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Treatment of Idiopathic Pulmonary Fibrosis with Losartan: A Pilot Project

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Abstract

Background—Idiopathic pulmonary fibrosis is a progressive interstitial lung disease with no current effective therapies. Treatment has focused on antifibrotic agents to stop proliferation of fibroblasts and collagen deposition in the lung. We present the first clinical trial data on the use of losartan, an antifibrotic agent, to treat idiopathic pulmonary fibrosis. The primary objective was to evaluate the effect of losartan on progression of idiopathic pulmonary fibrosis measured by the change in percentage of predicted forced vital capacity (%FVC) after 12 months. Secondary outcomes included the change in forced expiratory volume at 1 second, diffusing capacity of carbon monoxide, 6-minute walk test distance, and baseline/transition dyspnea index.

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Conflict of interest The authors have no conflicts of interest or financial ties to disclose.

Ethical standards The experiment complies with the current laws of the United States of America.

Methods—Patients with idiopathic pulmonary fibrosis and a baseline %FVC of 50 % were treated with losartan 50 mg by mouth daily for 12 months. Pulmonary function testing, 6-minute walk, and breathlessness indices were measured every 3 months.

Results—Twenty participants with idiopathic pulmonary fibrosis were enrolled and 17 patients were evaluable for response. Twelve patients had a stable or improved %FVC at study month 12. Similar findings were observed in secondary end-point measures, including 58, 71, and 65 % of patients with stable or improved forced expiratory volume at 1 second, diffusing capacity for carbon monoxide, and 6-minute walk test distance, respectively. No treatment-related adverse events that resulted in early study discontinuation were reported.

Conclusion—Losartan stabilized lung function in patients with idiopathic pulmonary fibrosis over 12 months. Losartan is a promising agent for the treatment of idiopathic pulmonary fibrosis and has a low toxicity profile.

Keywords

Pulmonary fibrosis; Angiotensin receptor blocker; Forced vital capacity; Dyspnea; Six-minute walk test

Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive lung disorder with no identifiable cause or proven effective treatment [1]. Even though IPF is considered rare, it is the most common idiopathic interstitial lung disease and has both high morbidity and mortality. The median survival of patients with IPF is 2–4 years, which has not changed over the past decade [2, 3]. There is considerable evidence that angiotensin II (AII) is involved in multiple models of fibrosis. Angiotensin II is known to activate the angiotensin II type 1 receptor, inducing transforming growth factor expression [4, 5], which stimulates lung fibroblast proliferation and lung procollagen production. Losartan's ability to alleviate fibrosis by reducing the expression of transforming growth factor β (TGF- β) has been demonstrated in multiple animal and human studies [6–22]. This study's main hypothesis was that losartan would attenuate progression of pulmonary fibrosis. We conducted a prospective 12 month uncontrolled pilot project, evaluating the potential of losartan to improve or stabilize lung function in patients with IPF. This study design was chosen to provide preliminary data to evaluate the efficacy and feasibility of using losartan in this rare patient population. We report our promising data to support conducting a larger placebo-controlled phase II study in IPF.

Methods

Patients with a diagnosis of IPF, based on the ATS/ERS international consensus statement [1], participated in this pilot project at the University of Cincinnati, Cincinnati, OH. Ethical/IRB approval was obtained prior to enrollment of patients. Twenty patients with IPF were followed for 12 months while taking losartan daily. Patients 21 years old with IPF, a baseline forced vital capacity (FVC) greater than or equal to 50 %, and a baseline 6-minute walk test (6MWT) distance greater than or equal to 200 m were included in the study.

Patients who needed more than 6 L/min of oxygen to maintain SpO₂ greater than 88 % during the 6MWT, were currently smoking or had quit within 6 months of study entry, had a lung transplant, or were taking any angiotensin II receptor blocker were excluded. Clinical use of non-angiotensin II receptor blocker antihypertensive agents was permitted during the study. Losartan 50 mg was administered orally once daily for 12 months. It was supplied at no cost to the patient or the enrolling center. Patients completed a daily log documenting when the study drug was taken and any potential side effects. Daily logs were reviewed at each study visit to identify adverse events or drug compliance issues. To specifically monitor for losartan-induced hypotension, patients also completed daily blood pressure diaries. Patients measured their blood pressure twice weekly while taking losartan and recorded the values in a blood pressure diary. The diaries were reviewed by research staff at study week 1, study week 4, and at each follow-up visit thereafter. Study visits occurred every 3 months for 12 months. These outpatient visits included a history and physical exam, urine pregnancy test if applicable, spirometry, lung volumes, diffusing capacity for carbon monoxide (DLCO), 6-minute walk test (6MWT), and assessment of dyspnea using the Baseline Dyspnea Index (BDI)/Transition Dyspnea Index (TDI). The BDI grades the severity of dyspnea at baseline. The TDI documents changes in dyspnea from a baseline assessment.

The primary end point of this study was change in %FVC from baseline to month 12. Secondary end points included other markers of lung function, including percent of predicted forced expiratory volume at 1 second (%FEV₁), percent of predicted DLCO (%DLCO), and 6MWT distance. We also followed dyspnea scores using the BDI/TDI. The primary response assessment was stable or improved %FVC. We defined stable FVC as a –5 % change in %FVC from baseline up to a +5 % change from baseline due to the known variability of the test [23]. An improved FVC was defined as a greater than 5 % increase in the %FVC after 12 months of treatment. Improvement in secondary measures of pulmonary function was defined as a 10 % or greater increase in predicted values of %FEV₁ and %DLCO, and a minimal importance difference (MID) of distance walked in the 6MWT of 28 m [24]. Patients who continued on the losartan for at least 6 months were evaluable for response. The change in %FVC was the primary study end point and determined the planned sample size. In addition, responders were compared to nonresponders in terms of %FEV₁, %DLCO, 6-minute walk test distance, and degree of dyspnea on the baseline and transition dyspnea index. These supplementary analyses were descriptive and secondary to the primary study question, which was to assess efficacy. Thus, neither power considerations nor adjustments for multiple comparisons were planned. Response rates and confidence intervals were constructed using exact methods. All the tests were two-sided with a significant level of 0.05. Probability (*p*) value <0.05 was considered to be statistically significant. Statistical analyses were performed using SAS ver. 9.2 (SAS Institute Inc., Cary, NC).

Results

Study Subjects

Twenty patients were accrued between April 2009 and October of 2010; 17 patients were evaluable for response. Of the three patients not evaluable, one had undergone a lung

transplant; one had enrolled in the study but did not start losartan, and one had died due to complications associated with disease after 6 months in the study. Patient demographics and baseline characteristics are summarized in Table 1. The study population was predominantly male with a mean age of 67 years. Most patients had moderate lung disease at baseline, with a mean %FVC of 73.96 %, mean %DLCO of 43.65 %, and an average 6MWT distance of 464.89 m. Nine of the 20 patients enrolled required chronic O₂ supplementation at baseline.

Efficacy Assessment

Twelve of 17 patients (71 %) had a stable or improved %FVC after taking losartan for 12 months. Figure 1 depicts the changes in %FVC for all participants. Figure 2 depicts the changes in %FVC for each responder at 3, 6, 9, and 12 months, with the red line showing the mean change in %FVC for all responders over the course of the study. No significant difference was observed between the baseline %FVC of the responders and nonresponders ($p = 0.82$). Of the five patients who did not respond to losartan therapy, their mean %FVC was 75.34 (± 9.70), which was similar to the baseline %FVC of the responders, 73.39 (± 17.71).

Similar results were observed for secondary outcomes, which are presented in Table 2: 58, 71, and 65 % of patients had a stable or improved %FEV₁, %DLCO, and 6MWT distance, respectively, at 12 months when compared with their baseline values.

At the end of study, 7 of 17 (29.41 %) patients had a stable or improved transition dyspnea score (less dyspnea) compared to the baseline dyspnea score, while 10 patients (58.82 %) reported more dyspnea (decreased transition dyspnea scores) compared to baseline evaluations.

Safety Assessment

Losartan was well tolerated in this patient population. Of the 17 patients who received losartan for 12 months, none discontinued the study agent because of side effects. The only side effects experienced included a rash in one patient and fatigue in another that resolved shortly after presentation. One patient died after 6 months in the study due to complications of IPF and the death was deemed unrelated to the study agent. There were no episodes of asymptomatic or symptomatic hypotension documented for any patients in the study.

Discussion

Losartan is an innovative antifibrotic agent that had not been used prospectively in a clinical trial prior to this study. Our open-label pilot project prospectively evaluated losartan in 20 patients with a diagnosis of IPF. We chose a dose of 50 mg because of multiple published studies documenting losartan's successful antifibrotic properties at 50 mg in hepatic, renal, and myocardial fibrosis [19–22, 25, 26]. Losartan may have attenuated the progression of the disease in over 50 % of patients with IPF. The primary objective of FVC as well as other markers of lung function, including FEV₁, was in most cases stable in over 50 % of patient after 12 months. Patients with stable or improved lung function also walked a greater distance for the 6MWT as seen with the 5 of 17 patients who walked more than 28 m when compared to baseline and with another 6 of 17 patients who had a stable 6MWT distance

after taking losartan for 12 months. We chose the baseline and transition dyspnea indexes to follow patient-reported outcomes of the most common symptom seen in patients with IPF that dramatically affects their quality of life. This index measures a patient's degree of breathlessness related to their activities of daily living, including their functional impairment and their magnitude of task and effort. Two patients had an improvement in their dyspnea index after 12 months of losartan therapy and 5 patients had a stable dyspnea index. The two patients with improvement in their dyspnea index also had an improvement in their FVC, FEV₁, and 6MWT distance at 12 months.

Losartan was well tolerated in our study. With only two patients with documented minimal side effects of rash and fatigue, which were self-limited, and no serious adverse events related to losartan, its safety is comparable to placebo. It was also safe to add to antihypertensive regimens without resulting in episodes of hypotension, which was closely monitored throughout the study.

The results of this prospective pilot project are promising and provide support for a future phase II study, which is necessary to establish losartan's effect on IPF. While the small number of patients and the lack of controls prevent establishment of statistically significant efficacy, the number of patients with stable or improved lung function is hopeful for this rare progressive disease.

The results of this study are encouraging when compared to those of previous pilot studies that evaluated new antifibrotic agents to treat IPF. Agents such as etanercept, a human tumor necrosis factor receptor, interferon- γ 1b, and tyrosine kinase inhibitors such as imatinib showed no difference in their predefined end points involving survival and/or pulmonary function [27–29]. Agents such as bosentan, an endothelin receptor antagonist that did not show superiority over placebo in the primary end point of the 6-minute walk distance up to month 12, still prompted further evaluation in phase III studies [30, 31].

The most recent agent with the potential to treat IPF is pirfenidone. This antifibrotic agent was evaluated in a pilot study in 1999 and it showed the possible trends of a stable FVC in patients with IPF [32]. Therefore, further testing was encouraged and recently completed using the CAPACITY trial. The published results include a reduction in the decline of FVC of –8.5 % in the pirfenidone group compared to a reduction of –11 % in the placebo group [33]. Although research with these novel agents has been completed, at this time the results do not recommend them for treating IPF [34].

IPF remains a fatal disease with significant morbidity and a mortality rate that has not changed over the past decade. Unfortunately, a safe and efficacious agent for treatment has not yet been identified. As we look to the future for novel antifibrotic therapies, losartan is a promising agent that is taken orally once a day. With few side effects and no symptoms that warranted discontinuation of the drug, this study provides further support for the safety of this agent. The potential attenuation of disease progression reported in this article makes losartan a reasonable agent to evaluate in a phase II placebo-controlled multicenter trial.

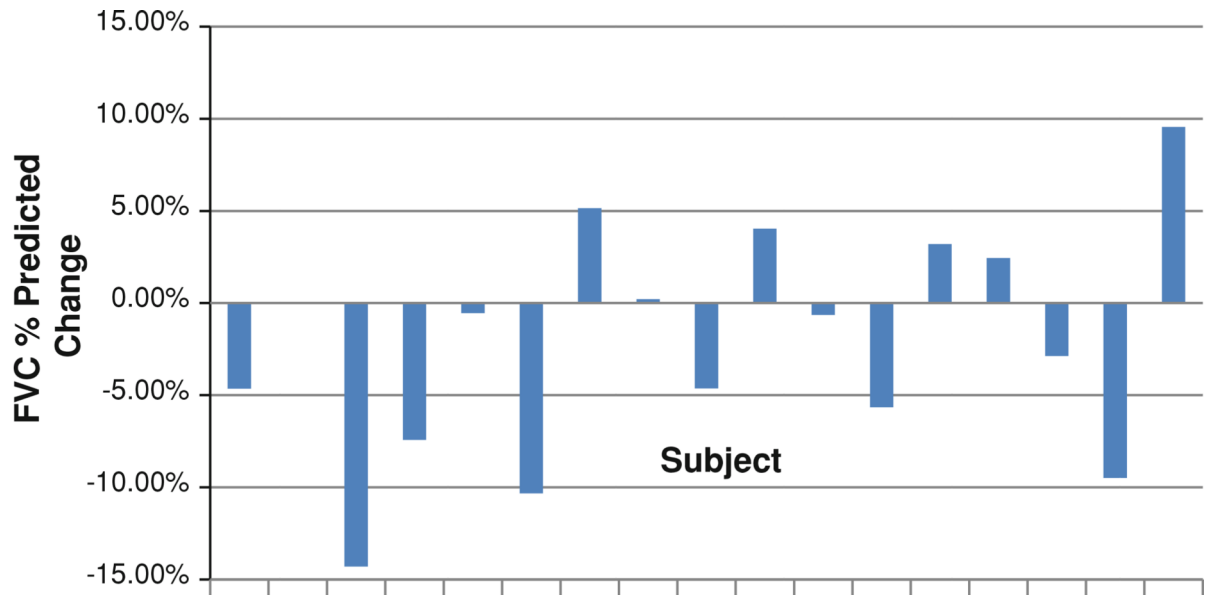
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	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
FVC % Predicted Change	-4.6	0.06	-14.0	-7.4	-0.5	-10.0	5.15	0.21	-4.6	4.04	-0.6	-5.6	3.20	2.44	-2.8	-9.4	9.56

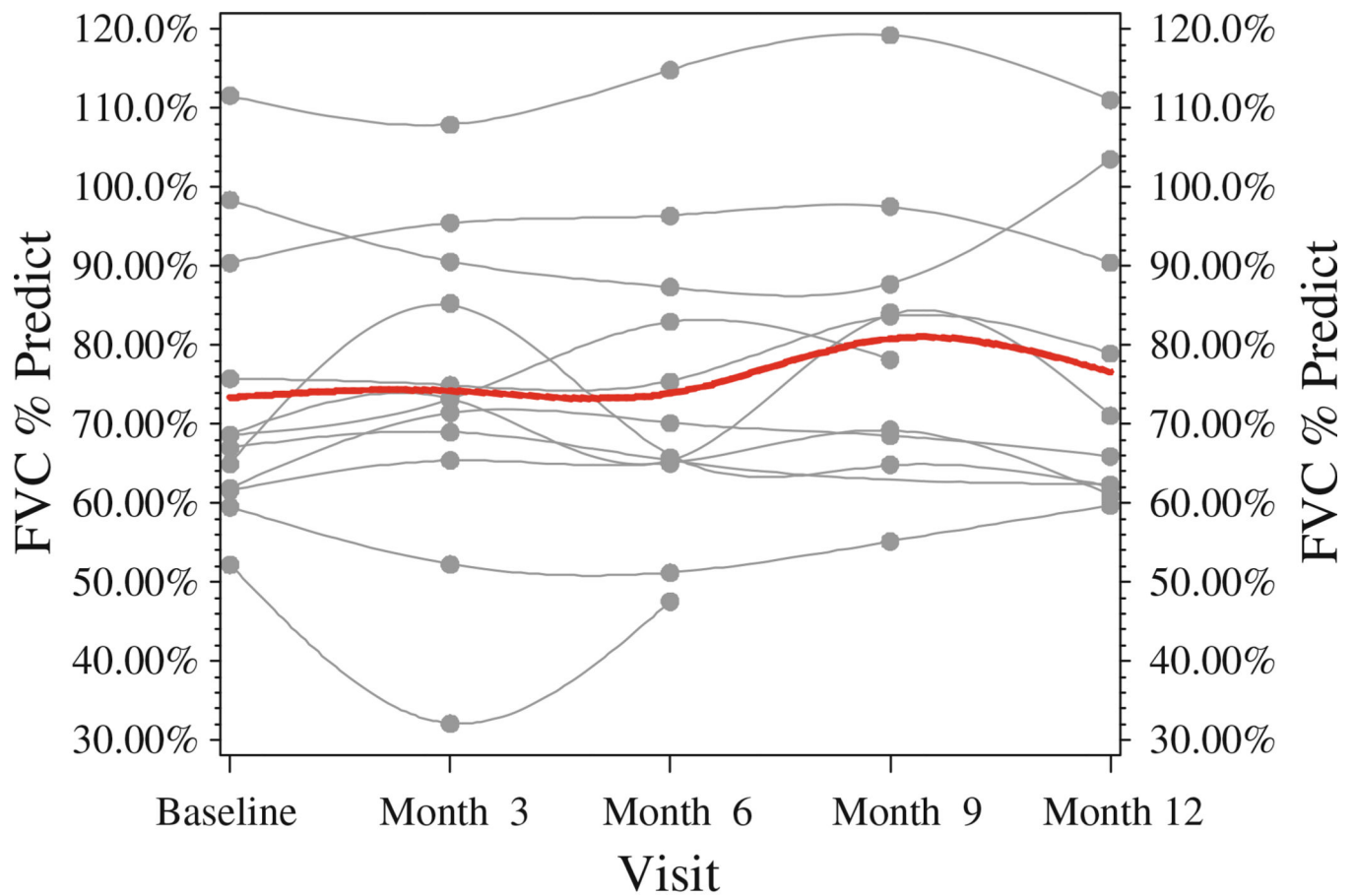
Fig. 1. Change in FVC % predicted over 12 months of losartan therapy

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^patients with stable or improved FVC % predicted at 12 months

Fig. 2.

Change in FVC % predicted at 3, 6, 9, and 12 months of losartan therapy for responders (patients with stable or improved FVC % predicted at 12 months) and their mean FVC % predicted change over time

Table 1Baseline characteristics of the study population ($N = 17$)

Age [mean (range)] (years)	67 (58–81)
M:F	13:4
FVC% predicted (mean \pm SD)	73.96 \pm 3.76
FEV ₁ % predicted (mean \pm SD)	85.44 \pm 3.79
DLCO% predicted (mean \pm SD)	43.65 \pm 16.91
6MWT distance (mean \pm SD) (m)	464.89 \pm 249.54

FVC forced vital capacity, FEV₁ forced expiratory volume 1 second, DLCO diffusing capacity for carbon monoxide

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Table 2

Change in secondary markers of lung function over 12 months of losartan therapy

<i>N</i> (%)	FEV₁	DLCO	6MWT distance
Stable	8 (47.06)	10 (58.82)	6 (35.29)
Improved	2 (11.76)	2 (11.76)	5 (29.41)
Deteriorated	7 (41.18)	5 (29.42)	6 (-1.38)

FEV₁ forced expiratory volume 1 second, *DLCO* diffusing capacity for carbon monoxide

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