

Real-world drug utilisation of nintedanib and pirfenidone for interstitial lung disease in Singapore

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Dear Editor,

Antifibrotic therapies such as nintedanib and pirfenidone have transformed interstitial lung disease (ILD) treatment, representing a significant advancement in managing progressive fibrosing conditions. While these agents are used across Asia, their use in Southeast Asia, for example in Singapore, Malaysia or Indonesia, remains significantly under-represented in literature. To address these knowledge gaps in real-world use of antifibrotics among Southeast Asian population, the authors conducted a retrospective drug use evaluation at the ILD subspecialty service in Tan Tock Seng Hospital in Singapore from January 2016 to October 2024, with the aim to evaluate the usage patterns and clinical outcomes of nintedanib and pirfenidone in patients with ILD.

A total of 44 patients were included in this analysis, 26 (59%) patients received nintedanib and 18 (41%) received pirfenidone. Among the nintedanib group, 5 patients were subsequently switched to pirfenidone, with 1 patient later returning to nintedanib therapy. For analysis purposes, patients were grouped according to their initial antifibrotic medication. All patients screened were included and no patients were excluded for data analysis.

Baseline characteristics were comparable between the groups, with no differences in age, race, body mass index, and smoking status (Supplementary Table S1). There were more males on pirfenidone than nintedanib (100% vs 80.8%, $P=0.048$). Baseline forced vital capacity (FVC) (percentage predicted) and diffusing capacity of the lungs for carbon monoxide (DLCO) (percentage predicted) were comparable between the groups. The median number of comorbidities was 3 (interquartile range [IQR] 2–4) in the pirfenidone group and 2 (IQR 1–4) in the nintedanib group. Patients with ≥ 3 comorbidities were more common in the pirfenidone group (61.1% versus [vs] 38.5%). The most prevalent comorbidities were diabetes mellitus, pulmonary hypertension, and liver disease,

with no significant differences in individual comorbidity patterns between the groups. Idiopathic pulmonary fibrosis (IPF) was the predominant diagnosis, though its prevalence differed significantly between the groups (nintedanib: 79.5% vs pirfenidone: 100%, $P=0.006$). The remaining nintedanib patients (20.5%) had progressive pulmonary fibrosis (PPF), comprising equal numbers of PPF, fibrotic hypersensitivity pneumonitis, and connective tissue disease-associated ILD.

Drug interruption/discontinuation was significantly more common in the pirfenidone group (77.8%) compared to the nintedanib group (53.8%, $P=0.049$) (Table 1). Dose reduction was observed in 26.9% of nintedanib patients but none in the pirfenidone group. The main reasons for treatment modifications were adverse events (nintedanib: 42.3% vs pirfenidone: 27.8%) and deaths (nintedanib: 15.4% vs pirfenidone: 27.8%), with no significant difference in overall modification reasons between groups ($P=0.804$). Other reasons included precautionary measures for cardiovascular concerns or worsening organ function, and miscellaneous factors such as financial concerns or pill burden.

Target dose achievement, defined as total daily dose of nintedanib 300 mg daily and pirfenidone 2403 mg daily, was higher in the nintedanib group (50.0% vs 33.3%, $P=0.272$). The mean daily dose achieved was 256 ± 50.8 mg for nintedanib and 1691 ± 607.5 mg for pirfenidone. Among patients not achieving target doses, adverse events were the primary reason in both groups, though more prominent in the pirfenidone group (50.0% vs 34.6%). Other reasons included advanced disease concerns, and precautionary dose limitations due to comorbidities such as chronic liver disease or progressive chronic kidney disease.

The safety analysis revealed distinct adverse event profiles between the 2 medications. Liver enzyme elevations were significantly more frequent with nintedanib (38.5% vs 11.1%, $P=0.046$) of which

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Table 1. Usage pattern, adverse event profile, and clinical outcomes of antifibrotic therapy in patients with interstitial lung disease.

	Nintedanib (n=26)	Pirfenidone (n=18)	P value
Drug interruption, no. (%) ^a	14 (53.8)	14 (77.8)	0.049
Dose reduction, no. (%)	7 (26.9)	0	
Reason for drug interruption or dose reduction, no. (%)			0.804
Side effect	11 (42.3)	5 (27.8)	
Deceased	4 (15.4)	5 (27.8)	
Precaution ^b	2 (7.7)	1 (5.6)	
Others ^c	4 (15.4)	3 (16.7)	
Achieved target doses of antifibrotic, no. (%)	13 (50.0)	6 (33.3)	0.272
Average total daily dose of antifibrotic, mean SD, mg	256.0±50.8	1691.0±607.5	
Reasons for not achieving target dose, no. (%)			0.100
Side effect(s)	9 (34.6)	9 (50.0)	
Precautions ^d	0	2 (11.1)	
Advanced disease	1 (3.8)	0	
Others ^e	0	1 (5.6)	
Not specified	3 (11.5)	0	
Adverse events, no. (%)			
Elevated liver enzymes	10 (38.5)	2 (11.1)	0.046
Pattern of liver injury			0.394
Hepatocellular injury	4 (15.4)	0	
Cholestatic injury	3 (11.5)	0	
Mixed injury	2 (7.7)	2 (11.1)	
Unable to be determined	1 (3.8)	0	
Gastrointestinal side effect	9 (34.6)	8 (44.4)	0.545
Dermatological side effect	0	1 (5.6)	0.409
General disorder ^f	0	3 (16.7)	0.062
No documented side effect experienced	10 (38.5)	8 (44.4)	0.761
Time from start of antifibrotic to follow-up pulmonary function test, mean SD, months	9.9±3.4	10.0±4.3	0.918
Change in FVC, mean SD, percentage predicted	4.0±14.1	-1.5±14.9	0.335
Change in DLCO, mean SD, percentage predicted	-1.76±9.7	-12.5±11.7	0.069
Mortality, no. (%)	13 (50.0)	12 (66.7)	
Time from start of antifibrotic to death, median (95% CI), weeks	85 (0–182)	110 (71–149)	0.542

CI: confidence interval; DLCO: diffusing capacity of the lungs for carbon monoxide; FVC: forced vital capacity; SD: standard deviation

^aDrug interruptions include patients who are deceased.

^bPrecautions comprise cardiovascular concerns (initiation of antiplatelet, myocardial infarction), new diagnosis of liver cirrhosis, worsening renal function.

^cOthers include advanced disease and uncertain benefits, revision of diagnosis of interstitial lung disease, financial concerns, patient defaulted as overseas, pill burden.

^dPrecautions include concerns about hepatotoxicity in view of chronic liver disease with hepatic steatosis, renal function in view of progressive chronic kidney disease.

^ePatient declined dose escalation and had wanted to try Ayurvedic medications.

^fGeneral disorders (e.g. fatigue, non-cardiac chest pain, general feeling of discomfort).

4 patients showed hepatocellular injury patterns, 3 showed cholestatic injury, and 2 showed mixed injury patterns while 2 on pirfenidone showed mixed injury patterns.

Gastrointestinal side effects including nausea, vomiting, diarrhoea, anorexia, and poor appetite were comparable between groups (nintedanib: 34.6% vs pirfenidone: 44.4%, $P=0.545$). General disorders such as fatigue, non-cardiac chest pain, and general feeling of discomfort were observed exclusively with pirfenidone (16.7%, $P=0.062$). Dermatological side effects were rare, with only 1 patient in the pirfenidone group experiencing an eczema flare. Notably, a substantial proportion of patients did not experience any side effects during antifibrotic therapy—encompassing 38.5% in the nintedanib group and 44.4% in the pirfenidone group ($P=0.761$).

Overall medication adherence was good in both treatment groups, as measured by medication possession ratio (MPR). The median MPR was 98.6% for nintedanib and 94.4% for pirfenidone ($P=0.394$). Good adherence, defined as $MPR \geq 80\%$, was achieved in 78.3% of the nintedanib group and 71.4% of pirfenidone group ($P=0.732$).¹

After a mean follow-up of 9.9 ± 3.4 months for nintedanib and 10.0 ± 4.3 months for pirfenidone, both groups showed no statistically different patterns in lung function changes (Table 1). Mean FVC change was comparable between the groups (nintedanib: $4.0 \pm 14.1\%$ predicted vs pirfenidone: $-1.5 \pm 14.9\%$ predicted, $P=0.335$). Similarly, mean DLCO change showed no significant difference between the groups (nintedanib: $-1.76 \pm 9.7\%$ predicted vs pirfenidone: $-12.5 \pm 11.7\%$ predicted, $P=0.069$). Survival analysis revealed no statistically significant difference between the treatment groups. Mortality rates over the study period were 50% in the nintedanib group and 67% in the pirfenidone group. Median survival was 85 weeks (95% CI 0–182) for nintedanib and 110 weeks (95% CI 71–149) for pirfenidone (log-rank $P=0.542$).

The study's retrospective design is limited by potential biases including incomplete documentation and under-reporting of mild adverse events. Treatment selection was based on physician discretion considering multiple factors including approved indications (pirfenidone restricted to IPF only), patient comorbidities, potential drug interactions, contraindications to specific antifibrotic agents, pill burden preferences, and cost considerations. Notably, nintedanib is cheaper than pirfenidone in this study's healthcare setting (about SGD700 or approximately USD550; 20% cheaper per month at full doses). While MPR is widely utilised for medication adherence

assessment, it has limitations including inability to confirm actual medication ingestion, and potential imprecision over short intervals.⁷

This study provided important real-world evidence on antifibrotic therapy use, safety, and effectiveness in patients with ILD in Singapore. Despite frequent dose modifications and substantial comorbidity burden, most patients maintained high medication adherence, and experienced lung function preservation comparable to international studies. However, adverse event profiles, particularly hepatic enzyme elevations, were more pronounced than in clinical trials, highlighting the need for enhanced monitoring and individualised management strategies.

Supplementary material

Supplementary Table S1. Baseline demographic and clinical characteristics of patients with interstitial lung disease treated with nintedanib or pirfenidone.

Ethics statement

Ethics approval was obtained from the National Healthcare Group Domain Specific Review Board (2024-4281). Waiver of informed consent was granted as this was a retrospective study involving minimal risk to participants and using only existing medical records data.

Declaration

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