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Open-Label Pilot Trial of Imatinib Mesylate (Gleevec) in the Treatment of Systemic Sclerosis- Associated Active Interstitial Lung Disease (SSc-ILD)

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Abstract

Purpose—Transforming growth factor-beta (TGF- β) and platelet-derived growth factor (PDGF) may play a critical role in systemic sclerosis- interstitial lung disease (SSc-ILD) and imatinib is a potent inhibitor of TGF- β and PDGF production. We report a phase I/IIa open-label pilot study of imatinib in patients with SSc-ILD. Our primary aim was to assess imatinib's safety; we also explored efficacy.

Methods—We recruited 20 SSc patients with FVC < 85% predicted, dyspnea on exertion, and presence of ground glass appearance on HRCT. Patients received oral imatinib therapy (up to 600 mg/day) for a period of 1 year. Adverse events, pulmonary function tests, and modified Rodnan skin score (MRSS) were captured every 3 months. The course of lung function, HAQ-DI and MRSS were modeled over the length of study to explore efficacy.

Results—The majority of patients were female (65%), Caucasian (75%) and had diffuse SSc (70%). The baseline mean (SD) FVC%predicted was 65.2 (14.0) and MRSS was 18.7 (10.1). Mean(SD) imatinib dose was 445 (125) mg/day. Of 20 patients, 12 completed the study, 7 discontinued due to adverse events (AEs), and 1 patient was lost to follow-up. Common AEs ($\geq 20\%$) included fatigue, facial/lower extremity edema, nausea and vomiting, diarrhea, generalized rash, and new onset proteinuria. Treatment with imatinib showed a trend towards an improvement of FVC%predicted of 1.74% ($p > 0.05$) and MRSS of 3.9 units ($p < 0.001$).

Conclusion—Use of high-dose daily (600 mg/day) imatinib in SSc-ILD was associated with a large number of AEs. Our AE experience suggests that doses lower than 600 mg/day imatinib may be appropriate and that further dose ranging is needed to understand the therapeutic index of imatinib in SSc.

Keywords

imatinib; clinical trial; systemic sclerosis; scleroderma-related lung fibrosis

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Introduction

Systemic sclerosis-associated interstitial lung disease (SSc-ILD) is present in nearly 70% of patients with SSc, with approximately 15% developing severe restrictive lung disease. The pathogenesis of pulmonary fibrosis is mediated through foci of dysregulated fibroblasts driven by profibrotic cytokine signaling(1). In lung biopsies of SSc patients, transforming growth factor-beta (TGF- β) expression is increased in the fibrotic lung tissue (2) as is its key mechanism for presentation, integrin $\alpha(v_1)\beta_6$ (3). In addition, TGF- β and other stimuli can induce connective tissue growth factor (CTGF) production, a cytokine that stimulates fibroblast growth and upregulates production of collagen and fibronectin (4). These profibrotic cytokines, including platelet-derived growth factor (PDGF), are overexpressed in bronchoalveolar lavage samples in patients with SSc(5).

Imatinib mesylate (Gleevec®) is a tyrosine kinase inhibitor that binds to c-abl and blocks its tyrosine kinase activity; c-abl is an important downstream signaling molecule of TGF- β (6;7). In addition, imatinib interferes with PDGF signaling by blocking the tyrosine kinase activity of PDGF receptors. In an *in vitro* model of bleomycin-induced pulmonary fibrosis, c-Abl inhibition by imatinib prevented TGF-beta induced extracellular matrix gene expression, transformation, and proliferation of fibroblasts (7;8). Similar results were replicated in an *in vitro* model of radiation-induced pulmonary fibrosis (9;10) and mouse models of scleroderma(11;12).

In chronic myeloid leukemia and gastrointestinal stromal tumors, the dose of imatinib approved is 400–600 mg/day (prescribing information). As our goal was to obtain data on the highest potentially tolerable dose in SSc-ILD, we attempted to achieve the imatinib dose of 600 mg/day in an open-label pilot clinical trial. We also explored efficacy of imatinib on lung physiology and skin fibrosis.

Patients and Methods

We recruited 20 SSc patients who met the American College of Rheumatology classification(13) of SSc at 2 Scleroderma Centers in U.S. The inclusion and exclusion criteria, detailed in the Supplementary file, were similar to a randomized controlled trial that compared daily oral cyclophosphamide vs. oral placebo for 1 year in patients with SSc-ILD(14). They included: adult patients with SSc, less than 10 years of SSc (defined from 1st non-Raynaud's sign or symptom), forced vital capacity (FVC%) < 85% of predicted, dyspnea on exertion (grade ≥ 2 on the Magnitude of Task component of the Mahler Baseline Dyspnea Index), and presence of ground-glass opacity on high resolution computer tomography (HRCT).

Putative disease-modifying medications (e.g., D-penicillamine, cyclophosphamide, azathioprine, methotrexate, and colchicine) were not allowed <1 month prior to imatinib start. Stable oral prednisone (or equivalent) ≤ 10 mg per day was allowed.

Eligible patients were administered oral imatinib (up to 600 mg/day) for 1 year. Imatinib was started at 100 mg/day and increased by 100 mg every 2 weeks. Safety laboratory work up (CBC with differential, renal panel, hepatic panel, and urinalysis) was performed every 2 weeks while the dose was being increased and then monthly thereafter.

Patients were seen every 3 months and data on adverse events(AEs)were collected; serious adverse events(SAE) were defined by the Food and Drug Administration standards.

Pulmonary function tests and patient-reported outcome measures (Mahler's Dyspnea Index and Health Assessment Questionnaire-Disability Index) were performed at baseline and

every 3 months. HRCT was performed at baseline and 12-month visit (details in the Supplementary file).

Primary outcome was the safety of daily imatinib. Secondary and exploratory analyses included change in the pulmonary function test, modified Rodnan skin score, and patient reported outcome measures. The study was approved by local institutional review boards and each patient signed the written consent form and HIPPA form. The clinical trial was conducted under IND#55,666 and registered with clinicaltrials.gov (NCT00512902).

Study drug and partial support was provided by Novartis Pharmaceuticals. The funding agency did not contribute to the design of the study, the carrying out or review of the study nor did it influence or review the content of the manuscript or influence the decision to submit this manuscript.

Statistical analysis

Descriptive analysis was done on all baseline data. Adverse events were grouped by body system and tabulated as number and percentages. Serious adverse events were enumerated and described as appropriate. Continuous variables are reported as mean (SD) and categorical variables as number (percentage). Efficacy was analyzed using linear mixed effects modeling of FVC% predicted, TLC% predicted, DLCO% predicted, and MRSS. The mixed effects model employed here allows all the available data to be used and does not assume that the data is missing completely at random (see details in the Supplementary file).

Results

We recruited 20 patients with SSc with average (SD) age of 46.1 (14.2) years, average disease duration of 54.2 (38.8) months, 65% were female, and 75% were Caucasian (Table 1). Mean (SD) FVC% predicted was 65.2 (14.0)% and DLCO% predicted was 50.5 (11.4)%. All patients had ground glass opacification on HRCT; 95% had some degree of pulmonary fibrosis and 37% had honey combing cysts.

Of 20 patients, 12 completed the 1-year study, 7 dropped out due to adverse events or progression of SSc-ILD, and 1 patient was lost to follow-up (Figure 1). The mean (SD) dose of imatinib was 445 (127) mg/day and median dose was 400 mg/day. There was no difference in the mean dose of patients who discontinued due to adverse events (N=5, mean dose 420 mg vs. 475 mg in patients who completed the study, $p=0.4$). There were no differences in the demographics between the 2 groups ($P=NS$; data not shown). Each investigator was allowed to decrease the dose due to side effects at his/her discretion. Only 6 (20%) patients reached the maximum dose of 600 mg/day.

Adverse events

Adverse Events not requiring Discontinuation—Adverse events were common in this 1-year open labeled trial (Table 2). Common adverse events ($\geq 20\%$) included fatigue, facial/lower extremity edema, nausea and vomiting, diarrhea, generalized rash, and new onset proteinuria. The majority of these AEs were managed by the investigator by either decreasing the dose of imatinib, temporary discontinuation of imatinib, or giving imatinib in divided doses. For patients with moderate-to-severe diarrhea, loperamide or atropine sulfate/diploxyate hydrochloride were prescribed on an as needed basis. Edema was common, ranging from 15% with generalized edema to 45% with pedal edema. The edema was controlled by decreasing the imatinib dose, divided daily doses, and/or addition of an oral daily loop diuretic.

At onset of the study, 6 patients had baseline proteinuria (trace to 1+) on routine urinalysis. Two of 6 had 24-hour urinary protein between 86–320 mg/dl. During the study, 6 (30%) developed new onset mild proteinuria (1+ to 2+ on urinalysis). 24-hour urinary protein in 3 patients ranged between 81–402 mg/dl over a period of 1 year. There was no worsening of serum creatinine/creatinine clearance or incident cases of renal crisis in any patient during the 12-month study. None of the patients had a decline in their left ventricular ejection fraction or developed clinical pulmonary hypertension during the study. One patient had mild hemoptysis early in the course of the study. Work up including bronchoscopy with cultures and cytology was unremarkable and hemoptysis resolved with discontinuing imatinib. Imatinib was restarted and patient had reoccurrence of hemoptysis. However, it was mild and the patient decided to continue the medication and completed the 12-month study.

Adverse events requiring Discontinuation and thought possibly or probably related to imatinib—There were 5 patients (25%) who discontinued imatinib due to related AEs. All AEs resolved after discontinuation of study medication.

One patient discontinued the study due to continuing generalized edema that was unresponsive to daily diuretics; it was found to be the result of severe hypothyroidism (TSH=125 with undetectable free T4; patient# 3 with SAE).

One patient discontinued for each of the following: increasing shortness of breath and diastolic dysfunction on right heart catheterization (patient# 2 with SAE), generalized rash that disappeared on stopping drug and reappeared after rechallenge of imatinib; elevated AST/ALT (2 times upper limit of normal) and severe diarrhea, each of which normalized when imatinib was stopped; elevated CPK's (200–400 IU/L) which normalized over 3 months after drug discontinuation (patient #1 with SAE)—this patient also had SSc-related active gastric antral vascular ectasia (GAVE) and anemia (see below).

Discontinuation thought to be due to underlying SSc—One patient developed GAVE, fatigue and anemia; this patient also developed what was thought to be imatinib-related elevated CPKs (patient #1 with SAE). Another patient developed diastolic dysfunction (patient #2 with SAE). Two patients had a decline in FVC by > 10% and both discontinued the drug at the end of 3 months.

Serious adverse events—There were 3 serious adverse events.

Patient #1 was admitted to the hospital with marked anemia, fatigue and marked proximal muscle weakness. Imatinib was discontinued. The patient was diagnosed with GAVE and scleroderma myopathy (CPK's in 200–400 U/L). Muscle biopsy from left thigh did not show evidence of active inflammatory myositis, and subsequent CPK's normalized approximately 3 months after stopping her imatinib. This patient's adverse events were judged related to both SSc and imatinib.

Patient# 2 complained of worsening dyspnea and generalized edema that continued despite decrease imatinib dose and addition of oral loop diuretics. Imatinib was subsequently stopped but symptoms of increasing shortness of breath continued. His repeat FVC% predicted showed a decline of 6% and a right heart catheterization (a month later) showed mean pulmonary artery pressure of 23 mmHg and pulmonary wedge pressure of 23 mmHg suggestive of diastolic dysfunction. There was no evidence of systolic dysfunction. The patient improved with medical management of his diastolic dysfunction. This patient's adverse events were judged related to both SSc and imatinib.

Patient# 3 presented with worsening dyspnea and generalized edema during her week 36 visit that was resistant to diuretics. Serum TSH was 125 (normal < 4.5) mIU/L with undetectable free T4 (normal range: 0.8–1.6). Imatinib was stopped and levothyroxine was initiated. Her TSH improved on oral levothyroxine and TSH was 41 and Free T4 of 0.9 after 3 months of therapy and is currently in normal range on daily levothyroxine. This was considered to be probably related to imatinib.

Other Discontinuations: One patient was lost to follow-up.

Efficacy

Treatment with imatinib led to trends towards improvement in estimated FVC% predicted by 1.74%, TLC% predicted by 4.17%, and DLCO% predicted by 1.46% over a 1 year period ($p > 0.05$ for all). The treatment was also associated with a mean improvement of MRSS by 3.9 units over 1 year period ($p < 0.001$). As sensitivity analyses, the data were reanalyzed using completers only analysis and by imputation of missing data; the results were similar (data not shown). Supplementary Figure 1 show the individual level data on FVC% and MRSS. Maximum baseline HRCT fibrosis predicted FVC% decline--the FVC% prediction model estimated a yearly improvement of + 4.9 (SE 2.1, $p = 0.02$)% predicted if the baseline fibrosis <20%, and decrement of 1.3 (SE 2.3, $p = 0.56$)% predicted for the $\geq 20\%$ group, with a p -value for the difference being 0.04.

HAQ-DI demonstrated neither statistical nor clinically important improvement over 1 year (HAQ-DI = -0.11, $p = 0.11$, minimally important difference (MID): 0.14(15)). Dyspnea index improved statistically but not clinically meaningfully TDI = 0.14, $p < 0.01$; MID: 1.5(16)).

Discussion

We present the first open label trial assessing safety of imatinib in the treatment of SSc-ILD. We also explored efficacy in this small open label trial. We found a large number of adverse events, the majority of which were managed with dose interruption or decrease in dose of imatinib. Twenty-five percent of our patients who developed what were thought to be drug-related AEs discontinued imatinib. On the other hand, the preliminary analysis suggests trend towards improvement of FVC% predicted and skin score, which may represent a positive effect of imatinib or it may represent the natural history of SSc in an open label study(17).

Adverse events seen during our clinical trial have been previously reported in imatinib clinical trials and were anticipated(18;19). The most common adverse events ($\geq 20\%$) included fatigue, facial/lower extremity edema, nausea and vomiting, diarrhea, and generalized rash. The majority of the adverse events are dose-related. In the early part of the study (first 5 patients), we continued to escalate the dose of imatinib to reach 600 mg/day but patients discontinued therapy. We later allowed de-escalation or stabilization of the dose so that the drug was tolerated by the patients. The median dose was 400 mg/day with only 6 (30%) patients able to reach 600 mg/day dose. The last 7 patients were dose titrated to maximum of 400 mg/day, resulting in improved tolerance and no discontinuations. For the study as a whole, the mean dose was 445 (125) mg/day. In another study, Gordon and colleagues showed that a dose of 400 mg/day is well tolerated(20) and this dose should be considered in future trials. Six (30%) of our patients developed new onset mild proteinuria (1+ to 2+ on urinalysis). We performed 24-hour urinary protein in 3 patients where urine protein ranged between 81–402 mg/dl but no patient developed worsening of serum creatinine/creatinine clearance or renal crisis in during the 12-month study. We are not clear of the reason for this adverse event. Sunitinib, another tyrosine kinase inhibitor, is associated with hypertension sometimes associated with proteinuria(19). We did not notice any significant increase in systemic blood pressure during the trial.

One patient developed elevated CPKs which slowly normalized off imatinib. The prescribing information reports that elevated CPKs are a rare side effect of imatinib, reported in 0.1–1% of patients participating in clinical trials; in another open trial using imatinib in SSc, 37% had an elevation of CPK(20). There were several adverse events which were surprising. One patient developed mild hemoptysis (patient didn't want to stop his imatinib and continued the study; the bronchoscopy and upper endoscopy were unremarkable and echocardiogram did not hint of pulmonary hypertension) which appeared to be related to imatinib. His hemoptysis improved after stopping the medication and reappeared after rechallenge. There are no previous reports of hemoptysis or abnormal coagulation reported with imatinib.

Another patient developed severe hypothyroidism. The current prescribing information for imatinib does report hypothyroidism as an adverse event and has been frequently seen with another tyrosine kinase inhibitor, sunitinib. Potential causes include inhibition of iodine uptake by thyroid tissue and destructive thyroiditis(18;19) or development of autoimmune thyroiditis.

As is usual in SSc studies, 4 patients discontinued secondary to SSc itself (2 had decline in FVC > 10% and 2 were judged to have adverse event related to both imatinib and SSc disease progression).

We noticed a trend toward improvement in physiological parameters and MRSS at the end of 12 months. There was an estimated improvement in the FVC% predicted by 1.74%, TLC % predicted by 4.17%, DLCO% predicted by 1.46% ($p > 0.05$ for all), and MRSS of 3.9 units ($p < 0.001$). The changes seen in this open label trial may be related to drug effect or may reflect the natural course of SSc; these need to be evaluated in a well controlled placebo controlled trial(17). Our study is not without limitations. First, this was an open label trial in a small numbers of patients, precluding any definitive conclusions regarding efficacy. Second, we didn't perform right heart catheterization at the initiation and at the end of the study, so we did not definitively exclude pulmonary hypertension, although our patients had had routine echocardiograms at baseline and end of the study visit without any suggestion of PH. It is nevertheless possible that some patients had mild pulmonary hypertension associated with ILD. Also, 7 of 20 patients were treated with different immunosuppressive agents 1–3 months before randomization. SLS showed that efficacy of cyclophosphamide can last up to 6 months after 1 year of therapy and the previous use of immunosuppressives may have affected the efficacy outcome of the study.

In conclusion, use of daily imatinib in SSc-ILD was associated with a large number of adverse events. There was also a trend towards improvement of FVC% predicted and MRSS. Future, controlled studies, should further explore lower dosing regimens (400 mg/day) or slower increases in dosing of imatinib in the treatment of SSc-ILD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Flow diagram showing patient withdrawals and adverse events during the 12-month study

Table 1

Baseline characteristics of patients

Age, mean (SD)	46.1 (14.2)
Female, N (%)	13 (65)
Race	
Caucasian	15 (75.0)
African American	3 (15.0)
Others	2 (10.0)
Diffuse SSc, n (%)	14 (70)
Disease duration in months, mean (SD)	54.2(38.8)
Modified Rodnan Skin Score (0–51), mean (SD)	18.7 (10.1)
Health Assessment Questionnaire (0–3), mean (SD)	1.04 (0.80)
Baseline dyspnea index (0–12), mean (SD)	7.69 (1.58)
Pulmonary function test	
Forced vital capacity (%), mean (SD)	65.2 (14.0)
Diffusion capacity of carbon monoxide (%), mean (SD)	50.5 (11.4)
Total lung capacity (%), mean (SD)	72.3 (11.9)
HRCT*	
Presence of any ground glass opacification, N (%)	19 (100)
Presence of any reticular changes, N (%)	18 (95)
Presence of any honeycombing, N (%)	7 (37)
Ground glass opacification (%), mean (SD)	13.5 (12.1)
Reticular changes (%), mean (SD)	14.1 (15.0)
Honeycombing (%), mean (SD)	1.1 (2.4)
Echocardiogram	
Estimated RVSP (mmHg), mean (SD)	30.6 (5.5)

* One HRCT was not available for visual read by thoracic radiologist

Table 2

Adverse events during the 1 year trial and reasons for discontinuation

	Adverse events	Discontinued
General		
Fatigue	7 (35)	0
Depression	2 (10)	0
Weight Loss	2 (10)	0
Cardiopulmonary		
Worsening FVC (>10%)	2 (10)	2
Diastolic dysfunction	1 (5)	1
Mild Hemoptysis	1 (5)	0
Endocrine		
Hypothyroidism	1 (5)	1*
New onset diabetes mellitus	1 (5)	0
Gastrointestinal		
Nausea/Vomiting	9 (45)	0
Diarrhea	5 (25)	1†
Elevated AST/ALT	2 (10)	1†
--Elevated AST/ALT> 3ULN	1 (5)	0
Hematology		
Neutropenia (< 3.5)	2 (10)	0
Anemia (<10 gm/dl)	1 (5)	0
Thrombocytopenia (< 100,000)	1 (5)	0
Infection		
Upper respiratory infection	4 (20)	0
Oral thrush	1 (5)	0
Urinary tract infection	1 (5)	0
Axillary abscess	1 (5)	0
Musculoskeletal		
Proximal muscle weakness/elevated CPKs	1 (5)	1
Renal		
Facial edema	7 (35)	0
Pedal edema	9 (45)	0
Generalized edema	3 (15)	1*
New-onset proteinuria	6 (30)	0
Skin		
Generalized rash	4 (20)	1
Lost to follow-up	1 (5)	1

* same patient;

† same patient