Original Article

A clinical study to monitor prescription patterns, clinical outcomes, and adverse drug reactions among patients of various interstitial lung diseases attending respiratory medicine outpatient department at tertiary care hospital in Northern India

Sabahat Hasan, Ajay Verma[1], Shoebul Haque, Farah Asif, Rajendra Nath, Surya Kant[1], Rakesh K. Dixit

Departments of Pharmacology and Therapeutics and [1]Respiratory Medicine, King Georges Medical University, Lucknow, Uttar Pradesh, India

Abstract

Aim: The aim of this study was to monitor prescription patterns, clinical outcomes, and adverse drug reactions (ADR) among patients of various interstitial lung diseases (ILDs).

Materials and Methods: This prospective study was conducted in the Department of Pharmacology and Therapeutics in collaboration with the Department of Respiratory Medicine, King George's Medical University, Lucknow, for a period of 12 months (October 2020–September 2021). A total of 77 patients were enrolled after satisfying the inclusion and exclusion criteria. The prescriptions were collected, and necessary details were noted on the case report form. After completion of the study, the data were analyzed for prescription patterns, clinical outcomes, and quality of life with the help of a validated questionnaire-King's Brief ILD (KBILD) questionnaire. At the same time, ADRs, if any, were assessed using Hartwig's Severity Assessment Scale and Naranjo Causality Assessment Scale.

Results: The most common ILD was acute/chronic hypersensitivity pneumonitis (HP). Average number of drugs per encounter was 4.45. Crepitations were the most common clinical signs. Clubbing and rhonchi were reported maximum in idiopathic pulmonary fibrosis. It was found that psychological, breathlessness and activities, chest symptoms, and total KBILD reduced significantly after 3 months as compared to baseline with a statistically significant difference as $P < 0.01$. ADRs were found in 23.38% (18) of the subjects. Maximum ADR reported was gastritis (9.09%), followed by hepatitis (3.90%).

Conclusion: The high proportion of patients clinically diagnosed with HP in our study highlights the importance of a detailed environmental exposure history in the diagnostic evaluation of patients with ILD to avoid inaccurate diagnoses. ADR-related hospital admissions are a significant problem in the health-care system.

Keywords: Adverse drug reactions, drugs, interstitial lung disease, King's brief interstitial lung disease

Address for correspondence: Dr. Sabahat Hasan, Department of Pharmacology and Therapeutics, King Georges Medical University, Lucknow - 226 003, Uttar Pradesh, India.
E-mail: drshs2019@gmail.com

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INTRODUCTION

Interstitial lung diseases (ILDs) are a heterogeneous group of acute and chronic diffuse lung diseases of known and unknown causes. ILDs are known manifestations of connective tissue diseases (CTDs), hypersensitivity pneumonitis (HP), occupational exposures, exposure to cigarette smoke, and inherited disorders. Etiology of other ILDs, particularly idiopathic pulmonary fibrosis (IPF) and sarcoidosis, is unknown. The prevalence of ILD in several countries has increased over time.[1,2]

Long-term exposure to occupational or environmental agents can have a toxic effect on the lungs. Common agents are mineral dust, organic dust, and toxic gases.[3] Organic dust includes mold spores and aerosolized bird droppings. Inhaled toxic gases (methane and cyanide) affect the airways either by direct injury or through reactive oxygen molecules. CTDs and vasculitides affect all areas of the lungs (bronchioles, parenchyma, and alveolus) which is why ILD is a common feature of rheumatology diseases.[4,5] More than 350 drugs have been identified to cause pulmonary complications whether through reactive metabolites or as a component of a general response.[6,7]

There is a myriad of symptoms associated with ILD, some related to the disease itself and others related to therapy side effects. Dyspnea, cough, and fatigue are the three most common symptoms in ILD. Dyspnea (also commonly referred to as breathlessness or shortness of breath) is the most common symptom of ILD[8] and is a strong driver of worsening of quality of life (QoL).[9] The emotional and psychological components of dyspnea (i.e., fear, frustration, and anxiety) may be equally or more detrimental to some patients than the physical constraints imposed by dyspnea.[10,11]

Recently, the King's Brief ILD (K-BILD) questionnaire[12] has been proposed as the first and so far, only ILD-specific health-related QoL (HRQoL) assessment tool. The K-BILD is a validated[13] and clinically oriented HRQoL tool.[14] Evidence shows that K-BILD is a suitable HRQoL measure in different countries, e.g., in the UK, Italy, France, Sweden, and the Netherlands, as shown by Wapenaar *et al*.[15]

Adverse drug reactions (ADRs) are common occurrences in a hospital setting, attributed to the severity and complexity of the disease process, the use of multiple drugs, drug interactions, and possible negligence. ADR could be observed in 10%–20% of hospitalized patients and may be responsible for prolonged hospital stays.[16] Little is known about the ADR in the therapy of ILD. The goal of this study was to assess the causality and severity of ADRs based on their reporting. The causality was seen by the Naranjo Algorithm or ADR Probability Scale[17] and severity was assessed by the Hartwig's Scale and will determine the extent to which it affects the everyday life of the patient.[18] We also analyzed the prescription patterns of various ILDs to assess prescription patterns along with the outcome and QoL. It assessed ADRs in these patients.

MATERIALS AND METHODS

This prospective study was conducted in the Department of Pharmacology and Therapeutics in collaboration with the Department of Respiratory Medicine, King George's Medical University, Lucknow, for a duration of 12 months (October 2020–September 2021), only after the approval of the Institutional Ethics Committee. All patients coming with ILD were screened. Patients who met all inclusion criteria and none of the exclusion criteria were selected for participation in this study. A total of 77 patients were enrolled and informed written consent was obtained from each patient.

Inclusion criteria

a. Age >18 years
b. Presenting with fever, dry cough, and shortness of breath on exertion
c. Any unexplained respiratory symptoms and high-resolution computed tomography findings consistent with ILD.

Exclusion criteria

1. Failure to give consent
2. Age <18 years
3. Pulmonary hypertension due to preexisting cardiac disease
4. Purely obstructive airway disease
5. Clinical suspicion of recent/active infection
6. Any existing malignant condition.

Sample size calculation

The sample size was calculated by the formula as given below;

Sample size (n) = $Z^2 \times p \times q / d^2$

p = prevalence of disease according to previous studies

$q = 1 - p$

d = allowable error (2%–10% of p), here d = 4% taken

As there is no data available regarding the prevalence of ILDs in India, the only source left is the ILD India

registry, in which the minimum prevalence is that of pneumoconiosis, i.e., 3%.[19]

After solving the above equation, the population size comes to 70. With consideration of 10% loss of sample during the study, we will take the total population size of (n) = 77.

Data collection

1. A case report form (CRF) designed as per the study protocol was filled according to the prescription of the patient. It included demographic details, patient's name, age, sex, smoking history, associated comorbid conditions, family history, investigation related to diagnosis, grading of severity of the disease, drugs prescribed, class of drugs, route of administration of those drugs, and concomitant medications
2. The prescriptions were collected from the patient and necessary details were noted on the CRF
3. After completion of the study, the data were analyzed for prescription patterns, clinical outcomes, and QoL with the help of a questionnaire-KBILD questionnaire[20]
4. At the same time, ADRs, if any, are assessed using Hartwig's Severity Assessment Scale[21] and Naranjo Causality Assessment Scale.[22]

Statistical analysis

Data were entered in the Microsoft Word and Excel sheets and analyzed. The data were presented using frequencies and percentages along with appropriate graphs and charts. Continuous variables were expressed as mean ± standard deviation (SD), whereas categorical variables are expressed in absolute numbers or percentages and analyzed using SPSS 22.00 for Windows; SPSS Inc, Chicago, IL, USA. For each assessment point, data were statistically analyzed using one-way ANOVA. Difference between the two groups was determined using Chi-square test and the level of significance was set at $P < 0.05$.

RESULTS

Acute/chronic HP, CTD-ILD, IPF, and sarcoidosis were revealed in 35.06%, 29.87%, 15.58%, and 12.99% of the subjects, respectively. Hence, the most common ILD was acute/chronic HP. Acute and chronic HP were found in 2 and 25 subjects, respectively. Among the CTD-ILD cases, rheumatoid arthritis (RA) (14) was the most common diagnosis. Cryptogenic organizing pneumonia (COP) and silicosis were found in 2 cases each. Maximum mean age was reported in IPF cases (61.59 years), followed by acute/chronic HP cases (54.18 years). The mean age in CTD-ILD and sarcoidosis was 48.03 and 45.17 years, respectively, which is comparatively lower as compared to IPF and acute/chronic HP cases. When mean age was compared according to the type of diagnosis using the ANOVA test, it was found to be statistically significant as $P < 0.01$. Females were found more in acute/chronic HP and CTD-ILD cases while males were reported more in IPF and sarcoidosis with statistically significant difference as $P < 0.01$. Approximately, equal distribution of ILD cases was found in rural and urban areas with statistically insignificant differences as $P > 0.05$. Maximum smoking habit was found in IPF cases (12.99%), followed by acute/chronic HP (11.69%), while minimum habit was revealed in sarcoidosis and other cases with statistically significant differences as $P < 0.05$ [Table 1].

Percentage of drugs prescribed by generic name, encounters with an antibiotic prescribed, encounters with an injection prescribed, and drugs prescribed from the essential drugs list or formulary was reported among 24.68%, 19.48%, 29.87%, and 59.74% of the subjects, respectively [Graph 1]. Average number of drugs per encounter was 4.45 while the WHO optimal value was ≤2.

Clubbing, rash, pedal edema, crepts, rhonchi, and loud P2 were found in 26, 5, 8, 69, 10, and 11 subjects, respectively. Hence, crepts were the most common clinical sign. All the clinical signs were comparable in all the diagnosis except clubbing and rhonchi. Clubbing and rhonchi were reported maximum in IPF and other cases, respectively, with significant differences as $P < 0.05$ [Table 2].

It can be clearly appreciated from Table 3 that psychological, breathlessness and activities, chest symptoms, and total KBILD reduced significantly after 3 months as compared to baseline with a statistically significant difference as $P < 0.01$.

Table 1: Gender and smoking-wise distribution among the study subjects

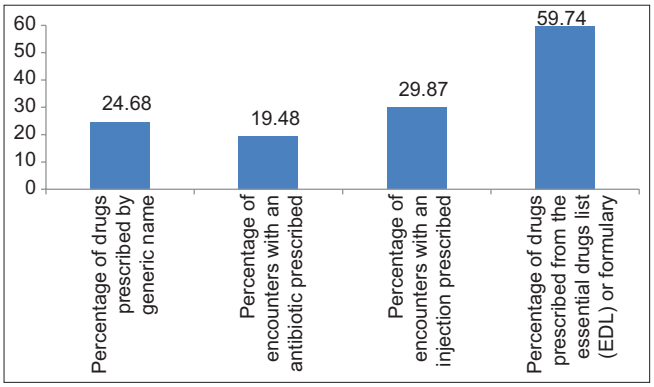
Diagnosis	Male, *n* (%)	Female, *n* (%)	χ^2	*P*
Acute/chronic HP	9 (11.69)	18 (23.38)	23.91	<0.01*
CTD-ILD	7 (9.09)	16 (20.78)		
IPF	8 (10.39)	4 (5.19)		
Sarcoidosis	6 (7.79)	4 (5.19)		
Others	1 (1.30)	4 (5.19)		
Total	31 (40.26)	46 (59.74)		
Diagnosis	**Smoking, *n* (%)**	**Nonsmokers, *n* (%)**	**χ^2**	***P***
Acute/chronic HP	9 (11.69)	18 (23.38)	14.32	0.026*
CTD-ILD	5 (6.49)	18 (23.38)		
IPF	10 (12.99)	2 (2.60)		
Sarcoidosis	1 (1.30)	9 (11.69)		
Others	1 (1.30)	4 (5.19)		
Total	26 (33.77)	51 (66.23)		

*Statistically significant. HP=Hypersensitivity pneumonitis, CTD=Connective tissue disease, ILD=Interstitial lung disease, IPF=Idiopathic pulmonary fibrosis

Table 2: Association of clinical signs and diagnosis

Signs	*n*	HP (*n*=27), *n* (%)	CTD-ILD (*n*=23), *n* (%)	IPF (*n*=12), *n* (%)	Sarcoidosis (*n*=10), *n* (%)	Others (*n*=5), *n* (%)	*P*
Clubbing	26	5 (18.52)	6 (26.09)	11 (91.67)	2 (20)	2 (40)	<0.01*
Rash	5	0	1 (4.35)	2 (16.67)	1 (10)	1 (20)	0.08
Pedal edema	8	5 (18.52)	2 (8.70)	1 (8.33)	1 (10)	0	0.11
Crepts	69	26 (96.30)	21 (91.30)	11 (91.67)	8 (80)	3 (60)	0.24
Rhonchi	10	5 (18.52)	2 (8.70)	1 (8.33)	1 (10)	1 (20)	0.036*
Loud P2	11	3 (11.11)	3 (13.04)	2 (16.67)	2 (20)	1 (20)	0.39

*Statistically significant. HP=Hypersensitivity pneumonitis, CTD=Connective tissue disease, ILD=Interstitial lung disease, IPF=Idiopathic pulmonary fibrosis



Graph 1: Prescription pattern of various interstitial lung diseases. EDL = Essential drugs list

ADRs were found in 23.38% (18) of the subjects and were confirmed by previous conclusive reports from drug product labels. Maximum ADR reported was gastritis (9.09%), followed by hepatitis (3.90%). According to Naranjo's Causality Assessment Scale, the majority of ADRs were classified as probable (14, 77.8%). Possible ADRs were found in 16.67% of the subjects. Doubtful ADRs were reported in 2.41% of the subjects. According to Hartwig's severity assessment level, mild, moderate, and severe ADRs were reported in 72.22%, 27.78%, and 0% of the subjects, respectively [Table 4].

DISCUSSION

In this study, acute/chronic HP, CTD-ILD, IPF, and sarcoidosis were revealed in 35.06%, 29.87%, 15.58%, and 12.99% of the subjects, respectively. Hence, the most common ILD was acute/chronic HP. Acute and chronic HP were found in 2 and 25 subjects, respectively. Among the CTD-ILD cases, RA (14) was the most common diagnosis. COP and silicosis were found in 2 cases each. Similarly, Singh *et al*.[19] in their study found that HP (47.3%) was the most common ILD, followed by CTD-ILD (13.9%) and IPF (13.7%). Valappil *et al*.[23] in their study showed that the most common cause for ILD was secondary to connective tissue disorder (45 patients [34.9%]). The second-most common ILD was IPF seen in 30 patients, forming 23.25% of the cohort. Sarcoidosis, a granulomatous ILD, was the third-most common ILD occurring in 22 (17.05%) patients.

Table 3: Comparison of King's Brief Interstitial Lung Disease at baseline and after 3 months

KBILD	Mean KBILD		*t*-test	*P*
	Baseline	3 months		
Psychological	54.96	18.75	33.72	<0.01*
Breathlessness and activities	40.22	19.08	21.07	<0.01*
Chest symptoms	63.13	27.52	38.91	<0.01*
Total	52.77	21.78	34.57	<0.01*

*Statistically significant. KBILD=King's Brief Interstitial Lung Disease

Table 4: Type of adverse drug reactions and adverse drug reactions in patients using Naranjo's Causality and Hartwig's Severity Assessment Scale

	n (%)
Type of ADRs	
Gastritis	7 (9.09)
Hepatitis	3 (3.90)
Anorexia	1 (1.30)
Skin reactions	2 (2.60)
Peripheral neuropathy	1 (1.30)
Dizziness	1 (1.30)
Psychosis	1 (1.30)
Vertigo	1 (1.30)
Weakness	1 (1.30)
Naranjo's causality	
Definite	0
Probable	14 (77.78)
Possible	3 (16.67)
Unlikely	1 (5.56)
Hartwig's severity	
Mild	13 (72.22)
Moderate	5 (27.78)
Severe	0
Total	18 (100)

ADRs=Adverse drug reactions

However, according to studies conducted by Sen and Udwadia[24] and Shafeeq *et al*.,[25] IPF was the most common ILD. Frank Reichenberger *et al*.[26] also revealed that the most prevalent ILDs are IPF, sarcoidosis, and HP. Kundu *et al*.[27] too reported that 92 patients of ILD were diagnosed in the study period with IPF (*n* = 35, 38.04%), CTD-ILD (*n* = 29, 31.5%), HP (*n* = 10, 10.9%), sarcoidosis (*n* = 5, 5.4%), and silicosis (*n* = 5, 5.4%) being the common causes. Dhooria *et al*.[28] revealed that sarcoidosis (42.2%), IPF (IPF, 21.2%), CTD-related ILDs (12.7%), HP (10.7%), and non-IPF idiopathic

interstitial pneumonia (9.2%) were the most common ILDs, which is in contrast to our study.

Epidemiologic information regarding ILDs has varied, likely in part because of differences in patient selection and study design. Prior prospective ILD registries have found dissimilarities between countries; it is unclear whether differences in ILD incidence and prevalence truly exist or occur because of selection bias.[26] Apparent geographic differences in ILD prevalence between and within countries, especially for HP, may in part be explained by differences in definitions used for HP and environmental/local cultural factors.

Clubbing, rash, pedal edema, crepts, rhonchi, and loud P2 were found in 26, 5, 8, 69, 10, and 11 subjects, respectively. Hence, crepts were the most common clinical sign. All the clinical signs were comparable in all the diagnoses except clubbing and rhonchi. Maximum smoking habit was found in IPF cases (12.99%), followed by acute/chronic HP (11.69%) while minimum habit was revealed in sarcoidosis and other cases in this study. According to Valappil *et al*.,[23] there were 42 (32.5%) smokers, whereas 87 (67.44%) patients were nonsmokers. Most common symptoms were gradually progressive dyspnea (94.5%), followed by dry cough (78.29%). Clubbing was a clinical sign in 28.6% of patients. Yadav and Srivastava[29] in their study reported that all the patients had breathlessness. Other common findings were clubbing (52.3%) and cyanosis (37.8%). Similarly, Dhooria *et al*.[28] reported that subjects with IPF were predominantly males (71%) and older in age than those with other diagnoses.

In this study, the average number of drugs per encounter was 4.45 while the WHO optimal value was ≤2. In some Indian studies, the average number of drugs per encounter has been reported in the range of 2.8–3.2.[30] Hussain *et al*.[30] in their study reported that in most of the prescriptions, three drugs were prescribed (31.90%), followed by two drugs (24.30%), four drugs in 21.30% of prescription, and one drug in 13.70% of prescriptions, more than four drugs were prescribed in 8.80% of prescription.

In this study, psychological, breathlessness and activities, chest symptoms, and total KBILD reduced significantly after 3 months as compared to baseline with statistically significant difference as $P < 0.01$ in this study. KBILD was the primary end-point in a crossover randomized controlled trial examining the effects of 2 weeks of ambulatory oxygen on HRQoL in 76 patients with fibrotic ILD (58% IPF, 69% male with mean ± SD age 68 ± 10 years, forced vital capacity 73% ±19% predicted and KBILD-T score 50.5 ± 11.2). Following the intervention, there was a significant improvement in the KBILD domain and total scores with ambulatory oxygen compared with placebo air (mean score change in KBILD-T 3.7 (95% confidence interval [CI] 1.8–5.6); $P < 0.0001$). This cohort had similar baseline characteristics and responses to intervention as the patients in our study. According to Patel *et al*.,[13] regarding change in KBILD-T, a total of 38% of patients deteriorated, 25% improved, and 37% remained the same, but the mean (95% CI) change in KBILD-T was not reported. These findings are similar to our study.

ADRs were found in 23.38% (18) of the subjects. Maximum ADR reported was gastritis (9.09%), followed by hepatitis (3.90%) in the present study. Phadnis and Marko[16] in their study found that a total of 58 ADRs were reported during the study period. The assessment by the WHO probability scale showed that out of 58 ADR 22 (37.93%) were probable and 17 (29.31%) were possible and 6 (10.34%) were certain. Most commonly involved system was gastrointestinal system with 24 (41.37%) ADRs. Severity assessment by modified Hartwig and Siegel Scale showed that 22 (37.93%) were moderate, 32 (55.17%) were mild, and 4 (6.89%) were severe ADRs. No lethal effects were observed or produced.

Relevance

The study will generate data that can be utilized for evidence-based medicine, prescription utilization for safety and risk assessment and treatment guidelines and best practices for patients with ILDs, as well as predictors of QoL.

Limitations

The sample size and study duration were small. Multicentric studies are needed to strengthen the reliability and generalizability of the current findings. It is possible that the response may have been affected by recall bias due to the follow-up period for some patients which may reflect the follow-up KBILD score rather than its change. A larger study is required to determine the KBILD, preferably with a standardized intervention, such as that within a clinical trial.

CONCLUSION

The high proportion of patients clinically diagnosed with HP in our study highlights the importance of a detailed environmental exposure history in the diagnostic evaluation of patients with ILD to avoid inaccurate diagnoses. Our findings should facilitate the clinical interpretation of health status measures in ILD. ADR-related hospital admissions are a significant problem in the health-care system

prompting the need for greater awareness among the health-care professionals, regarding not only the potential for ADRs but also in the prevention or minimization of the occurrence of ADRs.

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Conflicts of interest

There are no conflicts of interest.

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