Journal of Cardiovascular Disease Research
ISSN: 0975-3583, 0976-2833 VOL14, ISSUE 06, 2023

EFFICACY OF ANTIFIBROTICS ON SURVIVAL RATES IN SUBJECTS WITH IDIOPATHIC PULMONARY FIBROSIS

Dr. Sk Humayun Kabir,[1] Dr. Sourav Chakraborty,[2] Dr. Kaliprasanna Chatterjee,[3] Dr. Md Rashid Ahsan Lodhi[4*]

[1]MBBS, DTCD, MD, DNB, Assistant Professor, Department of Pulmonary Medicine, Shantiniketan Medical College, Bolpur, West Bengal
[2]MBBS, MD, DNB, Senior Resident, Department of Pulmonary Medicine, Shantiniketan Medical College, Bolpur, West Bengal
[3]MBBS, MD, Assistant Professor, Department of Pulmonary Medicine, Shantiniketan Medical College, Bolpur, West Bengal
[4*]MBBS, MD, Consultant, Biochemistry, The Mission Hospital, Durgapur, West Bengal

Address for correspondence:Dr. Md Rashid Ahsan Lodhi
nufayl.lodhi@gmail.com

ABSTRACT

Background: The effects of using antifibrotic agents in subjects with idiopathic pulmonary fibrosis or IPF are still controversial and unclear warranting further clinical research to get clarity.

Aim: The present clinical study aimed to assess the efficacy of antifibrotic treatment on the risk of acute exacerbation, hospitalization, and mortality in subjects with idiopathic pulmonary fibrosis.

Methods: The study assessed 606 subjects of idiopathic pulmonary fibrosis as confirmed by the biopsy were retrospectively assessed. In subjects who received antifibrotic treatment, propensity score matching was used to adjust any difference in baseline data. The mortality after acute exacerbation, acute exacerbation, hospitalization, and risk of all-cause mortality in the two groups was assessed using a Cox proportional hazard model. From 606 subjects, 237 pairs were finally assessed.

Results: There were 83% males and 17% females in the present study. The mean age of the study participants was 65.6±2.86 years. The mean follow-up duration for the present study was 28 months. A significant reduction in the risk of mortality after an acute exacerbation, acute exacerbation, respiratory-related exacerbation, and all-cause hospitalization, and the mortality was seen following antifibrotic treatment in subjects with idiopathic pulmonary fibrosis with $p<0.001$.

Conclusion: The present study concludes that antifibrotic treatment in subjects with idiopathic pulmonary fibrosis can result in significantly reducing the risk of mortality after an acute exacerbation, acute exacerbation, respiratory-related exacerbation, and all-cause hospitalization, and the mortality was seen following antifibrotic treatment.

Keywords: Fibrosis, idiopathic pulmonary fibrosis, antifibrotics, mortality risk, pulmonary fibrosis.

INTRODUCTION

IPF (idiopathic pulmonary fibrosis) is a condition causing progressive fibrosing interstitial lung diseases having a poor prognosis. The majority of the subjects with IPF (idiopathic pulmonary disease) are frequently hospitalized secondary to various non-respiratory or respiratory reasons in their complete disease duration.[1] Owing to these factors, IPF is associated with short-term mortality and a high social and economic burden on the affected subjects. Also, the acute exacerbation of the IPF lead to in-hospital deaths in nearly half of the subjects admitted secondary to the disease. Acute exacerbation also negatively affects the prognosis in subjects with idiopathic pulmonary fibrosis. Hence, assessment of the way the drug affects the hospitalization risk, and acute exacerbation additionally with mortality is vital for assessing the efficacy of management in subjects with idiopathic pulmonary fibrosis.[2]

Both the drugs used for idiopathic pulmonary fibrosis, namely nintedanib, and pirfenidone have resulted in a significant reduction of the rates of decrease in the FVC (forced vital capacity) of lungs in affected subjects assessed in the previous literature data. After this finding, various other literature data have been done to assess the effects of antifibrotics on clinical outcomes along with forced vital capacity.[3]

The mortality rates were significantly reduced with the use of Pirfenidone in subjects with IPF along with reduced risks for death after hospitalization and respiratory-related hospitalization. However, a lower risk of mortality and acute exacerbation was seen with nintedanib.[4] However, these findings have a limitation of being based on clinical trial data and the subjects assessed were a cohort chosen based on strict inclusion criteria and may not depict actual subjects having different levels of disease severity and different comorbidities.[5]

Till today, various observational studies have assessed the efficacy of antifibrotics in subjects with idiopathic pulmonary fibrosis. The correlation of the results of the studies done in the past clinical trials, the studies showed that treatment with antifibrotics decreases the rates of FVC decline along with reduced mortality risk.[6] However, most of these studies were underpowered and assessed a small study population. Recent literature data have reported a decrease in mortality following antifibrotic treatment in subjects with IPF in large populations. However, the majority of the studies assessed only whites and very few have assessed Asians. Also, the data reporting the role of antifibrotics in the reduction of acute exacerbation in IPF is scarce in the literature.[7] Hence, the present clinical study aimed to assess the efficacy of antifibrotic treatment on the risk of acute exacerbation, hospitalization, and mortality in subjects with idiopathic pulmonary fibrosis.

MATERIALS AND METHODS

The present clinical study aimed to assess the efficacy of antifibrotic treatment on the risk of acute exacerbation, hospitalization, and mortality in subjects with idiopathic pulmonary fibrosis. The study was carried out at Department of Pulmonary Medicine, Shantiniketan Medical College, Bolpur, West Bengal after obtaining clearance from the concerned Ethical committee. The study population was recruited from the subjects visiting the Institute with idiopathic pulmonary fibrosis.

The study assessed subjects from both genders with a confirmed diagnosis of idiopathic pulmonary fibrosis with biopsy. The exclusion criteria for the study were subjects with no baseline results for the pulmonary test, subjects who underwent lung transplants, subjects who did not attend follow-up visits following diagnosis, and subjects who received concomitant sildenafil. The study finally included 606 subjects with biopsies done on 202 subjects that were included. All the included subjects followed that diagnostic criterion by Latin American Thoracic Association, ERS (European Respiratory Society, and ATS (American Thoracic Society).

For evaluating the effects of antifibrotic agents, subjects were classified into two groups namely antifibrotic and no-antifibrotic groups. The antifibrotic group comprised subjects who either received nintedanib or pirfenidone for treating the IPF minimum once and the no-antifibrotic group included subjects who did not receive antifibrotics during the study course. The index data for the no antifibrotic group was when the IPF was diagnosed and for the antifibrotic group was the date of the first antifibrotic prescription. The subjects were followed from the index date to the study outcome or the recurrence.

The data for the study including both survival data and clinical data were retrieved retrospectively from the medical records of the Institute. Following the standard recommendations, total lung capacity, DLCO (diffusing capacity of the lung for carbon monoxide, and spirometric parameters were assessed for all the study subjects, and the results were described as percentages of the normal predicted values.

The outcomes of the study included the risks of mortality following acute exacerbation, acute exacerbation, nonrespiratory-related hospitalization, respiratory-related hospitalization, all-cause hospitalization, and all-cause mortality. Respiratory-related hospitalization was considered an unexpected admission secondary to acute respiratory worsening including acute exacerbation, pulmonary embolism, pneumothorax, and pneumonia. Non-respiratory related hospitalization was considered as unexpected admission secondary to non-respiratory causes such as acute coronary syndrome. Acute exacerbation was defined following the Collard et al in 2016.[8] Follow-up visits for the subjects were done every 3-6 months and the hospital records were reassessed to find the study outcomes.

The data gathered were analyzed statistically using the SPSS software version 22.0 (IBM Corp, Somers, NY, USA) with Fisher's exact test, Chi-square test, and student's t-test. Proportional hazard models were used to assess the relative risks for acute exacerbation, hospitalization, and mortality. The significance level was kept at $p<0.05$.

RESULTS

The present clinical study aimed to assess the efficacy of antifibrotic treatment on the risk of acute exacerbation, hospitalization, and mortality in subjects with idiopathic pulmonary fibrosis. The mean follow-up duration of the study subjects was 27.4 months with a range of 16-45 months. The mean age of the study participants was 65.8±3.24 years. Propensity score matching was done for any demographic differences and 237 matched pairs were made. There were 83.02% (n=225) males in an unmatched group with antifibrotic treatment and 80.95% (n=272) males in the no-antifibrotic drug group, whereas, there were 81.85% (n=194) males in the

antifibrotic and 83.12% (n=197) males in a no-antifibrotic group of the matched group. The difference was statistically non-significant with p=0.92. The demographic data of the study subjects are listed in Table 1.

In the unmatched group, 271 subjects received antifibrotic, and 336 subjects did not receive no-antifibrotic treatment. In the matched group, 237 subjects each were in the antifibrotic and no antifibrotic groups. The mean age of the study subjects was 65.3±7.6 and 67.4±8.3 years respectively in subjects on antifibrotic and no antifibrotic therapy in the unmatched group which was statistically significant with p<0.001 and was 65.6±7.6 and 65.6±8.1 years respectively in the matched group. The BMI between matched and unmatched groups was comparable with no statistical difference and p=0.214. Charlson's comorbidity index was also comparable between the two groups with p=0.74. DLCO was significantly higher in subjects with no antifibrotics with 57.4±19.1 compared to 52.7±15.4 in subjects in the unmatched group and on antifibrotics with p<0.001. However, in the matched group, DLCO was comparable in subjects on antifibrotic and no antifibrotic with p=0.94. FVC was also significantly higher in subjects with no antifibrotics with p<0.001 and was comparable in two groups in matched groups with 0.94. Smokers were divided as never, former, and current and were comparable between subjects on antifibrotic and no antifibrotic in unmatched groups with p=0.927 and in a matched group with p=0.502 (Table 1).

On assessing the drugs used for the treatment of idiopathic pulmonary thrombosis, the most commonly used drug was Pirfenidone used in 90.29% (n=214) of study subjects. Nintedanib was given to 17.72% (n=42) study subjects, and combined Pirfenidone and Nintedanib were used in 8.43% (n=20) study subjects. A shift from nintedanib to pirfenidone was seen in 2.10% (n=5) of study subjects. High dose N-acetylcysteine was given in 61.18% (n=145) subjects from the no antifibrotic group and in 0.4% (n=1) subjects from the antifibrotic group as shown in Table 2.

Concerning the clinical outcomes in antifibrotic and no-antifibrotic groups, the results are summarized in Table 3. Hospitalization secondary to non-respiratory related causes was significantly higher in subjects not on antifibrotic with 16.03% (n=38) subjects and in 8.86% (n=21) subjects on antifibrotic with p=0.001. Hospitalization for respiratory-related causes was seen in 21.94% (n=52) and 37.13% (n=88) subjects from antifibrotic and no-antifibrotic groups which was a significant difference with p<0.001. Hospitalization for all causes was seen in 74.19% (n=23) subjects on antifibrotic which were significantly higher compared to the no-antifibrotic group with 46.83% (n=111) subjects and p<0.001. Acute exacerbation was seen in 13.08% (n=31) and 21.94% (n=52) subjects respectively in antifibrotic and no-antifibrotic groups with p<0.001. Mortality following acute exacerbation was seen in 74.19% (n=23) and 100% (n=52) subjects from antifibrotic and no-antifibrotic groups with p<0.001. All-cause mortality was significantly higher in a no-antifibrotic group with 81.01% (n=192) subjects compared to 29.11% (n=69) subjects from the antifibrotic group with p<0.001.

DISCUSSION

The mean follow-up duration of the study subjects was 27.4 months with a range of 16-45 months. The mean age of the study participants was 65.8±3.24 years. Propensity score matching

was done for any demographic differences and 237 matched pairs were made. There were 83.02% (n=225) males in an unmatched group with antifibrotic treatment and 80.95% (n=272) males in the no-antifibrotic drug group, whereas, there were 81.85% (n=194) males in the antifibrotic and 83.12% (n=197) males in a no-antifibrotic group of the matched group. The difference was statistically non-significant with p=0.92. These results were comparable to the studies of Nishiyama O et al[9] in 2019 and Nathan S et al[10] in 217 where similar subjects and data were assessed by the authors.

It was seen that in the unmatched group, 271 subjects received antifibrotic and 336 subjects did not receive no-antifibrotic treatment. In the matched group, 237 subjects each were in the antifibrotic and no antifibrotic groups. The mean age of the study subjects was 65.3±7.6 and 67.4±8.3 years respectively in subjects on antifibrotic and no antifibrotic therapy in the unmatched group which was statistically significant with p<0.001 and was 65.6±7.6 and 65.6±8.1 years respectively in the matched group. The BMI between matched and unmatched groups was comparable with no statistical difference and p=0.214. Charlson's comorbidity index was also comparable between the two groups with p=0.74. DLCO was significantly higher in subjects with no antifibrotics with 57.4±19.1 compared to 52.7±15.4 in subjects in the unmatched group and on antifibrotics with p<0.001. However, in the matched group, DLCO was comparable in subjects on antifibrotic and no antifibrotic with p=0.94. FVC was also significantly higher in subjects with no antifibrotics with p<0.001 and was comparable in two groups in matched groups with 0.94. Smokers were divided as never, former, and current and were comparable between subjects on antifibrotic and no antifibrotic in unmatched groups with p=0.927 and in a matched group with p=0.502. These data were similar to the studies of Harari S et al[11] in 2015 and Song JW et al[12] in 2013 where authors assessed subjects with demographic data comparable to the present study.

In the 237 study subjects, on assessing the drugs used for the treatment of idiopathic pulmonary thrombosis, the most commonly used drug was Pirfenidone used in 90.29% (n=214) of study subjects. Nintedanib was given to 17.72% (n=42) study subjects, and combined Pirfenidone and Nintedanib were used in 8.43% (n=20) study subjects. A shift from nintedanib to pirfenidone was seen in 2.10% (n=5) of study subjects. High dose N-acetylcysteine was given in 61.18% (n=145) subjects from the no antifibrotic group and in 0.4% (n=1) subjects from the antifibrotic group. These results were consistent with the previous studies of Iwata T et al[13] in 2016 and Ley B et al[14] in 2011 where authors reported the use of similar drugs by subjects in their respective studies.

Hospitalization secondary to non-respiratory related causes was significantly higher in subjects not on antifibrotic with 16.03% (n=38) subjects and in 8.86% (n=21) subjects on antifibrotic with p=0.001. Hospitalization for respiratory-related causes was seen in 21.94% (n=52) and 37.13% (n=88) subjects from antifibrotic and no-antifibrotic groups which was a significant difference with p<0.001. Hospitalization for all causes was seen in 74.19% (n=23) subjects on antifibrotic which were significantly higher compared to the no-antifibrotic group with 46.83% (n=111) subjects and p<0.001. Acute exacerbation was seen in 13.08% (n=31) and 21.94%

(n=52) subjects respectively in antifibrotic and no-antifibrotic groups with p<0.001. Mortality following acute exacerbation was seen in 74.19% (n=23) and 100% (n=52) subjects from antifibrotic and no-antifibrotic groups with p<0.001. All-cause mortality was significantly higher in a no-antifibrotic group with 81.01% (n=192) subjects compared to 29.11% (n=69) subjects from the antifibrotic group with p<0.001. These results were in agreement with the previous findings by Raimundo K et al[15] in 2016 and Richeldi L et al[16] in 2016 where similar clinical outcomes from IPF were reported by the authors as seen in the present study.

CONCLUSION

Considering its limitations, the present study concludes that antifibrotic treatment in subjects with idiopathic pulmonary fibrosis can result in significantly reducing the risk of mortality after an acute exacerbation, acute exacerbation, respiratory-related exacerbation, and all-cause hospitalization, and the mortality was seen following antifibrotic treatment.

REFERENCES

1. Collard, H.R., Chen, S.Y., Yeh, W.S., Li, Q., Lee, Y.C., Wang, A., Raghu, G. Health care utilization and costs of idiopathic pulmonary fibrosis in U.S. Medicare beneficiaries aged 65 years and older. Ann. Am. Thorac. Soc. 2015;12:981–7.
2. Raghu, G. *et al.* An official ATS/ERS/JRS/ALAT statement: Idiopathic pulmonary fibrosis: Evidence-based guidelines for diagnosis and management. Am. J. Respir. Crit. Care Med. 2011;183:788–824.
3. King, T. E. Jr. *et al.* A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N. Engl. J. Med.* 2014;370:2083–92.
4. Song, J. W., Hong, S. B., Lim, C. M., Koh, Y. & Kim, D. S. Acute exacerbation of idiopathic pulmonary fibrosis: Incidence, risk factors, and outcome. *Eur. Respir. J.* 2011;37:356–63.
5. Brown, A. W. *et al.* Outcomes after hospitalization in idiopathic pulmonary fibrosis: A cohort study. *Chest* 2-15;147:173–9.
6. Oltmanns, U. *et al.* Pirfenidone in idiopathic pulmonary fibrosis: real-life experience from a German tertiary referral center for interstitial lung diseases. *Respiration.* 2014;88:199–207.
7. Zurkova, M. *et al.* Effect of pirfenidone on lung function decline and survival: 5-yr experience from a real-life IPF cohort from the Czech EMPIRE registry. *Respir. Res.* 2019;20:16.
8. Collard, H.R., Ryerson, C.J., Corte, T.J., Jenkins, G., Kondoh, Y., Lederer, D.J., Lee, J.S., Maher, T.M., Wells, A.U., Antoniou, K.M. *et al.* Acute exacerbation of idiopathic pulmonary fibrosis. An International Working Group Report. *Am. J. Respir. Crit. Care Med. 2016;*194:265–75.
9. Nishiyama, O. *et al.* Characteristics and association with survival of respiratory-related hospitalization in Japanese idiopathic pulmonary fibrosis patients. *Respir. Investig.* 2019;57:415–21.

10. Nathan, S. D. *et al.* Effect of pirfenidone on mortality: Pooled analyses and meta-analyses of clinical trials in idiopathic pulmonary fibrosis. *Lancet Respir. Med.* 2017;5:33–41.
11. Harari, S. *et al.* Efficacy of pirfenidone for idiopathic pulmonary fibrosis: An Italian real-life study. *Respir. Med.* 2015;109:904–13.
12. Song, J. W. *et al.* Blood biomarkers MMP-7 and SP-A: Predictors of outcome in idiopathic pulmonary fibrosis. *Chest* 2013;143:1422–9.
13. Iwata, T. *et al.* A phase II trial evaluating the efficacy and safety of perioperative pirfenidone for prevention of acute exacerbation of idiopathic pulmonary fibrosis in lung cancer patients undergoing pulmonary resection: West Japan Oncology Group 6711 L (PEOPLE Study). *Respir. Res.* 2016;17:90.
14. Ley, B., Collard, H. R. & King, T. E. Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. *Am. J. Respir Crit. Care Med.* 2011;183:431–40.
15. Raimundo, K. *et al.* Clinical and economic burden of idiopathic pulmonary fibrosis: A retrospective cohort study. *BMC Pulm. Med.* 2016;16:2.
16. Richeldi, L. *et al.* Nintedanib in patients with idiopathic pulmonary fibrosis: Combined evidence from the TOMORROW and INPULSIS((R)) trials. *Respir. Med.* 2016;113:74–9.

TABLES

	Unmatched groups		p-value	Matched groups		p-value
	Antifibrotic	**No-antifibrotic**		**Antifibrotic**	**No-antifibrotic**	
Number of subjects	271	336		237	237	0.92
Male gender	225 (83.02)	272 (80.95)	0.27	194 (81.85)	197 (83.12)	0.99
Age (years)	65.3±7.6	67.4±8.3	<0.001	65.6±7.6	65.6±8.1	0.902
BMI	25.2±3.2	23.6±3.3	<0.001	24.6±2.6	24.3±3.2	0.214
Charlson comorbidity index	1.6±1.2	1.7±1.3	0.44	1.6±1.2	1.7±1.3	0.74
DLCO	52.7±15.4	57.4±19.1	<0.001	53.1±15.4	53.1±18.2	0.94
FVC	66.4±13.5	70.4±17.6	<0.001	67.3±13.2	67.2±16.5	0.94
Smoking status						
Never	65 (23.98)	81 (24.10)	0.927	57 (24.05)	52 (21.94)	0.502
Former	173 (63.83)	215 (63.98)		149 (62.86)	156 (65.82)	
Current	35 (12.91)	40 (11.90)		31 (13.08)	28 (11.810	

Table 1: Comparison of baseline characteristics in antifibrotic and no-antifibrotic groups

Drug prescribed	**Number (n=237)**	**Percentage (%)**
Pirfenidone	214	90.29
Nintedanib	42	17.72
Pirfenidone and Nintedanib	20	8.43
Switch to Nintedanib from pirfenidone	16	6.75
Switch to pirfenidone from Nintedanib	5	2.10
High-dose N-acetylcysteine (NAC) in the no-antifibrotic group	145	61.18
High-dose N-acetylcysteine (NAC) in the antifibrotic group	1	0.4

Table 2: Various drugs used for IPF in study subjects

Parameter	**Antifibrotic**	**No-antifibrotic**	**p-value**
Number of subjects	237	237	

Hospitalization			
Non-respiratory related	21 (8.86)	38 (16.03)	0.001
Respiratory related	52 (21.94)	88 (37.13)	<0.001
All-cause	71 (29.95)	111 (46.83)	<0.001
Mortality after acute exacerbation	23 (74.19)	52 (100)	<0.001
Acute exacerbation	31 (13.08)	52 (21.94)	<0.001
All-cause mortality	69 (29.11)	192 (81.01)	<0.001

Table 3: Comparison of clinical outcomes in two groups of study subjects