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Imatinib and the Treatment of Fibrosis: Recent Trials and Tribulations

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Abstract Imatinib mesylate has become a therapy of interest for the treatment of systemic sclerosis because of its ability to inhibit c-Abl and platelet-derived growth factor receptor, tyrosine kinases involved in profibrotic pathways. Preclinical data using in vitro and murine models of fibrosis have demonstrated the antifibrotic properties of imatinib. Imatinib is currently used widely in the treatment of chronic myelogenous leukemia, gastrointestinal stromal tumors, and other conditions, and a large amount of information is available regarding the safety of the medication in these patient populations. Whether imatinib will be tolerable or effective in the treatment of systemic sclerosis is the subject of several investigations. The aim of this review is to summarize this body of research to date.

Keywords Imatinib · Systemic sclerosis · Scleroderma · Fibrosis · Tyrosine kinase inhibitor

Introduction

Systemic sclerosis (SSc), or scleroderma, is a multisystem connective tissue disease characterized by fibrosis of the skin and internal organs, vasculopathy, and immune dysregulation [1]. SSc carries the highest case fatality rate of the rheumatic diseases. The leading cause of mortality in SSc is lung disease, including interstitial lung disease (ILD) and pulmonary artery hypertension [2], but fibrosis and vasculopathy of multiple organ systems, including the skin, gastrointestinal, cardiac, renal, and musculoskeletal systems, contribute to the increased morbidity and/or mortality observed in SSc. Treatment of patients with SSc is challenging, and no treatment to date has been shown to be unequivocally or overwhelmingly efficacious for widespread fibrosis of the skin or lungs [3]. Despite that, improvements have been seen in survival of diffuse cutaneous SSc (dcSSc) patients today compared with their historical counterparts [4].

As more is learned about the pathophysiology and natural history of SSc, the design of clinical trials can be improved to meet the needs of SSc patients. SSc is a heterogeneous disease on both a clinical and molecular level, and it is possible that different subsets of patients will respond differently to a given treatment. Skin thickening is measured by the modified Rodnan skin score (mRSS), a validated measure of the degree of skin thickness in which 17 areas of the body are palpated by a trained assessor and scored from 0 (normal) to 3 (severe skin thickening), thus yielding a total score from 0 to 51 [5]. The natural history of SSc skin disease has been described, with an early period of initial worsening, then an intermediate period of leveling out and a late period in which the skin tends to soften [6]. In spite of this, even patients with late-stage disease can have significant morbidity and burden of disease due to skin thickening. Improvements have been shown in mRSS in early-stage patients in recent clinical [7•] and observational studies [8•], and this work underlines the importance of conducting randomized, double-blind, controlled trials in SSc.

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Profibrotic Growth Factors in Systemic Sclerosis

Although the etiology and pathogenesis of SSc are not completely understood, multiple cytokines and growth

factors, including transforming growth factor (TGF)-β, platelet-derived growth factor (PDGF), connective tissue growth factor, and endothelin-1, have been shown to contribute to the widespread fibrosis seen in SSc. These factors lead to the activation of fibroblasts and their transdifferentiation to myofibroblasts. The myofibroblasts are thought to play an important role in the increased production of extracellular matrix proteins, leading to increased stiffness of the skin [9•, 10•].

TGF-β is a key molecule in the pathogenesis of fibrosis. Increased expression of TGF-β and TGF-β–dependent genes has been observed in skin biopsy specimens from SSc patients compared with healthy controls [11], as well as from bronchoalveolar lavage fluid of patients with SSc and associated ILD [12]. TGF-β stimulates the production of extracellular matrix proteins and decreases the tissue matrix metalloproteinases that degrade them.

PDGF is another profibrotic cytokine. High levels of PDGF and its receptor also have been observed in the skin and bronchoalveolar lavage fluid of SSc patients [12, 13]. With respect to PDGF signaling, it is possible that agonistic autoantibodies to the PDGF receptor exist [14], but the role of these antibodies is controversial, and their sensitivity, specificity, and significance are not clear [15]. PDGF is also important in vascular regulation and angiogenesis and can play a role in the development of pulmonary artery hypertension [16].

Imatinib is capable of blocking the TGF-β and PDGF pathways. TGF-β exerts its effects via classical signaling pathways that include the activation of Smad protein transcription factors [17] and nonclassical pathways that have been identified more recently [12]. In the nonclassical pathway, the c-Abl protein is a kinase that plays a role in signal transduction, and treatment with imatinib has been shown to decrease the fibrotic effect of TGF-β via c-Abl in different systems [18•, 19, 20]. The PDGF receptor is itself a tyrosine kinase, and its blockade with imatinib also has been shown to decrease fibrosis. Blockade of the PDGF receptor with imatinib has been demonstrated to decrease contractility of SSc fibroblasts and to decrease syndecan 4 expression and ERK activation [21].

Preclinical Evidence for the Treatment of Fibrosis with Imatinib

Distler et al. [22] performed much of the initial important preclinical work that provided the impetus and background for multiple early clinical investigations. Cultured fibroblasts from SSc patients and healthy controls were treated with imatinib. Following this treatment, there was a dose-dependent inhibition of the synthesis of collagen Ia1, collagen Ia2, and fibronectin-1 when the fibroblasts were stimulated with TGF-β, PDGF, or left in their baseline state. This was observed on both an mRNA and a protein level [22]. Using the bleomycin-induced dermal fibrosis murine model, this group also showed that imatinib treatment prevented [22] and decreased established cutaneous fibrosis [23•]. A similar effect was observed in the tight-skin 1 (Tsk1) murine model [23•]. A similar effect was seen when the cultured fibroblasts were treated with dasatinib or nilotinib, two related tyrosine kinase inhibitors (TKIs), and these second-generation TKIs also led to the prevention of skin thickening in the murine model of bleomycin-induced cutaneous fibrosis [24]. Imatinib treatment in animal models of pulmonary, hepatic, and renal fibrosis also demonstrated an effect of imatinib in the reduction of established fibrosis [25–27].

Imatinib has been used in several studies investigating the profibrotic pathways in SSc. Pannu et al. [19] observed that activation of TGF-β–mediated Smad1 signaling occurs in a subset of SSc patients and contributes to persistent activation of SSc fibroblasts. This Smad1/CCN2 pathway is blocked by imatinib mesylate [19]. Bhattacharyya et al. [18•] delineated a novel signaling mechanism of TGF-β and were able to position early growth response factor 1 downstream of c-Abl in a TGF-β–mediated fibrotic response of murine embryonic fibroblasts. This pathway was inhibited by imatinib [18•]. Recently, microRNA29 (miR-29) has been observed to be downregulated in SSc. TGF-β, PDGF-B, and interleukin-4 treatment of normal fibroblasts reduced the levels of miR-29 in a similar fashion. Inhibition of PDGF and TGF-β pathways with imatinib reversed the downregulation of miR-29a [28].

Treatment of Fibrosis with Imatinib

Imatinib has been investigated in the treatment of various fibrotic diseases, including nephrogenic systemic fibrosis (NSF), sclerodermatous chronic graft-versus-host disease (cGVHD), and idiopathic pulmonary fibrosis (IPF). NSF and cGVHD have cutaneous manifestations that are similar to those of SSc, and IPF shares pulmonary phenotypic similarities with SSc-ILD. However, the conditions are distinct from SSc, and it cannot be assumed that similar treatment effects will be common to these disorders.

NSF generally occurs in patients with chronic kidney disease in association with exposure to gadolinium-containing contrast agents used in MRI and is characterized by scleroderma-like skin changes and contractures. Kay and High [29•] reported their experience treating two patients with NSF with imatinib, in whom decreased skin thickening and reduction in the mRSS were observed. These changes recurred upon cessation of the drug. One patient resumed treatment and again experienced improvement in

cutaneous fibrosis. Skin biopsies after treatment showed less fibrosis and decreased staining for type I procollagen; however, the quantity of gadolinium in the skin remained the same. Both patients experienced fluid retention with imatinib, which was managed with adjustment in their hemodialysis. They did not experience any other adverse events [29•].

Sclerodermatous cGVHD shares pathophysiologic similarities with scleroderma; thus, Olivieri et al. [30•] conducted a phase 1/2 clinical trial of imatinib treatment in patients with refractory cGVHD with fibrotic/sclerotic features. Nineteen patients were enrolled, an overall response rate at 6 months of 79% was observed, with 7 complete remissions (defined as resolution of all skin and organ manifestations) and 8 partial remissions (defined for skin as improvement of 50% of body surface area). Three patients had to discontinue therapy because of intolerance (two patients with severe anemia, one patient with JC virus), three discontinued because of lack of response, and two discontinued because of relapse of their original disorder.

Imatinib was studied for the treatment of IPF after the observation that imatinib treatment prevented histologic changes and decreased the hydroxyproline content of the lungs in a murine model of bleomycin-induced pulmonary fibrosis [31]. A double-blind, placebo-controlled, randomized trial of imatinib for IPF in 119 patients did not demonstrate efficacy for imatinib [32••]. No difference was noted between patients on imatinib compared with placebo with respect to time to disease progression, defined as a 10% decline in percent predicted forced vital capacity from baseline or time to death. Treatment had no effect on change in forced vital capacity or diffusion capacity of the lungs for carbon monoxide (DLCO) at 48, 72, or 96 weeks. There were also no differences between the groups with regard to serious adverse events, deaths, or dropout rate.

Safety and Tolerability from Other Patient Populations

The side effect profile of imatinib has been described in patients with chronic myelogenous leukemia (CML) and gastrointestinal stromal tumor (GIST) [33, 34]. The most common side effects in these patients include myelosuppression, nausea, fatigue, diarrhea, edema, and muscle cramps. Edema includes superficial edema, which is often responsive to diuretics, and periorbital edema, which is not always responsive to diuretics, and can also include more serious fluid retention with pleural and pericardial effusions. Cardiotoxicity has been reported in patients with CML treated with imatinib [35]. A retrospective chart review of all patients with hematologic malignancy treated with imatinib at the MD Anderson Center in Texas demonstrated an incidence of congestive heart failure of 1.7% [36]. Other risk factors for cardiovascular disease, such as age, diabetes mellitus, and hypertension, were seen in most of those who developed congestive heart failure—similar factors to what is seen in the general population [36]. As a large percentage of patients with SSc may have some degree of cardiac involvement due to their underlying disease, it is essential to remain vigilant to this possibility.

Other pertinent side effects with respect to the SSc population include imatinib effects on bone and muscle. Hypophosphatemia has been observed in patients with CML and GIST treated with imatinib and has been associated with changes in bone and mineral metabolism with possible inhibition of bone remodeling (formation and resorption), even in patients with normal serum phosphate levels [37]. Elevation of creatine kinase was recently recognized as common in patients with CML and GIST treated with imatinib therapy [38].

Systemic Sclerosis

Imatinib has been looked upon as a potential targeted therapy in SSc because of this solid rationale for its use. However, the clinical experience in this challenging patient group is still in its early stages. At the time of the writing of this article, the published literature contained only case reports of the use of imatinib, and the results of larger studies, most of which are uncontrolled, have been presented only in abstract form at scientific meetings.

Case Reports and Case Series

Several case reports suggested the clinical benefit of imatinib in treating the cutaneous and pulmonary manifestations of SSc and mixed connective tissue disease after 3–6 months of therapy. Sfikakis et al. [39] described a single patient with dcSSc and associated ILD who exhibited an improvement in mRSS from 44 to 33 and a change in forced vital capacity from 68.0% predicted to 88.3% predicted (accompanied by other improvements) with imatinib, 400 mg/d. Skin biopsies before and after treatment showed a normalization of collagen III distribution with treatment [39]. Van Daele et al. [40] described a patient with SSc and ILD who experienced an improvement in mRSS from 18 to 12 after 7 months of treatment with imatinib, 400 mg/d. Bronchial fibroblasts from that patient obtained via bronchoalveolar lavage prior to treatment showed a decreased PDGF-induced proliferation response in a fibroblast proliferation assay, and decreased TGF-β–induced collagen Ia1 synthesis by quantitative polymerase chain reaction with in vitro exposure to imatinib. Distler et al. [41] described a patient with mixed connective tissue disease with

pulmonary fibrosis who demonstrated an improvement in the ground-glass opacities seen on high-resolution CT scan of the chest, as well as an improved DLCO and 6-minute walk distance with imatinib treatment. Chung et al. [42•] reported similar outcomes in two patients treated with imatinib, 200 mg/d. Skin biopsies from these patients before and after treatment demonstrated decreased phosphorylation of PDGF receptor and Abl. They also performed gene expression analysis with microarray on RNA extracted from the skin before and after treatment and described the differential expression of 1,050 genes, which led to the hypothesis that there may be an imatinib-responsive gene signature in a specific subgroup of patients with SSc. Sabnani et al. [43] reported their experience treating five severely ill patients with end-stage ILD (mean DLCO, 25% predicted) with combination cyclophosphamide and imatinib. Of the five patients, two died of progression of lung disease, one went on to stem cell transplantation, and one went on to lung transplantation. The one patient with the most mild disease experienced some clinical improvement, with improvement in DLCO from 43% predicted to 50% predicted, total lung capacity from 82% to 88%, and forced vital capacity from 80% to 89%. Only two completed 1 year of this therapy. The authors noted that all patients tolerated the treatment, with one temporarily discontinuing for fluid-related issues [43]. Imatinib treatment for refractory pulmonary artery hypertension has been reported. Treatment of five patients, three of whom had SSc, was recently noted to lead to improved DLCO and decreased PDGF-BB levels but did not lead to changes in hemodynamics or exercise capacity [44]. Three patients in this study developed renal dysfunction.

Early-Phase Clinical Studies

At this point, the information available from the first early-phase clinical studies appears in the literature only in abstract form. Five different groups have reported their experience to date, with conflicting interpretations of their experiences summarized in Table 1. Each of the studies had different enrollment criteria, used different dosing regimens, and continued for different durations, all of which may contribute to different interpretations of these early data. What follows is a summary of what was available in abstract form at the time of the writing of this article, with two important caveats: 1) the understanding and interpretation of these data will be more sophisticated and valid upon actual publication of these studies and 2) no conclusion can be drawn about the safety or efficacy of imatinib in the treatment of SSc without well-powered, randomized controlled studies.

Our group recently completed a 1-year, single-center, phase 2a, single-arm, open-label clinical trial assessing the safety and efficacy of imatinib, 400 mg/d, in 30 patients with dcSSc [45]. Patients were enrolled with up to 10 years' disease duration but were prospectively stratified into earlier (n=20) and later (n=10) disease subgroups. The mean disease duration based on the time since the first non-Raynaud's symptom attributable to SSc appeared for the entire cohort was 3.4±2.3 years. All patients had an mRSS of at least 16. ILD, which was not a requirement for entry, was present in 53% of patients. Concomitant administration of immunosuppressive agents was not allowed during the course of the trial or in the 3 months prior to enrollment. Twenty-four patients completed 12 months of treatment with imatinib. Twenty-four serious adverse events were identified, two of which were attributed by the investigators as at least possibly related to study medication. One death occurred during the course of the trial due to pneumonia with respiratory failure in a patient with severe ILD and pulmonary artery hypertension, although it was not believed to be medication related. Adverse events were common, with 171 at least possibly related to imatinib. The most common were edema (80%), nausea (73%), myalgia (67%), and creatine kinase elevations (43%). A total of 97% of adverse events related to imatinib were grade 1 or 2, and despite these common adverse events, the medication overall was acceptable to most patients, with 80% remaining in the trial over the course of the year.

Among the 24 completers, an average improvement in the mRSS of 6.6±4.7 points (P<0.001) was noted. A similar degree of improvement in skin thickness was seen across different durations of disease. In the subgroup of patients (n=8) with very early disease (defined as<18 months), the mRSS improved by 7.9±5.7 points (P=0.006). Histologic improvements characterized by increased interstitial space between collagen fibers were observed in an assessment of skin biopsy specimens by a dermatopathologist blinded to pre- or post treatment status. Pulmonary function tests were performed as a measure of efficacy at baseline and after 12 months of treatment in all patients participating in the study. After 12 months of imatinib therapy, forced vital capacity improved from a mean of 82.9%±21.1% predicted to 89.3%±25.2% predicted (P=0.008.) The improvement in forced vital capacity was significantly greater in patients without ILD (10.7% predicted vs 2.1% predicted; P=0.01).

Pope et al. [46] planned to conduct a 6-month proof-of-concept, randomized controlled trial, but it was terminated early because of poor tolerability. This group had planned to enroll 20 patients with a 4:1 randomization stratified by presence or absence of background methotrexate use. The study was designed primarily to examine various biomarkers. Of ten patients enrolled, nine received active drug and one received placebo, making it difficult to compare the control and treatment groups. Five patients interrupted the dose or stopped the medication as a result of adverse events, including fluid retention, weakness, nausea, vomiting,

Table 1 Summary of trials investigating the use of imatinib in systemic sclerosis

Study	Patients, *n*	Disease subtype	Disease duration	Treatment duration	Disposition	Safety	Efficacy
Positive experience							
Spiera et al. [45]	30	Diffuse=30, ILD=16	Mean, 3.4±2.3 year (<10 year included)	1 year	24 completed study, 5 discontinued, 1 death	24 SAEs occurring in 8 patients	Improvement in mRSS (+6.6; P=0.001)
						AEs: edema in 80%, nausea in 73%, myalgia in 67%, Creatine kinase elevation in 43%	Improvement in FVC (+6.4%; P<0.01)
							DLCO unchanged (+5.5%; P=0.12)
							Health-related quality-of-life improvements
Chung et al. [47]	9	Diffuse=7, limited with ILD=2	Median, 1 year (range, 0.5–13 year)	24 week	7 completed study, 1 death, 1 discontinued	Death was due to pneumonia/sepsis in ILD patient	mRSS improved by 32% (P=0.005)
						AEs affected 67% of patients (gastrointestinal complaints, edema, infections)	Imatinib-responsive gene signature in subset
Saggar et al. [48]	20	Diffuse=14, limited=6, ILD=20	<10 year	1 year (interim report)	8 completed study, 4 continuing in study, 7 discontinued, 1 lost to follow-up	3 SAEs (GAVE/myopathy, diastolic dysfunction, hypothyroidism)	Stabilization of FVC (1.39%; P=0.3)
						Edema in 50%, leading to discontinuation in 1 patient	Improvement in DLCO (4.77%; P<0.05)
							Improvement in mRSS (−4.34; P<0.05)
Negative experience							
Distler et al. [49]	27	Diffuse=27	<18 month	24 week	16 completed study, 11 discontinued	5 patients with SAEs (generalized edema, erosive gastritis, anemia, upper respiratory infection, viral infection, neutropenia with infection, nausea, vomiting)	mRSS not improved
Pope et al. [46]	10	Diffuse=10 (9 imatinib, 1 placebo)	3.1 year (range, 0.5–6 year)	6 month	Trial terminated early (5 completed study, 5 discontinued)	1 SAE (fluid retention)	mRSS unchanged
						AEs: fluid retention, weakness, nausea, vomiting, chest pain, anemia, hair loss	Biomarkers mostly unchanged

AE adverse event; *DLCO* diffusion capacity of the lungs for carbon monoxide; *FVC* forced vital capacity; *GAVE* gastric antral vascular ectasia; *ILD* interstitial lung disease; *mRSS* modified Rodnan skin score; *SAE* serious adverse event

chest pain, worsening anemia, and hair loss, and there was one serious adverse event (marked fluid retention on active drug).

Chung et al. [47] treated nine dcSSc and limited SSc patients with imatinib and found that the medication was tolerated at low to moderate doses (100–200 mg) and may result in clinical improvement in a subset of patients. They noted the imatinib-responsive signature mentioned above in a subset of these patients.

Saggar et al. [48] reported in interim fashion on the use of high-dose imatinib, with a target dose of 600 mg/d in 20 patients with SSc-ILD. They reported stabilization of forced vital capacity and improvement in DLCO and mRSS. In this group, adverse events resulted in discontinuation in seven patients (three serious adverse events were noted). Dose modification and/or addition of diuretics allowed continuation of therapy in seven of ten patients who developed edema.

Distler et al. [49] reported the results of an industry-sponsored, multicenter study that did not demonstrate efficacy (defined as a 25% improvement in mRSS at 24 weeks) in a group of patients with early active dcSSc (disease duration<18 months) at an imatinib dose titrated up to a goal of 600 mg/d. Duration of therapy was 24 weeks, and patients were observed for an additional 24 weeks following cessation of treatment. Although no improvement in mRSS was noted at 24 weeks (mean increase, 9.9%), a trend toward improvement (mean decrease, 21%) was noted at 48 weeks (24 weeks of treatment and 24 weeks of follow-up off treatment.) Levels of collagen Ia1 and fibronectin in the skin were reduced. Sixteen of 27 patients were able to complete therapy, and 5 serious adverse events were noted. A retrospective exploratory analysis using these 27 patients as cases compared with historical controls from a database was undertaken [50]. The change in mRSS observed was not noted to be different from patients treated with "standard of care," meaning various immunomodulatory treatments in 84% of the controls and no treatment in 16%.

Conclusions

The preclinical investigations of imatinib in the treatment of SSc provide a strong rationale for its use. Case reports have described positive experiences in selected patients and provided further rationale for the early clinical experiences described to date. At this time, most of the experience with imatinib has been open label and uncontrolled and has been published in abstract form. The durations of the trials and dosing have been variable. Additionally, the patient selection has been different in all the above studies and has included early- and late-stage SSc as well as limited and diffuse cutaneous subtypes. This is important, as the natural history of SSc can be variable, with spontaneous regression of skin disease described in late-stage [6] and early-stage patients in clinical [7•] and observational studies [8•]. It is premature to draw conclusions with respect to the efficacy of imatinib in treatment of the cutaneous or pulmonary manifestations of SSc.

Not surprisingly, tolerability issues of imatinib in this patient group, especially with respect to fluid retention, have emerged as a potential concern in open-label trials. A considerable number of adverse events and serious adverse events were noted in all the experiences to date. Particularly in a patient group with a high burden of disease, attribution of adverse events is frequently complex. In a non-SSc population, imatinib is known to be relatively safe. Weighing the adverse events against the potential benefits will require further investigation.

It is possible that some of the translational investigations that are ongoing, including those evaluating gene expression profiling or other mechanistic studies, will afford additional insights into the relevance of the impact of imatinib therapy in this patient group. A conceivable scenario is the recognition of biomarkers that identify a subgroup of patients more likely to benefit from this therapy, but at this point in time, this has not been achieved in a validated manner.

True insight into whether this treatment strategy is efficacious will depend on the development of large-scale, randomized, placebo-controlled, multicenter trials of adequate duration with clear entry criteria. This will require collaboration between multiple centers and financial support from industry and/or government agencies.

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