2012), it is not surprising that multiple antagonists of its type 1 receptor have shown efficacy in different animal models of cardiac, liver, or renal fibrosis (Brown et al., 1999; Sakamoto et al., 2009; Kusunoki et al., 2012). These effects were not explained by their blood pressure–lowering capacity; at least for some members of this drug class, beneficial effects in fibrosis animal models may involve additional mechanisms, such as partial agonism at peroxisome proliferator–activated receptor-\(\gamma\) (Kusunoki et al., 2012). However, none of the angiotensin II receptor antagonists have been conclusively studied in SSc or IPF.

A key factor in all fibrotic diseases is the activation of fibroblasts and their transition into myofibroblasts, resulting in the ability to synthesize large amounts of extracellular matrix. This initially is often driven by noninfectious inflammation, and some investigators consider fibrosis to be a uniform response to chronic unresolved inflammation, which can be caused by many factors (Fielding et al., 2014). However, fibrosis development often persists after the initial inflammation has resolved spontaneously or was suppressed by medications. Accordingly, it is generally assumed that targeting the shared response of fibrosis may be a successful disease modifying strategy for SSc, IPF, and other fibrotic conditions (Zeisberg and Kalluri, 2013).