Clinical Experience with Pirfenidone in Connective Tissue Diseases Related Interstitial Lung Diseases

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Abstract

Objective: Pirfenidone is a new, anti-fibrotic drug used for the treatment of idiopathic pulmonary fibrosis (IPF). This study was designed to verify the effect of pirfenidone administered in connective tissue diseases related interstitial lung disease (CTD-ILD).

Methods: Twenty two patients diagnosed with CTD-ILD were administrated with a 6-months treatment with or without pirfenidone. At baseline and at months 3rd and 6th, pulmonary function tests, six minute walk distance (6MWD) and HRCT scores were performed.

Results: PFD group presented a significant improvement in TLC in the 3rd and 6th month points and DLco was greatly increased in 6th month point, which were all adjusted by the baseline levels, compared with control group (p=0.043, 0.048 and 0.043, respectively). During the follow-up period, TLC was also improved compared to the initial time point and DLco increased obviously in the 6th month point in PFD group (p=0.005, 0.004 and p <0.001 respectively). A lower ground glass score and fibrotic score in the PFD group approached statistical significance after 6-months treatment with pirfenidone when compared with control group (p=0.037 and 0.018, respectively) and decreased greatly in the 6th month point when compared to the former time points in PFD group (p=0.006 and 0.013, respectively), whereas no such changes were observed in the control group.

Conclusion: These results suggest that pirfenidone could improve the pulmonary function tests and HRCT scores of connective tissue diseases related interstitial lung disease. It is a potential therapeutic candidate for treatment.

Keywords: Pirfenidone; Connective tissue diseases; Interstitial lung disease

Abbreviations: ILD: Interstitial Lung Diseases; CTD: Connective Tissue Diseases; SSc: Systemic Sclerosis; DM: Dermatomyositis; PM: Polymyositis; RA: Rheumatoid Arthritis; MCTD: Mixed Connective Tissue Disease; SS: Sjögren Syndrome; SLE: Systemic Lupus Erythematosus.

Introduction

The interstitial lung diseases (ILDs) are a group of diffuse parenchymal lung disorders that are classified according to specific clinical, radiological and histopathological features and can be associated with underlying Connective Tissue Diseases (CTDs), such as Systemic Sclerosis (SSc), Dermatomyositis (DM) and Polymyositis (PM), Rheumatoid Arthritis (RA), Mixed Connective Tissue Disease (MCTD), Sjögren Syndrome (SS) and Systemic Lupus Erythematosus (SLE). The prevalence of ILD in CTDs varies from 1 to 80% [1].

However, ILD confers a significant impact on morbidity and mortality, making treatment a priority. In SSc patients, the lung (both pulmonary hypertension and pulmonary fibrosis) is the primary cause of scleroderma-related deaths over the 30-year time period [2]. Despite differences in underlying causes, the pathogenesis shows some sort of similarities including injury to structural cells, myofibroblast accumulation, expression of fibrogenic cytokines and fibroblast activation [3,4].

Historically, the management of CTD-ILD has mostly consisted of the suppression of inflammation with corticosteroid or immunosuppressive therapy based on anecdotal reports and uncontrolled treatment responses in small case series due to the low prevalence of cases of clinically significant ILD in individual CTDs. Treatment with cyclophosphamide (CYC) has been recommended in SSc-ILD [5], however, improvements in lung function are generally modest [6] and a meta-analysis of cyclophosphamide trials even did not confirm an improvement in pulmonary function [7].

Pirfenidone exerts its antifibrotic effect by regulating TGF-1 [8], which also plays a critical role in the pathogenesis of pulmonary fibrosis [9] and has been approved for idiopathic pulmonary fibrosis (IPF) in Europe, and USA so far [10,11]. But there are scarce reports of its use in other ILD associated with known causes like CTDs [9]. The aim of our study was to evaluate pirfenidone therapy in CTD-ILD patients.

Materials and Methods

Patients: Patients with clinically and radiologically and/or pathologically confirmed diagnosis of CTD-ILD [12-17], were
admitted in the Rheumatology department of Guangdong General Hospital, China from May 2015 through January 2016. A total of 22 patients were enrolled; 11 were received pirfenidone (DM, n=5; SSc, n=3; overlap syndrome, n=3), and the others were not (DM/PM, n=4; SSc, n=4; MCTD, n=1; SLE, n=1; RA, n=1).

We conducted our study consistent with the Declaration of Helsinki, and applicable laws and regulations of the countries in which the research was conducted. Research Ethics Committee, Guangdong General Hospital, Guangdong Academy of Medical Sciences approved the protocol (No. GDREC20160679H (R1)). All patients provided written informed consent.

**Physiologic Assessment:** Physiologic assessment was performed before the initiation, 3 months and 6 months after the initiation of pirfenidone therapy. Six minute walk distance (6MWD) and pulmonary function tests (PFT), including Forced vital capacity (FVC), Total lung capacity (TLC) and Diffusing capacity for carbon monoxide (DLco), were performed with all patients well-educated by instructors. All spirometric studies were performed using a calibrated pneumotachograph (autobox Vmax 29, Sensor Medics, Yorba Linda, CA, US). Data were expressed as a percentage of the predicted values.

**HRCT Images:** All HRCTs were performed with 1.0 or 1.5 mm-thick sections taken at 1 cm intervals throughout the entire thorax. No intravenous contrast was administered. The scans were performed using a MDCT unit (64-slice LightSpeed VCT, GE Medical Systems, Milwaukee, Wis). The radiologist scored ground glass opacity (CT-avl) and reticular opacity (CT-fib) on a scale of 0-5. The scoring system used for the evaluation of the HRCT scans has been described previously [18]. For the purpose of analysis, each lobe was scored by the interpreter and the mean of all lobes was incorporated into a fibrotic and ground glass score for each patient.

**Therapy:** In our hospital, the physicians did not stop prescribed treatment with steroids and immunosuppressants. Eleven patients of the pirfenidone group and 11 controls all received corticosteroids and prednisone starting at 300 mg/day and checking times between the two groups. All the results of the lung function and 6MWD are reported in Table 2. Patients received pirfenidone for 6 months in total.

**Statistical Analysis:** Clinical date were expressed as count and mean and standard deviation. We calculated the difference between the treatments (PFD) and control group using univariate (covariance) analysis. Subsequently, a p less than 0.05 was considered to denote the presence of a statistically significant difference. A repeated-measures ANOVA was conducted to assess the variations at different time points. Fisher’s exact test was used to provide p values. Data analysis was made with SPSS software (SPSS version 20, SPSS, Chicago, IL, USA).

**Results**

**Patients:** The majority of patients were female (both 90.9% in two groups), with a mean age of 50.2 ± 9.8 years in the control group and 52.0 ± 13.1 years in the pirfenidone group (p >0.05). All of them were non-smokers. Demographic and baseline characteristics are summarized in Table 1. There were no significant imbalances in clinically relevant baseline characteristics between the two study groups except the course which is obviously much longer in pirfenidone group (the median months 10.5 and 1.5 m, respectively and p=0.023).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control (N=11)</th>
<th>PFD (N=11)</th>
<th>P</th>
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<tbody>
<tr>
<td>Age, mean ± SD years</td>
<td>50.2 ± 9.8</td>
<td>52.0 ± 13.1</td>
<td>NS</td>
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<tr>
<td>Men/women</td>
<td>1/11</td>
<td>1/11</td>
<td>NS</td>
</tr>
<tr>
<td>Prednisone dosage</td>
<td>19.5 ± 15.4</td>
<td>18.4 ± 14.0</td>
<td>NS</td>
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<tr>
<td>Combination therapy</td>
<td>NS</td>
<td></td>
<td></td>
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<tr>
<td>CYC</td>
<td>4 (36.4)</td>
<td>5 (45.4)</td>
<td></td>
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<tr>
<td>Other ISD</td>
<td>6 (54.5)</td>
<td>5 (45.5)</td>
<td></td>
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<tr>
<td>Non (prednisone only)</td>
<td>1 (9.1)</td>
<td>1 (9.1)</td>
<td></td>
</tr>
<tr>
<td>Disease duration (months), median value</td>
<td>10.5</td>
<td>1.5</td>
<td>0.023</td>
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</tbody>
</table>

NS: Not significant; ISD: Immunosuppressive drug; CYC: Cyclophosphamide

| FVC | 67.2 ± 2.7 | 72.3 ± 2.7 | NS | 70.5 ± 3.0 | 73.4 ± 3.0 | NS |
| TLC | 61.6 ± 3.2 | 71.7 ± 3.2 | 0.043 | 62.6 ± 3.6 | 74.0 ± 3.6 | 0.048 |
| DLco| 50.6 ± 2.6 | 53.8 ± 2.6 | NS | 50.2 ± 3.6 | 61.3 ± 3.6 | 0.043 |
| 6MWD| 430.2 ± 14.7 | 452.3 ± 14.7 | NS | 406.9 ± 25.8 | 459.9 ± 25.8 | NS |

CT-avl: 1.8 ± 0.2 | 1.3 ± 0.2 | NS | 1.9 ± 0.3 | 1.0 ± 0.3 | 0.037 |
CT-fib: 1.2 ± 0.1 | 1.0 ± 0.1 | NS | 1.3 ± 0.1 | 0.9 ± 0.1 | 0.018 |

In order to treat for primary conditions, they were all administrated with prednisone combined with/without immunosuppressants. The average dosage of prednisone was (19.5 ± 15.4) mg/d in PFD group and was (18.4 ± 14.0) mg/d in control group, which showed no significance between the two groups. Only a proportion of them were received cyclophosphamide orally or intravenously (36.4% and 45.4%, respectively, p=0.904).

Pulmonary function and 6MWD. PFD group presented a significant improvement in TLC in the 3rd and 6th month point, which were both adjusted by the initial levels, compared with control group (p=0.043 and 0.048, respectively). Moreover, DLco was greatly increased in 6th month even though there was no obvious improvement during the first three months in PFD group compared with control group (p=0.043). No significant changes of FVC and 6MWD were observed in different checking times between the two groups. All the results of the lung function and 6MWD are reported in Table 2.
The table displays covariate-adjusted mean levels; NS: Not Significant; FVC: Forced Vital Capacity; TLC: Total Lung Capacity; DLco: Diffusing Capacity For Carbon Monoxide; 6MWD: Six Minute Walk Distance; CT-alv: HRCT Alveolar Score; CT-fib: HRCT Fibrotic Score.

Table 2: lung function, 6MWD, and CT scores value in 3rd and 6th months adjusted by the pretreatment levels in the two groups.

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<tr>
<td></td>
<td>CTR</td>
<td>PFD</td>
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<tr>
<td></td>
<td>0</td>
<td>3m</td>
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<tr>
<td>FVC</td>
<td>68.6 ± 5.3</td>
<td>67.6 ± 5.8</td>
</tr>
<tr>
<td>TLC</td>
<td>69.4 ± 4.4</td>
<td>66.3 ± 4.3</td>
</tr>
<tr>
<td>DLco</td>
<td>56.4 ± 5.5</td>
<td>52.5 ± 4.7</td>
</tr>
<tr>
<td>6MWD</td>
<td>451.0 ± 14.3</td>
<td>445.2 ± 15.7</td>
</tr>
<tr>
<td>CT-alv</td>
<td>1.5 ± 0.3</td>
<td>1.7 ± 0.3a</td>
</tr>
<tr>
<td>CT-fib</td>
<td>0.6 ± 0.2</td>
<td>0.7 ± 0.2</td>
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The table displays covariate-adjusted mean levels and data were analyzed using repeated-measures ANOVA.

Table 3: Changes in lung function, 6MWD, and CT scores in different time points.

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HRCT Scoring: Although not graphically presented, the pretreatment ground glass score and fibrotic score were not statistically significant between the PFD group and the control group. A lower ground glass score and fibrotic score adjusted by the initial levels in the PFD group approached statistical significance after 6-months treatment with pirfenidone when compared with control group (p=0.037 and 0.018, respectively), although there was no decrease between the two groups in the 3rd month. All the results of the HRCT scores are reported in Table 2. The table displays covariate-adjusted mean levels.

No significant changes were found in HRCT scores in different time points in the control group. Meanwhile a ground glass score decreased greatly in the 6th month point when compared to the former time points in PFD group (p=0.006 and 0.013, respectively). However, a fibrotic score decreased in both follow-up time points but shows no statistical significance. The CT scores in different time points are reported in Table 3 and data were analyzed using a repeated-measures ANOVA.

Complications of pirfenidone therapy. Treatment-emergent adverse events (TEAE) related to the use of pirfenidone (fatigue, n=2; cough, n=2; rash, n=2; dyspepsia, n=1) were observed during the first three months. Most side-effects were lost after symptomatic treatment, only cough (n=2) and gastroesophageal reflux (n=1) were persisted in fewer patients. The patients were able to tolerate pirfenidone and no life-threatening complications occurred.

Discussion

In our present study, we firstly investigated whether pirfenidone has a potentially protective effect on CTD-ILD patients in China. Our present findings showed a significant treatment effect of pirfenidone on changes in the DLco and TLC and HRCT scores over a period of six months but no significant effect on FVC and 6MWD. The TEAE reported during our study were all mild or moderate in severity and none were classified as serious or led to treatment discontinuation.

To our understanding, only a few of previous papers reported the clinical experience of pirfenidone on CTD-ILD. Miura and colleagues showed an increase in vital capacity (VC) in five patients with SSc-ILD suggesting pirfenidone might have been a useful treatment option for SSc-ILD [21]. This report had only brought into five patients and no other comparable cases of SSc-ILD. Besides, TLC and DLco were not regularly monitored. A retrospective observational study demonstrated a reduced decline in DLco in pirfenidone tolerant group in IPF compared with the intolerant group which is in line with our results [22]. Several randomized controlled trials have demonstrated a significantly reduced decline in FVC [1,23,24]. While little studies reported any changes in DLco [23]. Improvement in DLco in our study may suggest pirfenidone alleviate severity of interstitial fibrosis and enhance diffusing capacity. Moreover, all the trials showed deterioration in IPF and pirfenidone reduced the decline in pulmonary function tests [11,23,26,27]. In our study, FVC, TLC and DLco showed neither increase nor decrease in control group and TLC and DLco were greatly improved in pirfenidone group suggesting pulmonary functions don't worsen in short period in CTD-ILD. This may attribute to the combination therapy of steroids with/without...
immunosuppressants treating for CTD, which also lead to progression in ILD, and might explain the better prognosis in CTD-ILD than in IPF [28.]

PFT is an important marker for the diagnosis and follow-up of patients with ILD. Many randomized clinical trials have used the results of PFT in the assessment of the response to pirfenidone therapy while scarce trials have evaluated the utility of CT regularly [23,24,26]. Iwasawa and his team firstly analyzed quantitatively the effect of pirfenidone treatment on IPF using lung CT and observed the decline in VC correlated significantly with the increase in fibrotic lesion [29]. In our study, patients in pirfenidone group showed a significantly lower ground glass score after 6-months treatment compared with the baseline and a decreased fibrotic score during the follow-up period, which shows no statistical significance, suggesting pirfenidone may be more effective in anti-inflammation than anti-fibrosis. As a result, we consider CT as a candidate supplementary tool to assess the outcome of pirfenidone treatment in patients with CTD-ILD.

Pirfenidone has been reported to improve 6MWD distance with a RR of 0.74 (IC 0.64-0.86) compared to placebo, but the patients all were IPF instead of CTD-ILD patients [24]. Whereas there are no significant differences in 6MWD distance in both groups and different follow-up time points in our present study. Because patients are always suffering from other clinical symptoms, such as joint pains and muscle weakness, as well as lung associated symptoms, which are quite common in CTD and thus affect the result of 6MWD distance. This may suggest 6MWD distance may not be able to predict the outcome of pirfenidone treatment in CTD-ILD patients.

In relation to adverse effects treatment with pirfenidone were well tolerated in all patients in our study. Our findings were consistent with those in a meta-analysis in IPF and an open-label, phase II study in SSC-ILD [24,30,31].

Our study has additional limitations. This was an open, prospective, single-center study. Further randomized clinical studies are needed to evaluate effect of pirfenidone on CTD-ILD. To date, controlled treatment trials have not been performed in different entities of CTD-ILDs and it is not clear that such trials are truly feasible, given the low patient numbers, multiple options of combined immunosuppressive therapies.

In conclusion, we found that pirfenidone treatment should be considered as it achieved a clinical and laboratory significant improvement. Pirfenidone administration was generally safe and may attenuate inflammation and improve lung function at an earlier phase of CTD-ILD.

Acknowledgment

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Conflict of Interest

None.

References


