

A multicenter survey study of antifibrotic use for symptomatic patients with post-COVID-19 interstitial lung abnormalities

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ABSTRACT

Background: Little data exist on antifibrotic drugs for treating symptomatic patients with persistent interstitial lung abnormalities in the postacute phase of coronavirus disease 2019 (COVID-19). Herein, we describe the physician practices of prescribing pirfenidone and nintedanib for these patients and the physician-assessed response. **Materials and Methods:** This was a multicenter, retrospective survey study of subjects administered pirfenidone or nintedanib for post-COVID-19 interstitial lung abnormalities. Data on the demographic details, comorbidities, abnormalities on the computed tomography (CT) of the chest, treatment, antifibrotic drug use, and physician-assessed response were collected on a standard case record pro forma. We explored physician practices of prescribing antifibrotics (primary objective) and the physician-assessed response (secondary objective). **Results:** We included 142 subjects (mean age, 55.9 years; 16.2% women) at eight centers. The most common abnormalities on CT chest included ground glass opacities (75.7%), consolidation (49.5%), reticulation (43.9%), and parenchymal bands (16.8%). Of the 5701 patients discharged after hospitalization at six centers, 115 (2.0%) received antifibrotics. The drugs were prescribed an average of 26 days after symptom onset. One hundred and sixteen subjects were administered pirfenidone; 11 (9.5%) received the full dose (2400 mg/day). Thirty subjects were prescribed nintedanib; 23 (76.7%) received the full dose (300 mg/day). Of 76 subjects with available information, 27 (35.6%) and 26 (34.2%) had significant or partial radiologic improvement, respectively, according to the physician's assessment. **Conclusions:** Antifibrotic agents were administered to a minority of patients discharged after recovery from acute COVID-19 pneumonia. Larger, randomized studies on the efficacy and safety of these agents are required.

KEY WORDS: Coronavirus disease 2019, diffuse lung disease, interstitial lung disease, lung fibrosis, nintedanib, pirfenidone

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Submitted: 22-Sep-2021

Revised: 16-Nov-2021

Accepted: 09-Dec-2021

Published: 14-Mar-2022

Access this article online	
Quick Response Code: 	Website: www.lungindia.com
	DOI: 10.4103/lungindia.lungindia_568_21

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How to cite this article: Dhooria S, Maturu VN, Talwar D, Kumar S, Handa A, Agrawal PN, *et al.* A multicenter survey study of antifibrotic use for symptomatic patients with post-COVID-19 interstitial lung abnormalities. *Lung India* 2022;39:254-60.

INTRODUCTION

Patients with severe coronavirus disease 2019 (COVID-19) pneumonia may continue to have respiratory symptoms, hypoxemia, and interstitial lung abnormalities in the postacute phase. The radiologic abnormalities mostly include ground-glass opacities, consolidation suggestive of organizing pneumonia (OP).^[1,2] Some patients also develop reticulation and radiologic signs of fibrosis such as architectural distortion, traction bronchiectasis, and honeycombing.^[3]

The ideal treatment for post-COVID-19 interstitial lung abnormalities with symptoms (PC-ILAS) is unknown. There is a single randomised controlled trial (RCT, of prednisolone) and a few observational studies of glucocorticoids and antifibrotics for the treatment of PC-ILAS.^[4-8] The antifibrotic drugs, pirfenidone and nintedanib, have anti-inflammatory and antifibrotic properties by their action on various pathways and are effective in idiopathic pulmonary fibrosis (IPF) and other progressive fibrosing ILDs.^[9-13] It has been proposed that they may be useful in PC-ILAS; however, the opinion on their potential utility remains divided.^[4-7,9-11,14-19] In the absence of evidence, several physicians prescribe antifibrotic drugs to patients with PC-ILAS based on biological plausibility.^[5-7,17] Herein, we describe a multicenter study, wherein we aimed to explore physician practices of prescribing antifibrotic agents to patients with PC-ILAS. We hypothesized that a significant number of patients are prescribed these agents based on physician discretion.

MATERIALS AND METHODS

This is a multicenter, retrospective, descriptive survey study. The participating centers (Yashoda Hospitals, Hyderabad; Metro Centre for Respiratory Diseases, Noida; Sakra World Hospital, Bengaluru; Agrawal Hospital, Bhopal; Jindal Clinics, Chandigarh; Bombay Hospital and Medical Research Center, Mumbai; All India Institute of Medical Sciences, Bhopal; and, MMI Narayana Multispecialty Hospital, Raipur; all centers in India) were contacted by one of the authors (SKJ) and were encouraged to contribute data in a case record pro forma. The Institutional Ethics Committee provided ethical clearance. Being a retrospective observational survey study, the requirement of consent was waived.

Study subjects

Data of consecutive subjects presenting to the centers for COVID-19 care were screened.

Inclusion criteria

Subjects were included in the study if they satisfied all the inclusion criteria (a) diagnosed to have COVID-19 pneumonia between June and September 2020 and (b) prescribed one of the antifibrotic agents, pirfenidone or nintedanib, based on the physician's discretion.

Exclusion criteria

Subjects were excluded if the subjects (a) died during hospitalization without receiving any antifibrotic drug or (b) were discharged without being prescribed any of the antifibrotic agents.

Diagnosis and management of acute illness

Subjects were diagnosed and managed at the respective centers, according to local policies and practices. The diagnosis of COVID-19 was based on suggestive clinical presentation with acute onset of systemic and respiratory symptoms such as fever, cough, and breathlessness and a positive reverse transcriptase-polymerase chain reaction, or a positive rapid antigen test and/or characteristic radiologic abnormalities on a high-resolution computed tomography (HRCT) of the chest. Baseline laboratory parameters such as complete blood counts, C-reactive protein, lactate dehydrogenase, d-dimer, ferritin, and glycated hemoglobin were assessed in most subjects. Oxygen was administered to hypoxemic patients using traditional methods (nasal cannulae, Venturi mask, and reservoir mask) or high flow nasal cannula. Patients who could not maintain oxygen saturation on these modalities or had persistent respiratory distress received positive airway pressure therapy with either noninvasive ventilation or invasive mechanical ventilation. Subjects were administered remdesivir, glucocorticoids, tocilizumab, antibiotics, anticoagulants, and other drugs according to hospital protocols and physician discretion. Comorbidities such as diabetes mellitus, hypertension, coronary artery disease, and others were managed according to the best practices.

Management of post-COVID-19 interstitial lung abnormalities with symptoms

The treatment of PC-ILAS was advised by respective physicians based on their assessment of the residual radiologic and physiologic abnormalities observed after recovery from the acute illness. In general, antifibrotic agents were prescribed to patients, who were still breathless and/or hypoxemic at the time of discharge and had significant opacities on the HRCT or radiograph of the chest.

Data collection

The following data were collected: (i) demographic details; (ii) method used for COVID-19 diagnosis; (iii) comorbidities; (iv) symptoms during the acute illness; (v) laboratory parameters; (vi) radiologic abnormalities on chest radiograph and/or HRCT of the chest; (vii) drugs used to treat the acute COVID-19 illness; (viii) modality for oxygen or ventilatory support used during the acute illness; (ix) the antifibrotic drug prescribed along with the dose; (x) the timing of prescription of the antifibrotic drug; (xi) the physician-assessed radiologic response; (xii) self-reported adverse effects; and (xiii) death and its cause.

Radiologic abnormalities

On the chest radiograph, the abnormalities were characterized as (a) ground-glass haze (in the presence of

hazy lung fields); (b) consolidation (dense confluent opacities obliterating the underlying vascular markings with/without an air bronchogram); (c) airspace opacities (ill-defined, patchy areas of dense opacification); (d) linear opacities; and (e) nodular opacities. On the HRCT of the chest, the abnormalities were categorized as (a) ground-glass opacities; (b) consolidation; (c) reticulation; (d) parenchymal bands; (e) traction bronchiectasis; (f) architectural distortion; and (g) peribronchovascular thickening, using standard definitions.^[20]

Physician-assessed radiologic response

The physicians also assessed the radiologic response to the treatment administered as the temporal change in the radiologic abnormalities based on the chest HRCT scan, performed within 8 weeks of starting antifibrotic drugs. If a CT was not performed, a chest radiograph was used for response assessment. The response was categorized on a semiquantitative scale as (a) significant resolution (if there was more than 50% clearing of opacities); (b) partial resolution (if there was 10%–50% reduction in the opacities); (c) no change (if there was less than 10% change in the opacities, either increase or decrease); (d) appearance of reticular opacities (if new linear or reticular opacities appeared in regions that showed ground-glass opacities or consolidation); or (e) progression (if there was more than 10% increase over the preexisting opacities)

Study objectives

The primary objective of this descriptive study was to explore the physician practices of prescribing antifibrotics for subjects with PC-ILAS. The proportion of subjects who received antifibrotic agents among the patients discharged after hospitalization was calculated. The secondary objective was the physician-assessed temporal change in radiologic abnormalities.

Statistical analysis

Being a retrospective survey study, with the absence of any previous data, no sample size calculation was performed. We used the commercial statistical package SPSS (version 22.0, IBM Inc., United States) for performing all data analysis. Data are presented as mean with standard deviation (SD), median with interquartile range (IQR), or number (percentage).

RESULTS

Of the eight participating centers, six had inpatients hospitalized for the acute COVID-19 illness, while two centers received only outpatients. A total of 6236 patients were admitted during the study period, 535 (8.6%) died, while 5701 (91.4%) were discharged [Figure 1]. Of the discharged patients, 115 (2.0%) subjects were prescribed antifibrotic drugs. Four subjects, prescribed antifibrotic agents during hospitalization, died before discharge. Thus, a total of 119 subjects were inpatients at the six participating centers. At two participating centers, 23 additional subjects were prescribed antifibrotic agents on an outpatient basis. Thus, a total of 142 subjects (mean age: 55.9 years; 23 [16.2%] women) were included in the current analysis [Table 1]. The subjects had acute COVID-19 symptoms for a mean (SD) duration of 5.1 (3.1) days. Common symptoms included fever (130 [91.5%]), cough (124 [87.3%]), breathlessness (119 [83.8%]), and sputum production (10 [7.0%]). Among the 129 subjects for whom the clinical details during hospitalization were available, 75 (58.1%) had critical COVID-19 illness, 40 (31.0%) had severe disease, while 14 (10.9%) subjects had moderate disease, according to the World Health Organization criteria. About 89% required oxygen and/or positive pressure ventilation during hospitalization [Table 2]. The median (IQR)

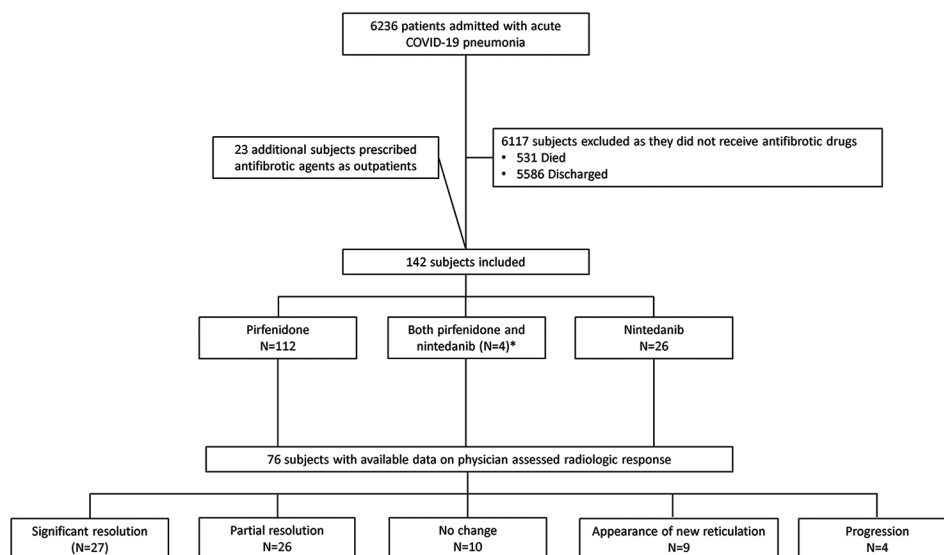


Figure 1: Flow of study subjects. *Consecutive administration due to intolerance to the first drug. COVID-19-coronavirus disease 2019

Table 1: Baseline characteristics of study subjects (n=142)

Parameter	All patients (n=142)	Inpatients (n=119)	Outpatients (n=23)	P
Age (years)	55.9±10.9	55.4±10.5	59.0±12.8	0.15
Men, n (%)	119 (83.8)	101 (84.9)	18 (78.3)	0.54
Residence				
Urban	108 (76.1)	92 (77.3)	16 (69.6)	0.43
Suburban	19 (13.4)	14 (11.8)	5 (21.7)	
Rural	15 (10.6)	13 (10.9)	2 (8.7)	
Body weight (kg)	75.1±14.9	76.6±15.8	68.8±8.7	0.003
Comorbid illnesses				
Any	92 (64.8)	76 (63.9)	16 (69.6)	0.60
Diabetes mellitus	56 (39.4)	51 (42.9)	5 (21.7)	0.06
Hypertension	55 (38.7)	48 (40.3)	7 (30.4)	0.37
Hypothyroidism	10 (7.0)	8 (6.7)	2 (8.7)	0.74
Chronic kidney disease	6 (4.2)	5 (4.2)	1 (4.3)	0.98
Coronary artery disease	4 (2.8)	2 (1.7)	2 (8.7)	0.06
Asthma	2 (1.4)	1 (0.8)	1 (4.3)	0.30
Morbid obesity	2 (1.4)	2 (1.7)	0	1.00
Others	15 (10.6)	12 (10.1)	3 (13.0)	0.67
Diagnostic modality				
RT-PCR	125 (88.0)	103 (86.6)	22 (95.7)	0.32
RAT	11 (7.8)	11 (9.2)	0	
Clinicoradiological	6 (4.2)	5 (4.2)	1 (4.3)	
Laboratory parameters				
Hemoglobin (g/dL)	13.2±1.8	13.2±1.8	12.3±1.9	0.12
Total leucocyte counts (×10 ³ /mm ³)	10.5±5.0	10.3±5.0	12.3±4.4	0.23
Neutrophil: lymphocyte ratio	7.8 (3.6-14.5)	8.5 (3.8-14.8)	3.1 (2.5-3.5)	<0.001
C-reactive protein (mg/L)	25.1 (8.0-63.3)	24.8 (7.3-62.1)	71.5 (9.5-120.0)	0.19
Lactate dehydrogenase (U/L)	327 (259-465)	370 (269-510)	280 (237-350)	0.04

The values represent either mean±SD, median (IQR), or n (%). SD: Standard deviation, IQR: Interquartile range, RAT: Rapid antigen test, RT-PCR: Reverse transcriptase-polymerase chain reaction

Table 2: Drugs and supportive therapies administered to study subjects during hospitalization (n=129)

Drug or supportive treatment	n (%)
Oxygen therapy	115 (89.1)
High flow nasal oxygen	16 (12.4)
Noninvasive ventilation	39 (30.2)
Invasive ventilation	12 (9.3)
Antivirals	
Favipiravir	13 (10.1)
Remdesivir	104 (80.6)
Other antimicrobials	
Azithromycin	48 (37.2)
Doxycycline	54 (41.9)
Broad spectrum antibiotics	62 (48.1)
Ivermectin	50 (38.8)
Antifungal agents	3 (2.3)
Immunomodulators	
Glucocorticoids	121 (93.8)
Tocilizumab	21 (16.3)
Hydroxychloroquine	11 (8.5)
Convalescent plasma	4 (3.1)
Anticoagulation	
Prophylactic	71 (55.0)
Therapeutic	17 (13.2)

oxygen saturation at admission was 87% (81%–93%). The median (IQR) neutrophil-lymphocyte ratio (NLR), serum ferritin, and d-dimer levels were 7.8 (3.6–14.5), 377 (193–709) ng/mL, and 601 (356–1502) ng/mL, respectively. The body weight, NLR, and lactate dehydrogenase were significantly different [Table 1] between the subjects enrolled as inpatients (n = 119) or outpatients (n = 23).

On the HRCT chest (n = 107), the most common reported abnormalities [Table 3] included ground-glass opacities (81, 75.7%), consolidation (53, 49.5%), reticulation (47, 43.9%), and parenchymal bands (18, 16.8%). For PC-ILAS, glucocorticoids were prescribed to 125 (88.0%) subjects. Pirfenidone and nintedanib were administered to 112 (78.9%) and 26 (18.3%) subjects, respectively, while 4 (2.8%) subjects were administered both the drugs consecutively due to intolerance to the first administered drug [Table 4]. The antifibrotic drug was started a mean (SD) of 26.2 (16.5) days after symptom onset. Of the 116 subjects who received pirfenidone, 73 (62.9%) received it in a daily dose ranging from 600 mg to 1200 mg; 11 (9.5%) subjects were administered the full daily dose (2400 mg) of pirfenidone. Twenty-three (76.7%) of the 30 subjects who received nintedanib were administered a daily dose of 300 mg; the remaining received a dose of 200 mg/day. Based on chest HRCT (n = 44) or chest radiograph (n = 32), 27 (35.6%) and 26 (34.2%) had significant or partial improvement, respectively [Table 2]. New reticulation appeared in 9 (11.8%) subjects. The radiologic response was not different between the outpatients and inpatients (P = 0.08).

Forty-three subjects required domiciliary oxygen at the time of discharge. Five subjects died. Three died during hospitalization due to refractory hypoxemia (one subject also had a pneumothorax). One other subject succumbed to refractory septic shock due to a urinary tract infection. The cause of death for the remaining subject, who died

after discharge, remained unknown. Anorexia, nausea, and dyspepsia were the most common adverse effects reported by the study participants [Table 5].

Table 3: Radiologic abnormalities and temporal change in study subjects

	<i>n</i> (%)
Radiologic abnormality	
Chest radiograph (<i>n</i> =70)	
Ground glass/haziness	57 (81.4)
Consolidation	37 (52.9)
Linear opacities	19 (27.1)
Airspace opacities	8 (11.4)
Nodular opacities	3 (4.3)
Computed tomography (<i>n</i> =107)	
Ground glass opacities	81 (75.7)
Consolidation	53 (49.5)
Reticulation	47 (43.9)
Parenchymal/atelectatic bands	18 (16.8)
Traction bronchiectasis	5 (4.7)
Architectural distortion	2 (1.9)
Peribronchovascular thickening	1 (0.7)
Physician assessed response (<i>n</i>=76)	
Chest radiograph (<i>n</i> =32)	
Significant resolution	10 (13.2)
Partial resolution	12 (15.8)
No change	6 (7.9)
Appearance of reticulation	3 (3.9)
Progression	1 (1.3)
Computed tomography (<i>n</i> =44)	
Significant resolution	17 (22.4)
Partial resolution	14 (18.4)
No change	4 (5.3)
Appearance of reticulation	6 (7.9)
Progression	3 (3.9)

Table 4: Drugs prescribed for postcoronavirus disease 2019 diffuse lung disease (*n*=142)

Drug	<i>n</i> (%)
Pirfenidone	116 (89.9)
Pirfenidone daily dose (mg)	
600	1 (0.9)
800	5 (4.3)
1200	67 (57.8)
1600	1 (0.9)
1800	30 (25.9)
2200	1 (0.9)
2400	11 (9.5)
Nintedanib	30 (21.2)
Nintedanib daily dose (mg)	
200	7 (23.3)
300	23 (76.7)
Glucocorticoids	125 (88.0)

Table 5: Treatment-related adverse effects reported by study subjects (*n*=142)

Adverse drug reaction	<i>n</i> (%)
Anorexia	5 (3.5)
Nausea	5 (3.5)
Dyspepsia	4 (2.8)
Giddiness	3 (2.1)
Vomiting	2 (1.4)
Rash	2 (1.4)
Dry mouth	2 (1.4)

DISCUSSION

We found that antifibrotics are prescribed by physicians to a minority of the patients with PC-ILAS relatively early in the post-acute phase (an average of 26 days after symptoms onset). Most such patients had a critical or severe illness during the acute phase of COVID-19. To our knowledge, this is the first study on the use of pirfenidone and nintedanib for patients with post-COVID-19 residual lung abnormalities.

We found that physicians prescribed antifibrotic agents to a small proportion (about 2%) of patients admitted for acute COVID-19, based on their discretion. This proportion might be an underestimate as the period during which this study was conducted, patients with mild COVID-19 illness were also being hospitalized, who are less prone to develop PC-ILAS. In the absence of any evidence of the efficacy of antifibrotic agents for acute or post-acute COVID-19, the practice of prescribing them is completely arbitrary. The physicians reported that 70% had significant or partial improvement in lung abnormalities on radiology. However, in the absence of a control group in our study, it cannot be concluded whether the resolution of abnormalities was a result of the use of antifibrotics, the concomitantly used glucocorticoids, or whether it was a part of the natural history of the disease. In the only previous study of antifibrotic drug use in COVID-19 to date, nintedanib was prescribed during the “acute” illness, to thirty subjects receiving mechanical ventilation.^[21] No reduction in mortality was observed compared to a historical control group. The duration of mechanical ventilation was significantly shorter, and the percentages of high-attenuation areas on chest CT were significantly lower with nintedanib, suggesting potential benefit. However, the study was underpowered to assess any of these outcomes.

In most developed countries, the off-label use of antifibrotic drugs is not permitted. Patients in the postacute phase of COVID-19 are observed for a few weeks without prescribing any glucocorticoids or antifibrotic agents and a majority recover completely.^[4] In a study from the United Kingdom, 837 subjects discharged after hospitalization for acute COVID-19 were followed up.^[4] At 4 weeks after discharge, 39% reported ongoing symptoms. However, based on physiologic and radiologic assessment, only 35 subjects had a functional deficit along with a radiologic OP pattern. Finally, only 30 were administered a short course of low-medium dose prednisolone and improved significantly. A recent RCT showed that low-dose prednisolone (10 mg/day for six weeks) might be sufficient to achieve significant clinico-physiologic and radiologic improvement in patients with severe PC-ILAS.^[5] Thus, it is probable that most patients with PC-ILAS have an

inflammatory lung disease that improves spontaneously over time. Few patients might have a persistent OP and may require glucocorticoids if they do not improve over the ensuing weeks.^[22]

In the current study, most subjects did not receive pirfenidone in the appropriate dose. Only about 10% of subjects prescribed pirfenidone received the full dose (2400 mg/day), while a majority (63%) received a daily dose of 600–1200 mg. This might be due to an actual as well as a perceived intolerance to higher doses of the drug. The frequency of adverse effects was lower than that reported previously, possibly because of the retrospective nature of the data collection, and the shorter duration and lower doses of antifibrotic agents used.^[12] In a previous prospective study, over 40% of IPF patients administered pirfenidone could tolerate the full dose and another 30% could tolerate a dose of 1800 mg/day, using a proper dose-escalation strategy.^[12] Moreover, pirfenidone improved survival significantly only when used in the full dose and not with a reduced dose.^[12] In the current study, about 23% of the subjects prescribed nintedanib received a reduced dose (200 mg/day), like previous studies in IPF and PF-ILD, wherein 20%–33% of subjects required dose reduction.^[9,11,23]

What are the clinical implications of this study? Physicians feel the need to prescribe antifibrotic agents to a minority of patients with PC-ILAS, based on biological plausibility and their discretion. With no scientific evidence to buttress or weaken the argument for their use, there is a risk of both the overuse and underutilization of these agents. Studies with robust methodology are urgently required to guide the use of antifibrotic drugs in clinical practice. Several randomized controlled trials are underway investigating the role of antifibrotic agents in acute COVID-19 as well as PC-ILAS (Clinicaltrials.gov identifiers; NCT04653831, NCT04282902, NCT04607928, NCT04856111, NCT04541680, NCT04338802, and NCT04619680). Till the time, evidence on the efficacy of these drugs is available, physicians must refrain from using antifibrotic agents. In most patients, PC-ILAS might be self-limited or at best require a short course of low-dose glucocorticoids after a period of observation for a few weeks.^[5] Nevertheless, a minority of patients with PC-ILAS do indeed develop clear signs of lung fibrosis.^[5-7] An accurate biomarker that could predict the progression to a fibrotic phenotype would be valuable.^[17]

This study has several limitations. It is a retrospective study without a control group. Due to the absence of a control group, we cannot draw firm conclusions on the efficacy of the antifibrotic agents. There was significant heterogeneity in the use of imaging tools. No uniform criteria were followed for prescribing antifibrotic agents and their dosages. A semi-quantitative nonvalidated scale was used to assess the radiologic response; the semiquantitative CT severity scores were not available. The assessor of radiologic outcomes was not blinded to

the clinical details. Physiologic outcomes such as arterial blood gases, lung function tests, exercise testing such as the six-minute walk test, and the requirement of domiciliary oxygen during the follow-up are not available. We did not collect the data on adverse effects systematically. Ideally, an exploratory study of antifibrotics will require a properly planned prospective study with three arms, two with these agents and the third arm without any intervention as their efficacy in post-acute COVID-19 is uncertain. However, the current study was only a survey. As the first study on the use of antifibrotics in PC-ILAS, it offers insights into the prescription practices of physicians.

CONCLUSIONS

Antifibrotic drugs are prescribed to a small proportion of subjects with PC-ILAS, who generally have a critical or severe disease during the acute illness. Randomized controlled trials are required to delineate the role of glucocorticoid and antifibrotic therapy for PC-ILAS.

Financial support and sponsorship

The study was supported by unrestricted educational grants from Cipla Limited and Lupin Limited.

Conflicts of interest

There are no conflicts of interest.

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