THERAPEUTIC ADVANCES in
Respiratory Disease

Original Research

Real-world therapeutic performance of pirfenidone for connective tissue disease-associated interstitial lung diseases

Ther Adv Respir Dis

2024, Vol. 18: 1–11

DOI: 10.1177/17534666241292507

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Abstract

Background: Pirfenidone (PFD) is commonly applied for antifibrotic treatment in patients with idiopathic pulmonary fibrosis but has rarely been studied in cases with connective tissue disease-associated interstitial lung diseases (CTD-ILDs).

Objectives: We aimed to examine the efficacy of PFD in patients with CTD-ILD based on real-world data.

Design: A retrospective cohort study.

Methods: This study assessed the clinical features of CTD-ILD patients with or without a 6-month PFD treatment. A linear mixed effects model was employed to evaluate the effectiveness of PFD in alleviating lung function changes. Differences in response to PFD were analyzed based on CTD subtype, imaging classification, and pattern of pulmonary function at baseline.

Results: A total of 289 patients with CTD-ILD were included, with 155 (53.6%) receiving PFD treatment and the remaining constituting the control group. Patients with the usual interstitial pneumonia (UIP) pattern were more likely to receive PFD treatment, and a relatively lower proportion of cases in the PFD group received immunosuppressive therapies compared to the control group ($p < 0.05$). At the 6-month follow-up, patients in the PFD group demonstrated a more significant improvement in forced vital capacity (FVC) and diffusion capacity for carbon monoxide (DLCO) (ΔFVC%: 2.9% vs 0.45%, $p = 0.009$; ΔDLCO%: 1.9% vs −1.1%, $p = 0.004$). In the linear mixed model analysis, there was a statistically significant group-time interaction between FVC% and DLCO% changes over time (FVC%: $\beta = 4.52$, $p < 0.001$; DLCO%: $\beta = 4.13$, $p = 0.003$). Furthermore, subgroup analysis indicated that pirfenidone may have superior therapeutic effects in patients with systemic sclerosis (SSc)-associated ILD, non-UIP pattern, and restrictive pattern of lung function at baseline.

Conclusion: This study provided real-world data demonstrating the effectiveness of PFD in terms of lung function improvement in patients with CTD-ILD.

Keywords: connective tissue disease, interstitial lung disease, linear mixed effects model, pirfenidone

Received: 19 June 2024; revised manuscript accepted: 1 October 2024.

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Introduction

Interstitial lung disease (ILD) characterized by lung dysfunction and interstitial changes on high-resolution computed tomography (HRCT) images, is a common, often fatal complication of systemic autoimmune diseases.[1] Due to the

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heterogeneous clinical manifestations of connective tissue disease-associated interstitial lung disease (CTD-ILD), no single management approach is appropriate for all possible clinical scenarios.[2] Although immunosuppression remains the mainstay for ILD treatment, the therapeutic dose, route, and duration are often determined by individual clinicians, and specific agents with high-level evidence are lacking.[3] In recent years, antifibrotic therapies have been recommended in patients with CTD-ILD at the fibrotic stage.[4,5] Nintedanib as one of the antifibrotic drugs was proven to slow the rate of decline in lung function of patients with progressive fibrosing autoimmune disease-related ILDs in subgroup analysis of the INBUILD trial and was also conditionally recommended for patients with progression despite first ILD treatment according to the recent guidelines from 2023 American College of Rheumatology (ACR)/American College of Chest Physicians (CHEST).[6,7] However, given the gastrointestinal adverse effects of nintedanib, pirfenidone as another representative potential option does warrant attention, although the treatment data remain limited.

Pirfenidone(5-methyl-1-phenyl-2[1H]-pyridone, PFD), a traditional antifibrotic agent, inhibits fibroblast proliferation primarily via the suppression of TGF-β1 (transforming growth factor-β1).[8] PFD was previously demonstrated to reduce the rate of decline in forced vital capacity (FVC) and improve survival in patients with idiopathic pulmonary fibrosis (IPF).[9,10] Given the overlapping pathogenic mechanisms between systemic sclerosis-associated ILD (SSc-ILD) and IPF, pirfenidone was assessed for safety in 63 cases in the LOTUSS trial, with an acceptable tolerability profile.[11] Furthermore, in an open-label, prospective study, pirfenidone reduced mortality in patients with subacute ILD associated with clinically amyopathic dermatomyositis compared with the control group.[12] Recent evidence suggests that pirfenidone attenuates disease progression in patients with rheumatoid arthritis-associated ILD (RA-ILD) when added to an existing treatment from TRAIL 1 study.[13]

However, pirfenidone utilization in clinical practice is highly dependent on the physician's subjective experience, and many patients administered pirfenidone have concurrent medicines or poor pulmonary function tests (PFTs) that would exclude them from clinical trials based on strict eligibility criteria.[3] Therefore, clinical data on pirfenidone efficacy in patients with CTD-ILD are urgently needed. This study examined a retrospective cohort to investigate the efficacy of pirfenidone in patients with CTD-ILD in a real-world setting.

Methods

Patient population

Patients with CTD-ILD were retrieved from the Chinese Rheumatism Data Center (CRDC), a prospective, nationwide registry that provides real-life data for Chinese rheumatic patients.[14] The time of registration was between May 2014 and February 2023. All enrolled patients were aged > 18 years and CTD-ILD diagnosis was performed by a collaborative multidisciplinary team according to criteria from the American College of Rheumatology (ACR)/European League Against Rheumatism; besides, patients with idiopathic inflammatory myositis (IIM) fulfilled the Bohan & Peter's criteria.[15–20] All patients were administered the standard treatment, and pirfenidone was supplemented in some cases by rheumatologists as appropriate, with a starting dose of 300 mg/day that was gradually increased to a maximum maintenance dose of 1800 mg/day unless the patient experienced intolerable side effects. Patients with nintedanib or missing data during the 6-month follow-up were excluded.

Data collection

The clinical data of eligible patients were extracted from the CRDC database. Demographic parameters included age, sex, body mass index (BMI), smoking status, and CTD subtype. Former smoker was defined as those who had at least a 10-pack-year smoking history and quit smoking for more than 6 months. PFT indexes at baseline and follow-up were recorded, including FVC, percentage of predicted FVC (FVC%), diffusing capacity for carbon monoxide (DLCO), and percentage of predicted DLCO (DLCO%). Imaging patterns (UIP vs non-UIP) at baseline were independently reviewed by two clinicians (Hui Huang and Lan Song) based on the HRCT reports in the CRDC system. Drugs (pirfenidone, glucocorticoids (GCs), and immunosuppressants) administered during the follow-up period were also examined. The reporting of this

study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.[21]

Statistical analysis

Continuous variables were reported as mean (standard deviation) or median (interquartile range (IQR)), as appropriate, and compared using the two-sample independent *t*-test or the Mann-Whitney *U* test. Categorical variables were presented as numbers (%) and compared using the Chi-square test or Fisher's exact test. To assess differences in changes over time between groups, lung function indexes (FVC% and DLCO%) were analyzed using a linear mixed effects model (LMM), which effectively handles missing data through full information maximum likelihood estimation. The LMM included fixed effects for time and group, covariates for imaging pattern and glucocorticoid use, while participant ID was incorporated as a random effect. Data analysis was performed using SPSS (IBM Corp., version 26, Armonk, NY, USA), and R software (R Core Team, version 4.2.2, Vienna, Austria). Statistical significance was set at $p < 0.05$ with two-sided testing.

Results

Clinicodemographic characteristics of CTD-ILD patients

The final cohort consisted of 289 CTD-ILD cases, including 134 patients administered the standard treatment (control group) and 155 administered additional treatment with pirfenidone (PFD group). Baseline characteristics are summarized in Table 1. No differences were detected in age, gender, BMI, and smoking status between the PFD and control groups. The included patients were mostly categorized as IIM (55.7%), SSc (22.8), RA (11.1%), Primary Sjogren's syndrome (pSS) (6.6%) and systemic lupus erythematosus (SLE) (3.8%), while the proportion of RA patients was significantly higher in the PFD group compared with the control group (15.5% vs 6.0%, $p < 0.05$). As for imaging findings, a definite UIP pattern was detected in 16.3% of the included patients, who were more likely to receive PFD (21.3% vs 10.4%, $p < 0.05$). In addition, both FVC and DLCO at baseline were significantly lower in the PFD group compared with the control group ($p < 0.05$). In terms of immunosuppressive treatment, control cases were more likely to take higher doses of glucocorticoids and to receive immunosuppressants such as cyclophosphamide, mycophenolate mofetil, and methotrexate ($p < 0.05$).

Evaluation of changes in the magnitude of pulmonary function over the follow-up period

As shown in Figure 1, absolute changes in FVC% and DLCO% from baseline to 6 months were compared between the PFD and control groups. FVC% was improved in both groups, with a more pronounced increase in the PFD group (2.9% (−2.0%, 12.0%) vs 0.45% (−3.5%, 6.6%), $p = 0.009$) at the 6-month follow-up. The change in DLCO% also differed between the two groups, with an increase of 1.9% in the PFD group, while no improvement was found in control cases (1.9% (−2.4%, 7.5%) vs −1.1% (−6.5%, 4.4%), $p = 0.004$). No differences were found at the 3-month period between the two groups.

Multilevel analysis of lung function changes

Considering the potential confounders, a LMM was applied to estimate the changes in FVC% and DLCO% with or without PFD. The overall trends of PFT indexes were shown in Figure 2, with the PFD group exhibiting greater recovery over time than control cases. Further, after the adjustment for imaging pattern and glucocorticoid use, the group × time interaction indicated a significant difference between PFD and control group, and both FVC% and DLCO% improved with the follow-up as shown in Table 2.

Subgroup analysis of pulmonary function

CTD types. Changes in FVC% and DLCO% from baseline to 6 months were compared in the PFD and control groups (Figure 3, Supplemental Table S1). Significant improvements in both ΔFVC% (3.9% (−0.7%, 8.2%) vs −2.0% (−4.9%, 2.7%), $p = 0.025$) and ΔDLCO% (1.2% (−0.1%, 5.3%) vs -5.0% (−8.0%, 0), $p = 0.001$) were detected in the PFD group of SSc patients compared with the control group. IIM-ILD patients administered PFD had poorer lung function at both baseline and 6 months compared with controls, with better recovery although statistical significance was not reached. However, no significant difference was found in patients with SS and RA regardless of PFD use. SLE-ILD was not included in the final analysis due to the limited sample size.

Table 1. Baseline characteristics of patients.

Characteristic	Total (*n* = 289)	Pirfenidone (*n* = 155)	Control (*n* = 134)	*p* Value
Age (years)	54.8 (12.3)	54.7 (12.6)	54.8 (12.0)	0.960
Gender, female	228 (78.9)	122 (78.7)	106 (79.1)	0.935
BMI	24.1 (4.0)	24.0 (3.9)	24.2 (4.1)	0.586
CTD subtypes				0.035
IIM	161 (55.7)	85 (54.8)	76 (56.7)	
RA	32 (11.1)	24 (15.5)	8 (6.0)	
SSc	66 (22.8)	29 (18.7)	37 (27.6)	
pSS	19 (6.6)	9 (5.8)	10 (7.5)	
SLE	11(3.8)	8 (5.2)	3 (2.2)	
Smoking status				0.528
Never smoker	255 (88.2)	137 (88.4)	118 (88.1)	
Former smoker	30 (10.4)	17 (11.0)	13 (9.7)	
Active smoker	4 (1.4)	1 (0.6)	3 (2.2)	
ILD pattern on HRCT				0.013
UIP	47 (16.3)	33 (21.3)	14 (10.4)	
non-UIP	242 (83.7)	122 (78.7)	120 (89.6)	
Pulmonary function test				
FVC, mL	2.5 (0.7)	2.3 (0.6)	2.6 (0.7)	0.004
FVC%	78.8 (16.0)	74.8 (14.9)	81.9 (16.4)	<0.001
DLCO, mL	5.0 (1.7)	4.2 (1.3)	5.3 (1.7)	<0.001
DLCO%	58.3 (15.9)	54.7 (16.6)	62.4 (14.0)	<0.001
Concurrent medication use				
Glucocorticoids dosage (mg/day)	5.0 (0, 15.0)	0 (0, 10.0)	7.5 (5.0, 20.0)	<0.001
Cyclophosphamide	71 (24.6)	21 (13.5)	50 (37.3)	<0.001
Mycophenolate mofetil	48 (16.6)	18 (11.6)	30 (22.4)	0.014
Tacrolimus	36 (12.5)	15 (9.7)	21 (15.7)	0.124
Methotrexate	14 (4.8)	3 (1.9)	11 (8.2)	0.013

*Data are *n* (%), mean (SD) or medium (IQR).
DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity; HRCT, high resolution computed tomography; ILD, interstitial lung disease; SSc, systemic sclerosis.

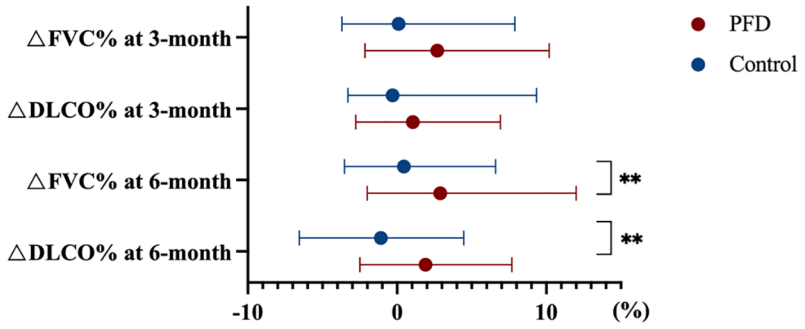

Figure 1. Changes in FVC% and DLCO% from baseline to 3- and 6-month follow-ups were represented by dot plots, with the median indicated by a dot and the interquartile range shown as the line outside the dot. The variation (Δ) was calculated as the difference between follow-up values and baseline values.
DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity.

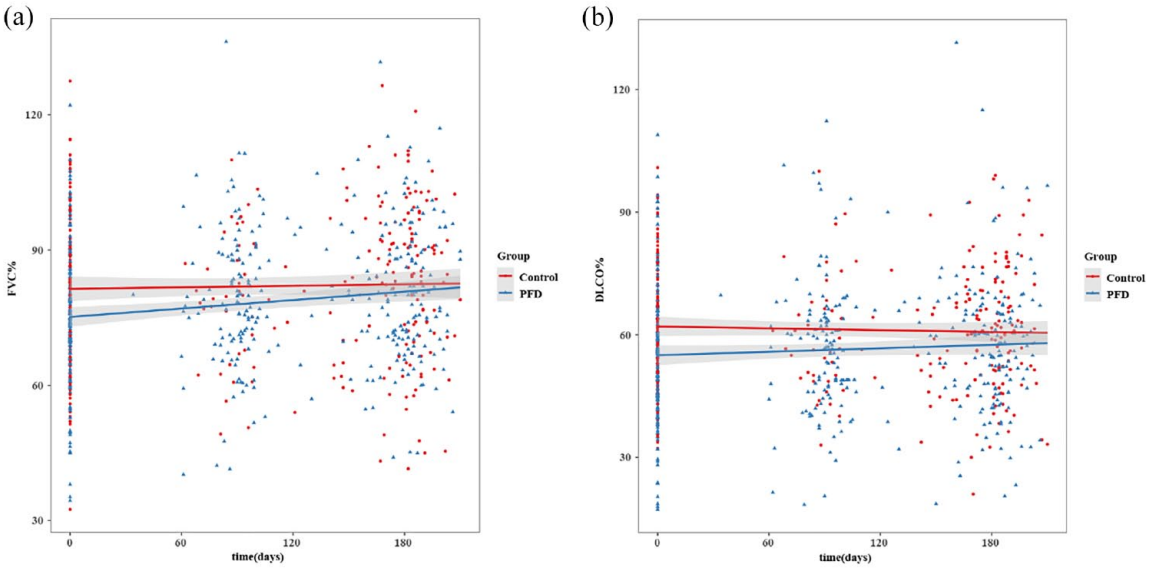

Figure 2. Longitudinal comparisons of changes in FVC% and DLCO%. Changes in lung function over time from baseline as estimated by linear regression for (a) FVC% and (b) DLCO% between the PFD and control groups. Colored dots (measurements) and lines (over time) in both graphs reflect individual patient data.
DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity.

Imaging patterns. Subtype analysis based on HRCT manifestations showed that DLCO% in patients with UIP pattern improved by 2.1% in the PFD group compared with the standard treatment (2.1% (−1.5%, 5.9%) vs −8.0 (−14.5%, −2.8%), $p=0.026$). In patients with non-UIP pattern, changes in both FVC% (3.0% (−1.1%, 13.8%) vs 0.1% (−3.2%, 6.1%), $p=0.004$) and DLCO% (1.6% (−2.4%, 7.3%) vs −1.0 (−5.4%, 4.2%), $p=0.005$) was more likely to yield a better response to PFD, despite with worse pulmonary function compared with the control group (Figure 4, Supplemental Table S2).

Patterns of baseline lung function. Furthermore, patients with the restricted subtype (baseline FVC% < 80, DLCO% < 80%) significantly benefited from PFD treatment regarding the magnitude of change in FVC% (4.1% (−0.6%, 16.8%) vs −0.3 (−3.5%, 8.5%), $p=0.011$) and DLCO%

Table 2. Linear mixed effects of changes in lung function.

Measures	FVC%			DLCO%		
	β	SE	*p* Value	β	SE	*p* Value
Group(ref = Control)	−7.04	1.92	<0.001***	−6.53	1.86	<0.001***
Time3(ref = time0)	−0.70	1.40	0.616	−1.36	1.62	0.404
Time6(ref = time0)	1.08	0.88	0.220	−1.45	1.01	0.151
Group × Time3	4.69	1.65	0.005**	2.61	1.91	0.173
Group × Time6	4.52	1.20	<0.001***	4.13	1.38	0.003**

*Values indicate the estimated effect (β) and corresponding standard error (SE) after adjustment for imaging pattern and glucocorticoid use.
**$p < 0.01$. ***$p < 0.001$.

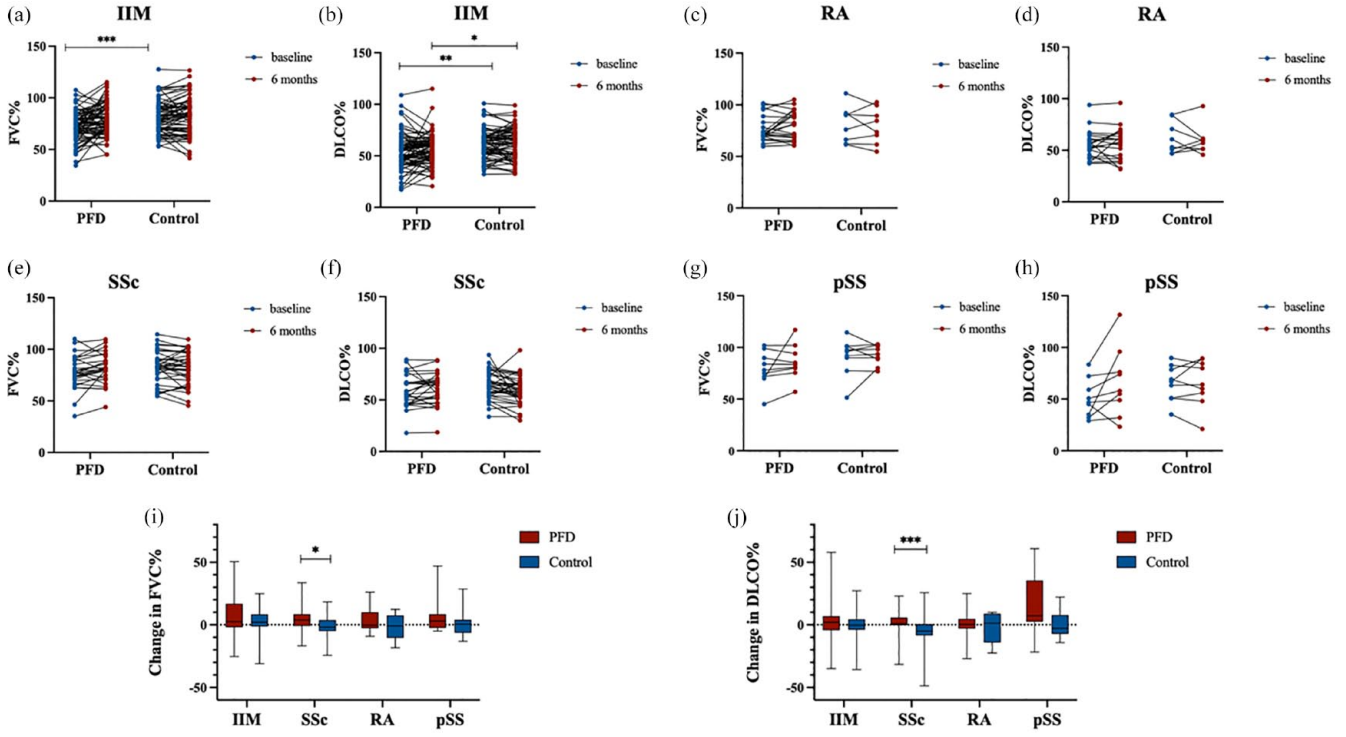

Figure 3. Changes in FVC% and DLCO% for different CTD subgroups. Blue and red dots represent lung function values, respectively, at baseline and 6-month follow-up in patients with IIM-ILD (a and b), RA-ILD (c and d), SSc-ILD (e and f), and pSS- ILD (g and h). The magnitudes of FVC% (i) and DLCO% (j) changes are shown as box plots. Boxes show IQRs and medians (midlines).
DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity; IIM, idiopathic inflammatory myositis; IQR, interquartile range; SSc, systemic sclerosis.

(2.0% (−1.9%, 8.2%) vs −0.6% (−7.1%, 4.3%), $p = 0.010$), although the patients administered the standard treatment alone had better pulmonary function status compared with PFD-treated patients during the 6-month follow-up period (Figure 5, Supplemental Table S3).

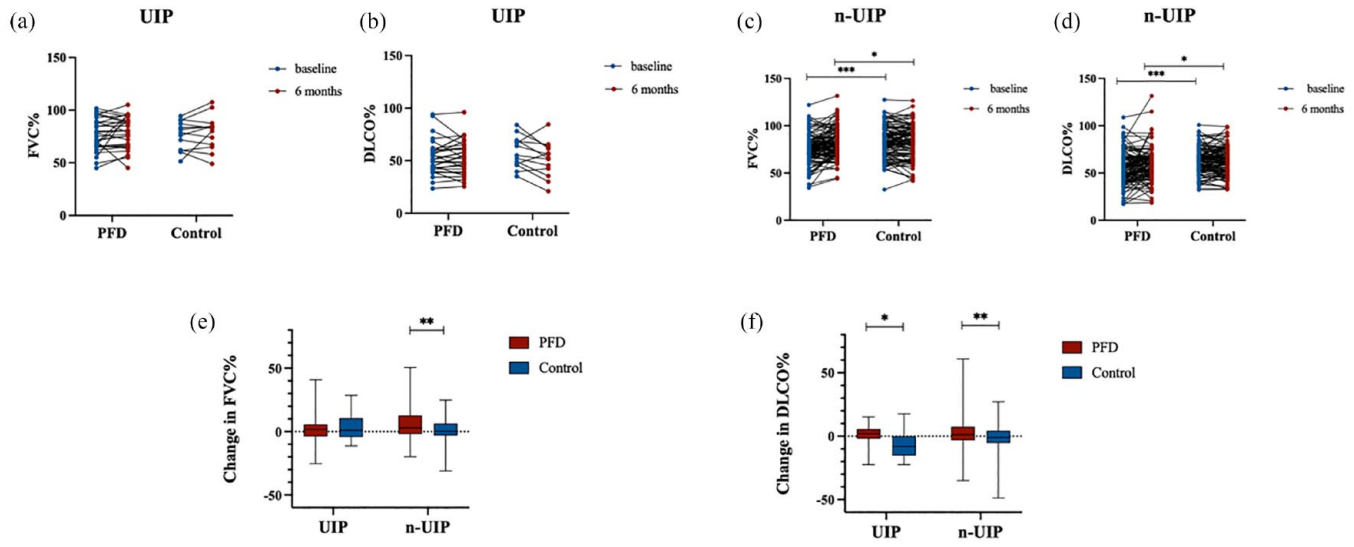

Figure 4. Changes in FVC% and DLCO% for patients with different HRCT findings. Blue and red dots represent lung function values, respectively, at baseline and 6-month follow-up in patients with UIP pattern (a and b), and non-UIP pattern (c and d). The magnitudes of FVC% (e) and DLCO% (f) changes are shown as box plots. Boxes show IQRs and medians (midlines).
DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity; IQR, interquartile range; UIP, usual interstitial pneumonia.

Discussion

In this historical, retrospective cohort study, we evaluated the effectiveness of pirfenidone in patients with CTD-ILD based on real-world data. The pirfenidone group had lower FVC and DLCO at baseline, with significant improvements at 6-month follow-up compared with the control group. The approach of repeated measures for a single patient over time statistically corrected for heterogeneity in the patient background and balanced potential confounding factors. Furthermore, cases with different CTD subtypes, HRCT findings, and baseline lung function patterns demonstrated distinct responses to pirfenidone. This study reported the additional treatment data of CTD-ILD patients and provided a real-world reference for pirfenidone administered in clinical practice.

Patients with pirfenidone treatment responded well at the 6-month follow-up in this study as shown by improved FVC% and DLCO%. Given the substantial variability across CTDs in both ILD prevalence and characteristics, a detailed subtype analysis was performed.[2] In the study population, patients with IIM (55.7%) accounted for the highest proportion, followed by SSc cases (22.8%), and individuals with SSc-ILD significantly benefited from PFD treatment, consistent with the previous findings of a prospective, single-center study based on 30 patients with SSc-ILD administered pirfenidone combined with immunosuppressants.[22] However, no difference was detected in cases with other CTDs, probably due to the limited sample size resulting from the low incidence or loss of follow-up due to mild symptoms. It should also be noted that patients with IIM-ILD probably had more referrals due to acute status, and the exclusion of patients with nintedanib use, especially SSc and RA-associated ILD, maybe the considerable factors for the proportions of CTD subtypes. Therefore, well-designed studies across CTD subtypes are required to confirm the above effect. Additionally, the proportion of patients with RA was higher in the PFD group than in the control group. The active use of PFD may be associated with the high susceptibility of the UIP pattern and the known benefit from antifibrotic agents in patients with RA-ILD from the TRAIL 1 study.[13,23]

The RELIEF trial previously suggested that the addition of pirfenidone to the existing treatment attenuates FVC decline in fibrotic ILDs other than IPF.[24] Considering the crucial role of HRCT in the diagnosis, follow-up, and prognosis of ILD cases, it is currently believed that distinct subtypes respond differently to drug reactions.[25] In

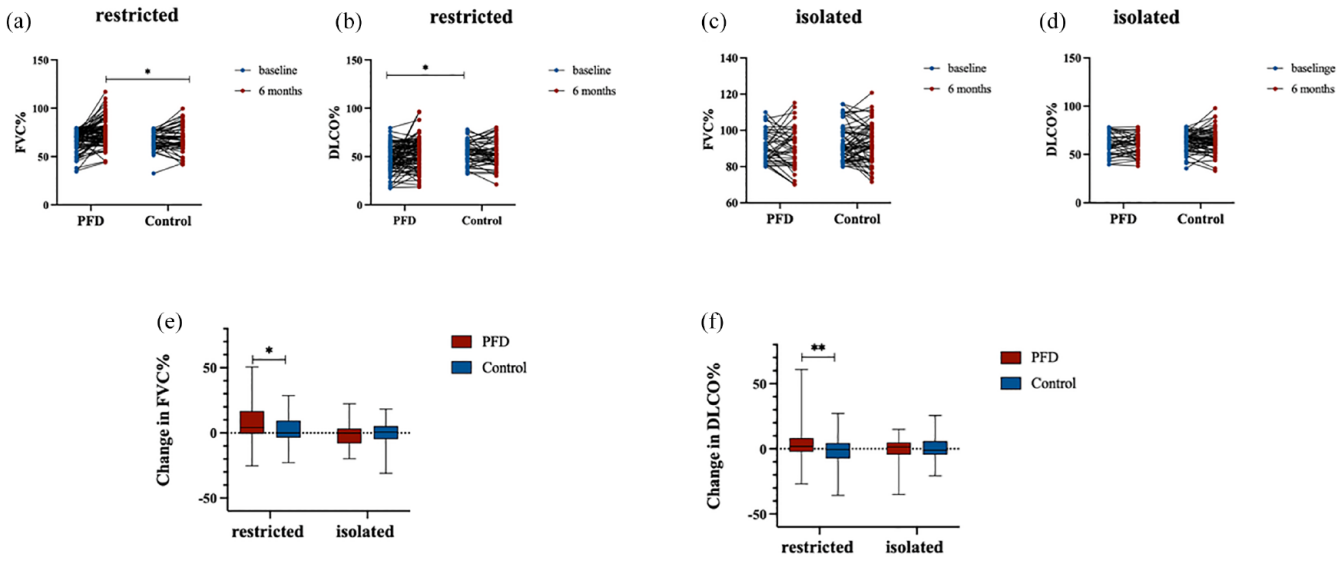

Figure 5. Changes in FVC% and DLCO% for patients with different impairment patterns of baseline lung function. Blue and red dots represent lung function values, respectively, at baseline and 6-month follow-up in patients with restricted subtype (a and b), and isolated DLCO% reduction subtype (c and d). The magnitudes of FVC% (e) and DLCO% (f) changes are shown as box plots. Boxes show IQRs and medians (midlines).
DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity; IQR, interquartile range.

another retrospective study, IPF patients with a possible UIP pattern responded better to pirfenidone than those with the UIP pattern.[26] Consistently, we determined that patients without the UIP pattern even benefited more from pirfenidone treatment as measured by changes in FVC% and DLCO% compared to those with the UIP pattern. This might be explained by the notion that the beneficial effect is greater in cases with reversible stages on HRCT images and closely related to the dual anti-inflammatory and antifibrotic effects of pirfenidone as elucidated.[8] These findings draw attention to the management of CTD-ILD without the UIP pattern, in which little-studied cases may be the population with potential benefits from the drug. Although patients with mild disease may have poor adherence to antifibrotic therapy in the clinic, available data suggest pirfenidone attenuates disease progression, even at low doses.[27] Further strategies for determining the optimal starting time and effective dose are still required.

To assess potential differences in the response to pirfenidone in CTD-ILD patients with distinct baseline pulmonary function levels, the patients were stratified with restricted (FVC% $<$ 80, DLCO% $<$ 80) and isolated DLCO% reduction (FVC% $\geq$ 80, DLCO% $<$ 80) based on the previous assessment of SSc.[28] Isolated DLCO impairment is considered the earliest abnormality on PFTs in patients with ILD due to alveolar-capillary barrier damage, which accounted for 35.6% in the current cohort, basically consistent with previous findings.[29] The restricted group responded better to pirfenidone than the control group, indicating that the curative effect of pirfenidone in CTD-ILD patients with isolated diffuse impairment is not quantitatively significant but favorable for active use in subjects with poor lung function at baseline. Moreover, 20 patients in this study had normal ranges for FVC% and DLCO%, which may be a subclinical state of ILD defined as radiographic abnormalities without symptoms or physiologic abnormalities with potential disease progression at any point.[30] Therefore, timely identification, regular monitoring, and initiation of fibrosis treatment are recommended to prevent disease progression. In addition, effective, high-level evidenced strategies are urgently needed.

Actually, pirfenidone is often added to patients with poor response to glucocorticoids and immunosuppressants, especially those with UIP patterns and worse lung function, given the effectiveness of pirfenidone in the treatment of IPF. In addition, the 2018 Chinese expert-based

consensus statement regarding the diagnosis and treatment of CTD-ILD also recommends using antifibrotic therapies conditionally based on disease activity.[31] Such selection bias in real-world settings seems often difficult to avoid completely, despite statistical corrections. Although our data showed a clear trend toward longitudinal improvement in lung function over time in the treatment group, the results should be interpreted with caution, as only patients with medication records and pulmonary function test reports within 6-month follow-up were included, which may overestimate the drug effectiveness to some extent. We look forward to well-designed clinical trials to further confirm the benefits of pirfenidone in the treatment of CTD-ILD.

Limitations

There were some limitations. First, as a real-world study, missing data were inevitable, for example, loss of adverse events, despite a thorough examination of patients' medical records; missing images of HRCT in some cases, while the distinction between UIP and non-UIP patterns based on the radiological labels in CRDC system is relatively reliable. Second, group assignments were unrandomized because PFD addition was primarily determined by patients' financial circumstances, medical insurance, and self-assessment of disease severity within the real-world setting. The imbalanced subgroup distribution may underestimate the benefits of pirfenidone especially in SSc and RA-associated ILD. Thirdly, the individualized dosage of PFD and combined use of glucocorticoids or immunosuppressants in real-world clinical practice may mask the effects of PFD. Finally, although the baseline bias was attenuated by adjusting for glucocorticoids and HRCT pattern in the LMM, the generally worse condition of patients in the PFD group was a non-negligible confounder. Further multicenter, prospective studies with long-term follow-up are warranted to confirm the current results.

Conclusion

In conclusion, this real-world study showed that pirfenidone improved lung function decline in patients with CTD-ILD, especially in those with SSc-ILD. Patients with non-UIP patterns on HRCT scans may be a population with potential drug benefits, and the curative effect differed in patients with distinct baseline lung function patterns. Further, well-designed clinical trials are required to confirm the effect of pirfenidone treatment in specific subgroups of patients with CTD-ILD.

Declarations

Ethics approval and consent to participate

The study was approved by the ethics committee of Peking Union Medical College Hospital (JS-2038). Written Informed consent was obtained from all participants when they were registered in CRDC.

Consent for publication

Not applicable.

Author contributions

Xueting Yuan: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing.

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Shengyun Liu: Data curation; Investigation; Writing – review & editing.

Qiang Shu: Data curation; Investigation; Writing – review & editing.

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Shuang Zhou: Data curation; Investigation; Writing – review & editing.

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Hui Huang: Data curation; Investigation; Writing – review & editing.

Mengtao Li: Data curation; Investigation; Writing – review & editing.

Yanhong Wang: Formal analysis; Investigation; Methodology; Software; Supervision; Writing – review & editing.

Qian Wang: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Writing – review & editing.

Xiaofeng Zeng: Data curation; Investigation; Writing – review & editing.

Acknowledgements

We thank Ms. Qijia Liu for helpful discussion and research assistance with this study. We also appreciate greatly the contributions of patients by the subcenters from the CRDC registry, as listed in Supplemental Table S4.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported in part by the Chinese National Key Technology R&D Program, Ministry of Science and Technology (2022YFC2504600), CAMS Innovation Fund for Medical Sciences (CIFMS) (2021-I2M-1-005), The Non-profit Central Research Institute Fund of Chinese Academy of Medical Sciences (2021-PT320-002), and National High Level Hospital Clinical Research Funding (2022-PUMCH-C-020).

Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

All data relevant to the study are included in the article or uploaded as online supplemental information.

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Supplemental material

Supplemental material for this article is available online.

References

1. Mathai SC and Danoff SK. Management of interstitial lung disease associated with connective tissue disease. *BMJ* 2016; 352: h6819.
2. Joy GM, Arbiv OA, Wong CK, et al. Prevalence, imaging patterns and risk factors of interstitial lung disease in connective tissue disease: a systematic review and meta-analysis. *Eur Respir Rev* 2023; 32(167): 220210.
3. Jee AS and Corte TJ. Current and emerging drug therapies for connective tissue disease-interstitial lung disease (CTD-ILD). *Drugs* 2019; 79(14): 1511–1528.
4. Kondoh Y, Makino S, Ogura T, et al. 2020 guide for the diagnosis and treatment of interstitial lung disease associated with connective tissue disease. *Respir Investig* 2021; 59(6): 709–740.
5. Hoffmann-Vold AM, Maher TM, Philpot EE, et al. The identification and management of interstitial lung disease in systemic sclerosis: evidence-based European consensus statements. *Lancet Rheumatol* 2020; 2(2): E71–E83.
6. Matteson EA-O, Kelly C, Distler JA-O, et al. Nintedanib in patients with autoimmune disease-related progressive fibrosing interstitial lung diseases: subgroup analysis of the INBUILD trial. *Arthritis Rheumatol* 2022; 74(6): 1039–1047.
7. Johnson SR, Bernstein EJ, Bolster MB, et al. 2023 American College of Rheumatology (ACR)/American College of Chest Physicians (CHEST) guideline for the treatment of interstitial lung disease in people with systemic autoimmune rheumatic diseases. *Arthritis Rheumatol* 2024; 76(8): 1182–1200.
8. Ruwanpura SM, Thomas BJ and Bardin PG. Pirfenidone: molecular mechanisms and potential clinical applications in lung disease. *Am J Respir Cell Mol Biol* 2020; 62(4): 413–422.
9. Noble PW, Albera C, Bradford WZ, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. *Lancet* 2011; 377(9779): 1760–1769.
10. King TE Jr., Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2014; 370: 2083–2092.
11. Khanna D, Albera C, Fischer A, et al. An open-label, phase II study of the safety and tolerability of pirfenidone in patients with scleroderma-associated interstitial lung disease: the LOTUSS trial. *J Rheumatol* 2016; 43(9): 1672–1679.

12. Li T, Guo L, Chen Z, et al. Pirfenidone in patients with rapidly progressive interstitial lung disease associated with clinically amyopathic dermatomyositis. *Sci Rep* 2016; 6: 33226.
13. Solomon JJ, Danoff SK, Woodhead FA, et al. Safety, tolerability, and efficacy of pirfenidone in patients with rheumatoid arthritis-associated interstitial lung disease: a randomised, double-blind, placebo-controlled, phase 2 study. *Lancet Respir Med* 2023; 11(1): 87–96.
14. Li M, Tian X, Zhang W, et al. CRDC: a Chinese rheumatology research platform. *Clin Rheumatol* 2015; 34(8): 1347–1352.
15. Bohan A and Peter JB. Polymyositis and dermatomyositis (first of two parts). *N Engl J Med* 1975; 292(7): 344–347.
16. Raghu G, Remy-Jardin M, Richeldi L, et al. Idiopathic pulmonary fibrosis (an Update) and progressive pulmonary fibrosis in adults: an Official ATS/ERS/JRS/ALAT clinical practice Guideline. *Am J Respir Crit Care Med* 2022; 205(9): e18–e47.
17. van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. *Ann Rheum Dis* 2013; 72(11): 1747–1755.
18. Shiboski CH, Shiboski SC, Seror R, et al. 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary Sjögren's syndrome: A consensus and data-driven methodology involving three international patient cohorts. *Ann Rheum Dis* 2017; 76(1): 1468–2060.
19. Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2010; 69(9): 1580–1588.
20. Aringer M, Costenbader K, Daikh D, et al. 2019 European league against rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. *Arthritis Rheumatol* 2019; 71(9): 1400–14012.
21. von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 2007; 147(8): 573–577.
22. Wang J, Wang X, Qi X, et al. The efficacy and safety of pirfenidone combined with immunosuppressant therapy in connective tissue disease-associated interstitial lung disease: a 24-week prospective controlled cohort study. *Front Med (Lausanne)* 2022; 9: 871861.
23. Liang M, Matteson EL, Abril A, et al. The role of antifibrotics in the treatment of rheumatoid arthritis-associated interstitial lung disease. *Ther Adv Musculoskelet Dis* 2022; 14(1759-720X (Print)): 1759720X221074457.
24. Behr J, Prasse A, Kreuter M, et al. Pirfenidone in patients with progressive fibrotic interstitial lung diseases other than idiopathic pulmonary fibrosis (RELIEF): a double-blind, randomised, placebo-controlled, phase 2b trial. *Lancet Respir Med* 2021; 9(5): 476–486.
25. Biondini D, Balestro E, Lacedonia D, et al. Pretreatment rate of decay in forced vital capacity predicts long-term response to pirfenidone in patients with idiopathic pulmonary fibrosis. *Sci Rep* 2018; 8(1): 5961.
26. Ma M, Cao M, Gao Y, et al. Diagnostic finding on high-resolution computed tomography (HRCT) predicts a good response to pirfenidone in patients with idiopathic pulmonary fibrosis. *Medicine (Baltimore)* 2023; 102(19): e33722.
27. Kim J, Chung C, Cho HS, et al. Factors associated with dose reduction of pirfenidone in patients with idiopathic pulmonary fibrosis: a study based on real-world clinical data. *PLoS One* 2023; 18(2): e0281295.
28. Occhipinti M, Bruni C, Camiciottoli G, et al. Quantitative analysis of pulmonary vasculature in systemic sclerosis at spirometry-gated chest CT. *Ann Rheum Dis* 2020; 79(9): 1210–1217.
29. Oliveira RP, Ribeiro R, Melo L, et al. Connective tissue disease-associated interstitial lung disease. *Pulmonology* 2022; 28(2): 113–118.
30. Doyle TJ, Hunninghake GM and Rosas IO. Subclinical interstitial lung disease: why you should care. *Am J Respir Crit Care Med* 2012;185(11):1147–1153.
31. Group of Pulmonary V, Interstitial Diseases Associated with Rheumatic Diseases CAoR, Immunology P, et al. 2018 Chinese expert-based consensus statement regarding the diagnosis and treatment of interstitial lung disease associated with connective tissue diseases. *Zhonghua Nei Ke Za Zhi* 2018; 57(8): 558–565.