

CLINICAL EXPERIENCE WITH PIRFENIDONE IN FIVE PATIENTS WITH SCLERODERMA-RELATED INTERSTITIAL LUNG DISEASE

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ABSTRACT. Interstitial lung disease is the most common complication and cause of death among patients with scleroderma. Scleroderma-related interstitial lung disease has usually been treated with cyclophosphamide; however, its effect was evaluated to be modest and long-term administration of this drug is associated with adverse effects. Herein, we report our clinical experience of administering pirfenidone, which is an antifibrotic agent, in five patients with scleroderma-related interstitial lung disease. All patients demonstrated an increase in vital capacity. (*Sarcoidosis Vasc Diffuse Lung Dis* 2014; 31: 235-238)

KEY WORDS: Antifibrotic agent, interstitial lung disease, pirfenidone, scleroderma, vital capacity

INTRODUCTION

The most common cause of death among patients with scleroderma is now interstitial lung disease (ILD). Among five patients with scleroderma-related ILD (SSc-ILD) (table), four of them demonstrated a progressive decline of vital capacity (VC). Excessive deterioration of lung function is associated with increased mortality among ILD patients (1). We selected pirfenidone as the initial agent for the following reasons: 1) The pathogenesis of SSc is related to fibrosis. 2) Pirfenidone exerts its antifibrotic effect by regulating transforming growth factor beta1, which also plays a critical role in the pathogenesis of SSc (2). 3) Among patients with idiopathic pulmonary fibrosis,

the reduction in VC was significantly smaller in the pirfenidone group than the placebo group (3). 4) A meta-analysis of cyclophosphamide trials did not confirm an improvement in pulmonary function (4). Pirfenidone was administered to the five SSc-ILD patients after obtaining informed consent. We focused on the change in VC because deteriorated lung function is a prognostic factor, and forced vital capacity (FVC) had been validated as an outcome measure in randomized controlled trials in SSc-ILD patients (1).

Case history

Five patients with SSc-ILD, who were not previously treated except case 5, showed a favorable effect with pirfenidone treatment. All patients other than case 4 were female, never smokers, and demonstrated slowly progressive dyspnea and declines in VC. Patients were diagnosed and classified using Japanese guidelines for the diagnosis and severity scales for scleroderma based on the LeRoy and Medsger criteria (5). Case 1, 2, 3 and

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Table 1. Demographic, clinical and haemodynamic characteristics of patients at the time of right heart starting pirfenidone.

	Case 1	Case 2	Case 3	Case 4	Case 5
Age (years)	69	66	62	71	55
Gender	Female	Female	Female	Male	Female
Observation period before treatment (years)	6	8	1	0	10
Smoking history	no	no	yes	no	no
Type of scleroderma	limited	limited	limited	limited	Diffuse
Japanese disease severity	Severe	mild	mild	mild	severe
Autoantibodies					
anti Scl-70 antibody	Positive	Positive	Positive	Positive	Positive
Anti centromere antibody	Negative	Negative	Negative	Negative	Negative
Radiologic findings					
HRCT pattern	NSIP	NSIP	NSIP	NSIP	UIP
Emphysema	no	no	no	yes	no
Surgical biopsy	no	no	no	no	no
Pulmonary Function Test					
%VC	32.9	86.5	82	99.1	44
%DL ^{CO}	N/A	N/A	N/A	40.3	10.7
Pulmonary hypertension	no	no	no	no	yes
Treatment					
Dose of pirfenidone	1800	1200	1800	1200	1200
Combination therapy	no	no	no	no	prednisolone
Proton pump inhibitor	no	yes	no	no	no
Home Oxygen therapy	no	no	no	no	no

*Type of scleroderma was classified according to Japanese guidelines based on the LeRoy and Medsger criteria: limited (distal cutaneous changes), diffuse (proximal cutaneous changes).

Disease severity was classified according to Japanese guidelines: mild (%VC ≥80), moderate (79%VC ≥65), severe (64%VC ≥50), very severe (%VC <50). Definition of abbreviations: VC Vital capacity; DL_{CO}, lung diffusing capacity of carbon monoxide; N/A: not available.

HRCT: high resolution computed tomography. NSIP: nonspecific interstitial pneumonia. UIP: usual interstitial pneumonia

4 were diagnosed as having limited cutaneous SSc with skin involvement limited to the hands. Case 5 was diagnosed as having diffuse SSc with cutaneous involvement proximal to elbows, knees, and clavicles. They were classified according to Japanese guidelines as: case 1 and 5, very severe (%VC 32.9%, and 44.0%; <50%); cases 2, 3, and 4, mild (%VC 86.5%, 82.0%, and 99.1%; ≥80%). Anti-Scl-70 antibodies were positive in all cases. Computed tomography (CT) demonstrated nonspecific interstitial pneumonia in 4 cases, and usual interstitial pneumonia in case 5.

Case 1: VC percent predicted (%VC) decreased by 10.7% (-240mL) over 12 months, but increased by 18.3% (+390mL) 12 months after pirfenidone therapy. The highest rate of change was 28.9% (620mL) at

17 months, and the latest one is 15.2% (+320mL) at 25 months.

Case 2: %VC deteriorated by 16.4% (-410mL) over 12 months, but improved by 21.6% (+480mL) 12 months after therapy, which was the best rate, and lately by 12.2% (+190mL) at 34 months.

Case 3: VC decreased by 14.1% (-220mL) over 10 months, but it recovered by 22.8% (+510mL) 5 months after therapy.

Case 4: VC increased by 21.9% (+700mL) 8 months after pirfenidone therapy. Prior data were not available.

Case 5: 10mg of prednisone per day had been administered by her personal physician for 10 years, but VC decreased by 13.6% (-380mL) over 12 months. 3

months after adding pirfenidone, VC increased by 3.8% (+110mL).

After pirfenidone therapy, dyspnea was attenuated in cases 1, 2 and 3. Sclerodactyly was relieved in case 4. Anti-Scl-70 antibody titers decreased in cases 1, 2 and 5. Ground glass attenuation decreased on chest computed tomography in cases 1 and 4 (figure1). The reduction of ground glass attenuation was also recognized in Japanese phase 2 trial, but honeycomb was not altered (6). The results suggest that pirfenidone might improve early fibrosis.

Only case 2 experienced the adverse event. One month after the initiation of pirfenidone, she developed heartburn, which resolved after reducing the dose to 400 mg t.i.d.

In SSc-ILD patients, gradual deterioration of pulmonary function is generally observed, but some cases with excessive deterioration of lung function demonstrated increased mortality (1). In the cyclophosphamide trial, the change in FVC at 12 months was $-1.0\% \pm 0.92\%$ in the cyclophosphamide group and $-2.6\% \pm 0.9\%$ in the placebo group (7).

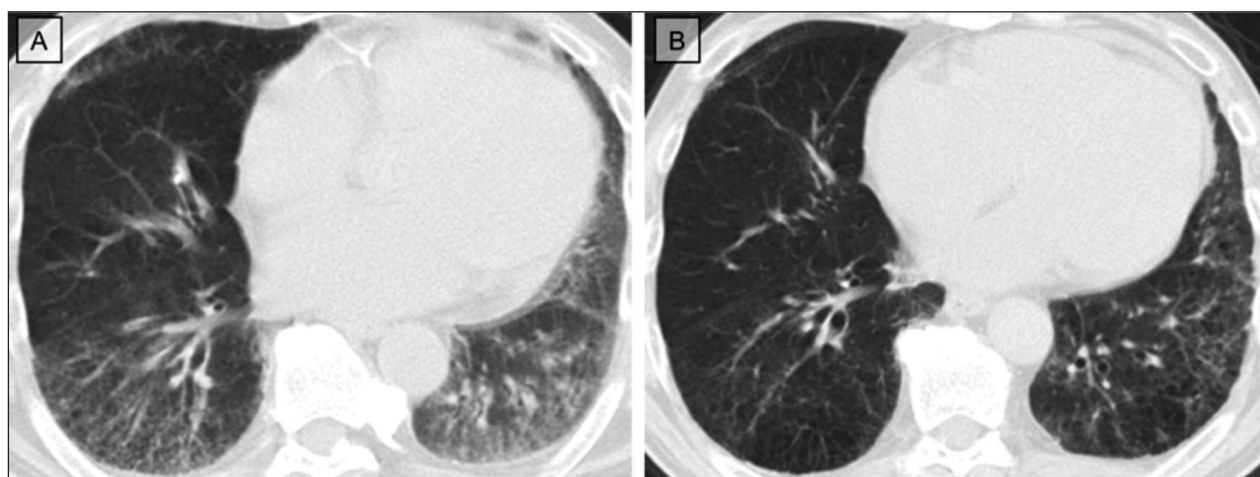


Fig. 1. Computed tomography of case 4. A) Before administration of pirfenidone, CT showed basal reticular shadows and ground-glass attenuation. B) One month after initiating pirfenidone, bibasilar ground-glass attenuation decreased and the volume of the left lower lung increased.

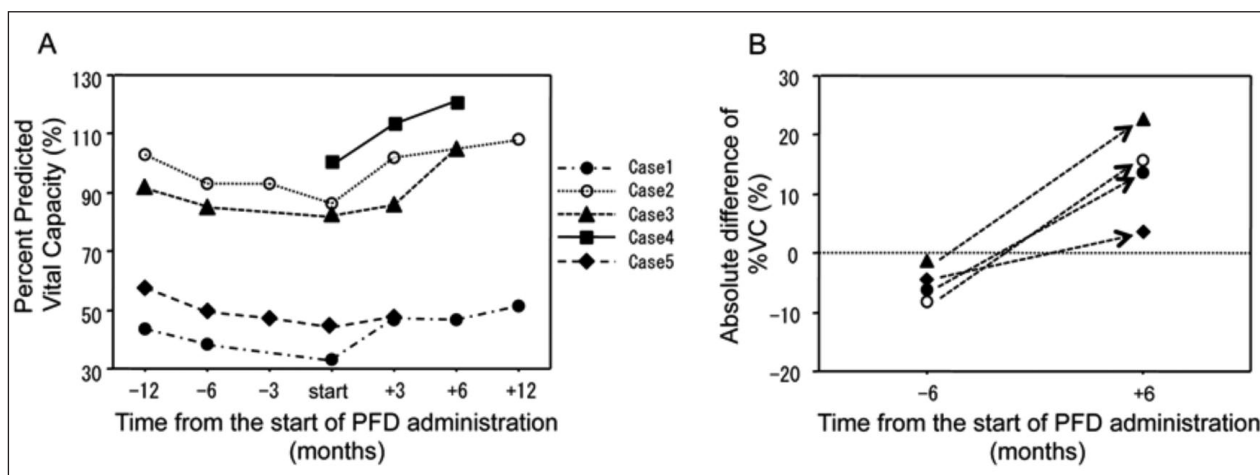


Fig. 2. A) The change of percent predicted vital capacity (%VC) of 5 cases. B) The change of absolute differences of %VC 6 months before and after the administration of pirfenidone in 4 cases. Case 4 was excluded because prior data were not available. Absolute differences of %VC were calculated as follows; %VC at entry - %VC pre-treatment, and %VC post-treatment - %VC at entry. While an effort was made to collect %VC at a three or six months interval, in the case data were not available on the exact date, the nearest data set within three months were utilized.

We considered it worth reporting that the decline in VC not only stabilized but increased (figure 2) with better rate upon pirfenidone administration compared to the cyclophosphamide trial, and no serious adverse events were reported.

In all cases patients had more than 10% decline in VC over the 10-20 months prior to commencing their pirfenidone treatment. This suggests that a predictive indicator for the effectiveness of pirfenidone on patients with scleroderma-related pulmonary fibrosis. This rationale is in line with Okuda's report on idiopathic pulmonary fibrosis which states that patients who experienced more than 150 ml reduction in their FVC in six months demonstrated significant improvement post pirfenidone therapy (8).

There are limitations in this study. This was a retrospective study conducted at a single institution. We had only 5 cases and no other comparable naïve cases of SSc-ILD. Total lung capacity and lung diffusing capacity of carbon monoxide were not monitored regularly. Subjective symptoms of patients were evaluated by qualitative comments.

Pirfenidone may be a useful treatment option for SSc-ILD. A well-controlled clinical trial is needed.

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