Review

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Rationale for the evaluation of nintedanib as a treatment for systemic sclerosis–associated interstitial lung disease

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Abstract

Interstitial lung disease is a common manifestation of systemic sclerosis. Systemic sclerosis–associated interstitial lung disease is characterized by progressive pulmonary fibrosis and a reduction in pulmonary function. Effective treatments for systemic sclerosis–associated interstitial lung disease are lacking. In addition to clinical similarities, systemic sclerosis–associated interstitial lung disease shows similarities to idiopathic pulmonary fibrosis in the pathophysiology of the underlying fibrotic processes. Idiopathic pulmonary fibrosis and systemic sclerosis–associated interstitial lung disease culminate in a self-sustaining pathway of pulmonary fibrosis in which fibroblasts are activated, myofibroblasts accumulate, and the excessive extracellular matrix is deposited. Nintedanib is a tyrosine kinase inhibitor that has been approved for the treatment of idiopathic pulmonary fibrosis. In patients with idiopathic pulmonary fibrosis, nintedanib slows disease progression by decreasing the rate of lung function decline. In this review, we summarize the antifibrotic, anti-inflammatory, and attenuated vascular remodeling effects of nintedanib demonstrated in in vitro studies and in animal models of aspects of systemic sclerosis. Nintedanib interferes at multiple critical steps in the pathobiology of systemic sclerosis–associated interstitial lung disease, providing a convincing rationale for its investigation as a potential therapy. Finally, we summarize the design of the randomized placebo-controlled SENSCIS® trial that is evaluating the efficacy and safety of nintedanib in patients with systemic sclerosis–associated interstitial lung disease.

Keywords

Fibroblasts, fibrosis, scleroderma, systemic sclerosis–associated interstitial lung disease, tyrosine kinase inhibitor

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Introduction

Systemic sclerosis (SSc) is a rare connective tissue disease associated with high morbidity and mortality.[1–3] SSc is characterized by systemic (multi-organ) immunological, vascular, and fibrotic abnormalities, and is highly heterogeneous in its manifestations and clinical course.[2,3] Skin thickening, sclerosis, and ulceration, particularly of the fingers, are common and can cause considerable disability,[4,5] while the disease can also affect the pulmonary, cardiovascular, esophageal/gastrointestinal, musculoskeletal, and renal systems.[3] Interstitial lung disease (ILD) and pulmonary arterial hypertension are the leading causes of SSc-related death.[6] A *meta*-analysis of data from 13,529 patients estimated that survival following diagnosis of SSc was 74.9% at 5 years and 62.5% at 10 years.[1]

Systemic sclerosis–associated interstitial lung disease (SSc-ILD) is characterized by progressive pulmonary fibrosis, deterioration in lung function, symptoms of cough and dyspnea, and reduced quality of life.[7–9] SSc-ILD shows

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similarities to idiopathic pulmonary fibrosis (IPF), a more common progressive-fibrosing ILD, in its natural history but tends to progress more slowly than IPF and to be associated with a non-specific interstitial pneumonia pattern on high resolution computer tomography (HRCT) rather than usual interstitial pneumonia, as seen in IPF.[10] Acute deteriorations in lung function, while less common than in IPF, may also occur in patients with SSc-ILD.[11,12]

Current treatment of SSc

There are no approved treatments for SSc, but a multitude of drugs are used to treat certain manifestations of SSc and its related comorbidities.[3] Immunosuppressant therapy is most frequently used, including glucocorticoids, cyclophosphamide (CYC), mycophenolate mofetil (MMF), azathioprine, and methotrexate.[13,14] In Scleroderma Lung Study I (SLS I), conducted in 158 patients with SSc-ILD, treatment with CYC for 1 year provided a modest but significant benefit on forced vital capacity (FVC) percent predicted versus placebo, as well as improvements in dyspnea and skin thickening.[15] However, the use of CYC is limited due to its toxicity. In Scleroderma Lung Study II (SLS II), in which 142 patients with SSc-ILD received oral MMF for 2 years or oral CYC for 1 year followed by placebo for 1 year, improvements in FVC percent predicted, dyspnea, and skin thickness were observed at 2 years in both groups, with no significant between-group difference, but with fewer adverse event–related treatment discontinuations in patients receiving MMF versus CYC.[16] The latest treatment guidelines for SSc issued by the European League Against Rheumatism Collaborative Initiative (EULAR) and the EULAR Scleroderma Trials and Research Group (EUSTAR) recommend tailored CYC therapy for SSc-ILD, particularly in the case of progressive disease.[17] These guidelines also recommend that autologous hematopoietic stem cell transplantation (HSCT) should be considered for patients who have rapidly progressive SSc at risk of organ failure, with careful evaluation of the risk–benefit profile for individual patients. HSCT has shown not only considerable benefits in selected patients with SSc but also significant treatment-related mortality.[18] There is a considerable unmet need for new therapies for SSc-ILD with proven efficacy and safety, and several novel compounds, with varying mechanisms of action, are under investigation as potential treatments for this condition.[19]

Pathogenesis of SSc and SSc-ILD

The pathogenesis of SSc is extremely complex, but it is believed that the clinical manifestations of SSc result from distinct but highly interdependent processes: (a) vascular damage involving microvascular endothelial cells leading to fibroproliferative vasculopathy and capillary rarefication, perivascular inflammation, and autoimmune activation; (b) abnormalities in the innate and adaptive immune system resulting in autoantibody production, cell-mediated autoimmunity, and the release of profibrotic mediators; and ultimately (c) activation of fibroblasts to myofibroblasts, leading to excessive extracellular matrix (ECM) deposition in skin, blood vessels, and internal organs.[20,21]

Damage to vascular endothelial cells, which may result from physical trauma, ischemia reperfusion injury, infectious agents, cytotoxic T cells, autoantibodies, or oxidative stress, induces the release of chemokines and growth factors such as endothelins, platelet-derived growth factor, and vascular endothelial growth factor.[22,23] These change endothelial permeability and stimulate recruitment and proliferation of leukocytes. These factors and cells would normally control the healing process. However, in patients with SSc, repetitive vascular damage and a failure to resolve the inflammatory response and repair the endothelium evoke adaptive and innate immune mechanisms, including the buildup of macrophages and neutrophils, which recruit lymphocytes to sites of injury. The contribution of endothelial apoptosis to the pathogenesis of SSc is incompletely understood. Apoptosis of endothelial cells might contribute to tissue injury when they are engulfed by macrophages and immature dendritic cells, which then present antigens to T cells,[24] or activate the complement and coagulant pathway, resulting in vasculopathy.[25,26] The role of monocytes/macrophages is also debated. Classically activated macrophages of the M1 type and alternatively activated macrophages of the M2 type belong to several subgroups stimulated by mediators like interferon gamma (IFNγ), tumor necrosis factor (TNF), interleukin (IL)-4, IL-6, IL-13, IL-10, and macrophage colony-stimulating factor (M-CSF). M1 and more prominently M2 signatures have been described in the blood, skin, and lung of patients with SSc, but their relevance remains to be defined.[27]

Plasma cells secrete specific autoantibodies against host cell antigens and can worsen tissue injury.[28] Chemokines and growth factors originating from the endothelium recruit and activate mesenchymal progenitor cells and resident fibroblasts. Profibrotic factors secreted by activated T cells stimulate the activation of fibroblasts, as well as the synthesis and secretion of ECM.[29] Differentiation of fibroblasts into contractile myofibroblasts expressing alpha smooth muscle actin (αSMA) augments the pathologic processes. Continued production and deposition of ECM components, particularly fibrillar collagen types I and III, within connective tissues causes fibrosis, tissue contraction, and scarring.[30] This inflammation phase involves the activation of T cells and the development of T cells with mainly type 2 T-helper-cell profibrotic cytokine profiles (IL-4, IL-5, and IL-13). Additional T-cell subgroups and B cells, with abnormalities in phenotype and function, are also present. Mesenchymal cell populations, including fibroblasts,

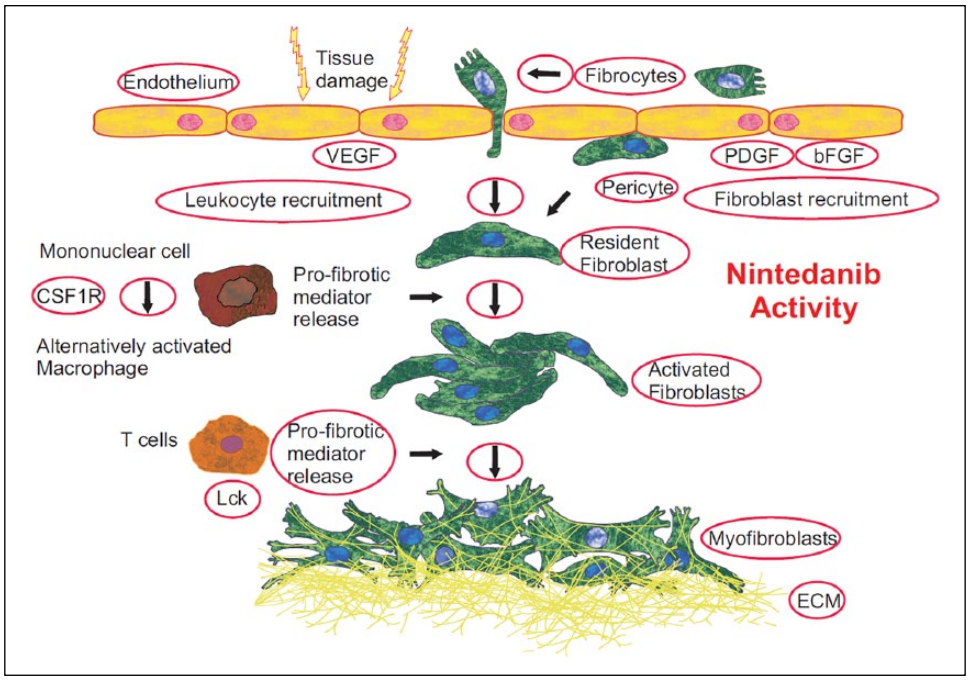

Figure 1. Effects of nintedanib on pathogenic mechanisms with potential relevance in SSc.
This figure depicts pathogenic mechanisms of SSc that have been shown to be targeted by nintedanib in experiments on human cells or in animal models resembling aspects of SSc and lung fibrosis. Nintedanib potently targets fibroblast growth factor receptor (FGFR), platelet-derived growth factor receptor (PDGFR), vascular endothelial growth factor receptor (VEGFR), lymphocyte-specific tyrosine-protein kinase (Lck), and colony-stimulating factor 1 receptor (CSF1R). Nintedanib also exerts vascular effects, that is, inhibits the proliferation of endothelial cells and pericytes. Nintedanib reduces the recruitment of lymphocytes to the lung. Nintedanib inhibits the differentiation and migration of fibrocytes, and the migration, proliferation, and contraction of fibroblasts. By reducing the number of fibroblasts and their transformation to myofibroblasts, the secretion of extracellular matrix (ECM) is reduced. Furthermore, nintedanib blocks the differentiation of alternatively activated macrophages and the release of profibrotic mediators from T cells involved in the initiation of fibrosis.

pericytes, and circulating progenitor cells, are activated and expanded, further contributing to tissue damage.[31]

SSc-ILD shows similarities to IPF in the pathophysiology of the underlying fibrotic cascade. Although the initiating and amplifying events are described to be different,[10] the pathogenesis of both these diseases ends with fibroblast activation, migration, proliferation, and myofibroblast accumulation with excessive ECM deposition, representing a common and self-sustaining final pathway of lung fibrosis.[32] While this suggests that drugs that target fundamental fibrotic pathways in IPF may also be effective in SSc-ILD, the pathological and clinical differences between these diseases mean that robust clinical trials are needed to ascertain the utility of drugs used in IPF in patients with SSc-ILD.

Mechanism of action of nintedanib in SSc and SSc-ILD

Nintedanib is a small-molecule tyrosine kinase inhibitor (TKI), which binds competitively to the adenosine triphosphate (ATP) binding pocket of kinases, blocking their downstream signaling.[33] Nintedanib targets platelet-derived growth factor receptor (PDGFR) α and β, fibroblast growth factor receptor (FGFR) 1–3, and vascular endothelial growth factor receptor (VEGFR) 1–3.[34,35] Nintedanib also inhibits Flt-3 (Fms-like tyrosine-protein kinase), Lck (lymphocyte-specific tyrosine-protein kinase), Lyn (tyrosine-protein kinase Lyn), Src (proto-oncogene tyrosine-protein kinase Src) kinases,[34] and the colony-stimulating factor 1 receptor (CSF1R).[36,37] Several of these kinase targets, including PDGFR,[38] FGFR,[39] VEGFR,[33,40] Src,[41,42] and CSF1R[43] are associated with pathogenic processes in lung fibrosis, while the Src-family kinases Lck and Lyn are involved in the activation of T cells and B cells.[44,45] Recently, additional potential kinase targets were described for nintedanib,[37] but their relevance for its antifibrotic activity is unknown (Figure 1).

Nintedanib was originally developed to be a treatment for non-small cell lung cancer by blocking neo-angiogenesis and with it, tumor growth. Preclinical pharmacodynamic exploration revealed that nintedanib attenuates the proliferation of three cell types involved in angiogenesis: endothelial cells, pericytes, and smooth muscle cells.[34] Later, nintedanib was developed as a treatment for IPF, which shows several similarities in pathogenic pathways to cancer.[46] Based on clinical trial data showing that nintedanib reduces the progression of IPF by slowing decline in lung function,[47,48] nintedanib has received regulatory approval as a treatment for IPF in many countries worldwide. The antifibrotic effects

Table 1. Exploration of nintedanib in dermal fibroblasts from patients with SSc.[52]

Model system/characteristics	Effects of nintedanib
TGFβ- and PDGF-induced ECM components and markers of fibroblast to myofibroblast transformation	Collagens 1a1 and 1a2, fibronectin, αSMA, mRNA ↓ Collagen, stress fibers, and TGFβ signaling ↓
TGFβ- and PDGF-induced proliferation and migration of fibroblasts	TGFβ- and PDGF-induced proliferation ↓ TGFβ- and PDGF-induced migration ↓

SSc: systemic sclerosis; TGFβ: transforming growth factor beta; PDGF: platelet-derived growth factor; ECM: extracellular matrix; αSMA: alpha smooth muscle actin; ↓: significant reduction (independent of concentration used).

and safety of nintedanib demonstrated in patients with IPF are regarded as providing proof of concept for its investigation in patients with SSc-ILD.

The mechanism of action of nintedanib in lung fibrosis has been characterized based on in vitro studies and in vivo models. Nintedanib inhibits the proliferation, migration, and contraction of lung fibroblasts from patients with IPF,[33] as well as attenuates the differentiation and migration of profibrotic fibrocytes[49] and the transformation of lung fibroblasts to myofibroblasts.[35] Recently, nintedanib was also shown to restore the elastic modulus of fibrotic matrices to reverse the myofibroblastic phenotype of pericytes.[50] Nintedanib has demonstrated antifibrotic and anti-inflammatory activity in rodent models of pulmonary fibrosis created using various triggers.[33,35,51] In these models, nintedanib attenuated the accumulation of lymphocytes in bronchoalveolar lavage fluid; reduced levels of IL-1β, the chemokine CXCL1/KC, and the tissue inhibitor of metalloproteinases-1; blocked expression of fibrosis-related marker genes such as transforming growth factor beta 1 (TGFβ1) and procollagen 1; reduced histology scores of inflammation, granuloma formation, and fibrosis in the lungs; reduced lung tissue density and the collagen content of lung tissue; and improved static lung compliance.[33,35,51] In mice with bleomycin-induced pulmonary fibrosis, nintedanib also attenuated vascular proliferation, resulting in the normalization of the distorted microvascular architecture.[51]

Recent in vivo investigations have revealed antifibrotic and anti-inflammatory activities of nintedanib in animal models of aspects of SSc. In bleomycin-induced skin fibrosis, graft versus host disease-induced skin fibrosis, tight skin (fibrillin-1 transgenic), and Fra-2 murine models of SSc, nintedanib reduced myofibroblast accumulation and ECM deposition in skin and lung, attenuated skin and lung fibrosis, and reduced dermal thickening.[52,53] In Fra-2+/– transgenic mice, nintedanib attenuated pulmonary vascular remodeling by reducing the number of vascular smooth muscle cells, pulmonary vascular wall thickness, and the number of occluded pulmonary vessels.[53] In addition, nintedanib improved vascular remodeling in the skin of Fra-2+/– mice, with a reduction in the number of endothelial cells undergoing apoptosis and an increase in the number of vessels in the dermis.[53] In in vitro studies, nintedanib has been shown to block the release of profibrotic mediators from human peripheral blood monocytic cells and T cells,[54] and reduce the M2 polarization of human macrophages exposed to macrophage colony-stimulating factor, IL-4, and IL-13.[36,53] In experiments in dermal fibroblasts from patients with SSc, nintedanib inhibited fibroblast migration and proliferation; decreased the expression of ECM markers: collagens 1a1 and 1a2, and fibronectin; and reduced transformation of fibroblasts to myofibroblasts as detected by reductions in αSMA and stress fibers.[52] An overview of the preclinical exploration of nintedanib in dermal fibroblasts from patients with SSc and in in vivo models of SSc/SSc-ILD is presented in Tables 1 and 2.

The comparable effects of nintedanib in animal models of lung fibrosis and SSc suggest that the effective dose may be comparable in patients with IPF and SSc. Nintedanib effectively inhibited fundamental processes of skin fibrosis (i.e. the proliferation and migration of dermal fibroblasts) at concentrations of 100 nM, which are close to the exposure levels achieved in humans (59–74 nmol/L) after steady-state oral dosing of nintedanib 150 mg twice daily in patients with IPF.[55,56]

Clinical investigation of nintedanib in SSc-ILD

The efficacy and safety of nintedanib in patients with SSc-ILD are being assessed in the SENSCIS® trial (ClinicalTrials.gov: NCT02597933; EudraCT: 2015-000392-28).[57] A total of 580 patients with an age of ⩾18 years with onset of SSc (first non-Raynaud's symptom), ⩽7 years before screening, ILD (⩾10% fibrosis of the lungs on HRCT), FVC ⩾40% predicted, and diffusion capacity of the lung for carbon monoxide 30% to 89% predicted were enrolled. Patients receiving low-dose prednisone and/or stable background therapy with MMF or methotrexate were allowed to participate. While non-clinical data suggest that the potential risk of nintedanib to increase digital ulceration in patients with SSc is low,[53] and studies of patients with IPF who undergo lung transplant following treatment with nintedanib suggest that nintedanib does not have adverse events on wound healing,[58–60] given that nintedanib is an inhibitor of the VEGF receptor, patients with >3 fingertip ulcers or a history of severe digital necrosis have been excluded from the trial as a precautionary measure.

Table 2. Exploration of nintedanib in mouse models of SSc/SSc-ILD.[52,53].

Model system	Model characteristics	Treatment regimen	Effects of nintedanib
Bleomycin-induced skin fibrosis	Skin damage-induced/inflammation-induced fibrosis	Preventive (weeks 0–3) and therapeutic (weeks 3–6)[a]	*Skin* Myofibroblast count ↓ Dermal thickness ↓ Hydroxyproline ↓
Graft versus host disease-induced skin fibrosis	Resembles aspects of early inflammatory stage of SSc	Therapeutic (weeks 4–8)[a]	*Skin* Myofibroblast count ↓ Dermal thickness ↓ Hydroxyproline ↓
Tight skin (fibrillin-1 transgenic)	Resembles aspects of later stage of SSc with less inflammation but early autoantibody production and massive fibrosis	Therapeutic (weeks 5–10)[b]	*Skin* Myofibroblast count ↓ Hypodermal thickness ↓ Hydroxyproline ↓
Fra-2 (AP-1 family transcription factor +/–)	Resembles aspects of skin and lung fibrosis, including microvascular disease and pulmonary hypertension with typical vascular lesions	Therapeutic (weeks 9–16)[b]	*Skin* Myofibroblasts count ↓ Dermal thickness ↓ Hydroxyproline ↓ MVEC apoptosis ↓ Capillary loss ↓ M2 macrophages ↓ *Lung* Myofibroblast count ↓ ECM ↓ Vessel wall thickness ↓ Occluded vessels ↓ VSMC ↓ MVEC apoptosis ↓ *Heart* Extent of fibrosis ↓ Perivascular inflammation ↓ Endothelial cells apoptosis ↓

SSc-ILD: systemic sclerosis–associated interstitial lung disease; MVEC: microvascular endothelial cells; ECM: extracellular matrix; VSMC: vascular smooth muscle cells.
[a]Weeks after induction of pathology.
[b]Weeks after birth.

Patients in the SENSCIS trial were randomized to receive nintedanib 150 mg twice daily or placebo, stratified by the presence of anti-Scl-70/anti-topoisomerase I antibody, which has been linked with accelerated progression of ILD.[61] The primary endpoint is the annual rate of decline in FVC (mL/year) evaluated over 52 weeks. Key secondary endpoints are absolute changes from baseline in the modified Rodnan skin score (a measure of skin thickening in patients with SSc) and in the St George's Respiratory Questionnaire total score (a measure of health-related quality of life) at week 52. The SENSCIS trial is due to be completed near the end of 2018.

Conclusion

A high need exists for effective treatments for SSc-ILD. Nintedanib is an approved treatment for IPF, which shows clinical and mechanistic similarities to SSc-ILD. Nintedanib interferes at multiple critical steps in the pathobiology of SSc/SSc-ILD, and has demonstrated anti-inflammatory and antifibrotic activities and attenuated vascular remodeling in several models of SSc/SSc-ILD, providing a strong rationale for its investigation as a treatment for SSc-ILD. The efficacy and safety of nintedanib in patients with SSc-ILD, including patients on certain immunosuppressive regimens, are currently being investigated in the SENSCIS trial.

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Declaration of conflicting interests

L.W. and M.G. are employees of Boehringer Ingelheim. J.H.W.D. is a member of a speaker's bureau and has served on advisory boards for Boehringer Ingelheim; he has also conducted non-clinical studies on behalf of Boehringer Ingelheim and is an

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