EVALUATION OF EFFICACY AND SAFETY OF PIRFENIDONE IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS

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"EVALUATION OF EFFICACY AND SAFETY OF PIRFENIDONE IN PATIENTS WITH IDIOPATHIC PULMONARY FIBROSIS"

ABSTRACT

Idiopathic pulmonary fibrosis (IPF) is a chronic and ultimately fatal disease characterized by a progressive decline in lung function. In Pulmonary fibrosis tissue, deep in lungs becomes thick and stiff, or scarred, over time called as fibrosis. IPF belongs to a large group of more than 200 lung diseases known as interstitial lung diseases (ILD), characterized by the involvement of lung interstitium. In idiopathic pulmonary fibrosis, it is believed that after injury, aberrant activation of alveolar epithelial cells provokes the migration, proliferation, and activation of mesenchymal cells with the formation of fibroblastic/myofibroblastic foci, leading to the exaggerated accumulation of extracellular matrix with the irreversible destruction of the lung parenchyma.Pirfenidone is a drug developed by several companies worldwide, for the treatment of IPF.It inhibits TGF-β stimulated collagen production and reduces the production of fibrogenic mediators such as TGF-β and also TNF-α and IL-1β in both cultured cells and isolated human peripheral blood mononuclear cells**.** A prospective observational study was conducted for a period of six months on twenty five patients. Inclusion Criteria was Patients diagnosed with Idiopathic Pulmonary Fibrosis (outpatients), Patients of age above 40 years and with Forced Vital Capacity (%FVC) ≤ 40% at screening. Exclusion Criteria was Pregnant and lactating women, Patients with history of chronic obstructive pulmonary disease. It was found that patients with IPF were more in the age group 51-60 years most commonly observed in men. Symptoms in IPF were categorised as shortness of breath, cough, clubbing of fingers and tiredness. It has been observed that after undergoing treatment with Pirfenidone, the no. of patients suffering with IPF has reduced to moderate and mild condition from severe condition, indicating the efficacy of the drug. Photosensitivity and LFT changes are two commonly noted ADR's. The study concluded that Pirfenidone is a promising new treatment for IPF which reduced disease progression, as reflected by lung function, exercise tolerance, and progression-free survival, in patients with idiopathic pulmonary fibrosis and the treatment was associated with an acceptable side-effect profile.

KEYWORDS: Idiopathic pulmonary fibrosis, fibrosis, Forced Vital Capacity, Pirfenidone.

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a chronic and ultimately fatal disease characterized by a progressive decline in lung function**.** In Pulmonary fibrosis tissue, deep in lungs becomes thick and stiff, or scarred, over time. The formation of scar tissue is called fibrosis. The term 'Idiopathic is used because the cause of pulmonary fibrosis is still unknown. IPF belongs to a large group of more than 200 lung diseases known as

interstitial lung diseases (ILD), characterized by the involvement of lung interstitium.[1-13] The interstitium, the tissue between the air sacs in the lung, is the primary site of injury in ILDs. However, these disorders frequently affect not only the interstitium but also the airspaces, peripheral airways, and vessels. It is currently believed that idiopathic pulmonary fibrosis (IPF) is an epithelial-fibroblastic disease, in which unknown endogenous or environmental stimuli disrupt the homeostasis of alveolar epithelial cells, resulting in diffuse epithelial cell activation and aberrant epithelial cell repair. In the current hypothesis regarding the pathogenesis of idiopathic pulmonary fibrosis, exposure to an inciting agent (eg, smoke, environmental pollutants, environmental dust, viral infections, gastroesophageal reflux disease, chronic aspiration) in a susceptible host may lead to the initial alveolar epithelial damage.[14-17] In idiopathic pulmonary fibrosis, it is believed that after injury, aberrant activation of alveolar epithelial cells provokes the migration, proliferation, and activation of mesenchymal cells with the formation of fibroblastic/myofibroblastic foci, leading to the exaggerated accumulation of extracellular matrix with the irreversible destruction of the lung parenchyma. Research has demonstrated that prostaglandin E_2 deficiency, in lung tissue of patients with pulmonary fibrosis, results in increased sensitivity of alveolar epithelial cells to FAS-ligand induced apoptosis but induces fibroblast resistance to Fas-ligand induced apoptosis**.** Therefore, apoptosis resistance in the fibroblasts and myofibroblasts participating in the repair of the alveolar epithelium may contribute to the persistent and/or progressive fibrosis in idiopathic pulmonary fibrosis. [18-21]

ETIOLOGY

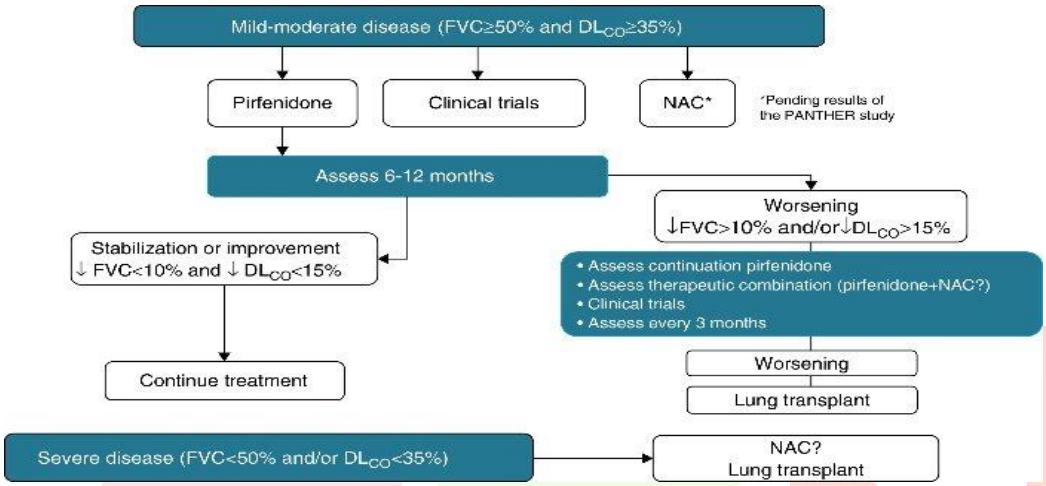
Environmental pollutants include inorganic dust (silica and hard metal dusts) and organic dust (bacteria and animal proteins). Medicines that are known to cause pulmonary fibrosis in some people include nitrofurantoin (an antibiotic), amiodarone (a heart medicine), methotrexate and bleomycin (both chemotherapy medicines) and many other medicines.In most cases, however, the cause of lung scarring isn't known. These cases are called idiopathic pulmonary fibrosis (IPF). With IPF, it is thought that something inside or outside of the lungs attacks lungs again and again over time.These attacks injure the lungs and scar the tissue inside and between the air sacs. This makes it harder for oxygen to pass through the air sac walls into the bloodstream. [21-27]

The following factors may increase risk of IPF: Cigarette smoking, Viral infections, including Epstein-Barr virus (which causes mononucleosis), influenza A virus, hepatitis C virus, HIV, and herpes virus 6,Genetics also may play a role in causing IPF. Some families have at least two members who have IPF. Researchers have found that 9 out of 10 people who have IPF also have gastroesophageal reflux disease (GERD).Symptoms include Shortness of breath, A dry hacking cough, Gradual, unintended weight loss, Fatigue or malaise, Aching muscles and joints, Clubbing.Complications include pulmonary hypertension, Cor pulmonale, Respiratory failure, Lung cancer**.**

Tests: No single test can diagnose IPF. Several tests may be recommended such as Medical History-To diagnose IPF, patient may be asked about his age , history of smoking , things in the air at job or elsewhere that could irritate lungs , history of legal and illegal drug use , other medical conditions that a person has , family's medical history , how long patient had symptoms.

Diagnostic Tests: Chest X Ray, High-Resolution Computed Tomography (HRCT), Lung Function Tests, Pulse Oximetry, Arterial Blood Gas Test, Exercise Testing, Lung Biopsy etc

Treatment



PIRFENIDONE

Pirfenidone is a drug developed by several companies worldwide, for the treatment of idiopathic pulmonary fibrosis (IPF). In 2008, it was first approved in Japan for the treatment of IPF after clinical trials, under the trade name of Pirespa. In October 2010, the Indian Company Cipla launched it as Pirfenex.

Mechanism of Action

Pirfenidone has well-established antifibrotic and anti-inflammatory properties in various in vitro systems and animal models of fibrosis. A number of cell-based studies have shown that pirfenidone reduces fibroblast proliferation. It inhibits TGF-β stimulated collagen production and reduces the production of fibrogenic mediators such as TGF-β. Pirfenidone has also been shown to reduce production of inflammatory mediators such as TNF-α and IL-1β in both cultured cells and isolated human peripheral blood mononuclear cells

Adverse Effects are dyspepsia, nausea, gastritis, gastroesophageal reflux disease (GERD) and vomiting.Dizziness,Weight loss,Photosensitivity reactions, rash, pruritus and dry skin.Elevation in hepatic enzyme levels, especially those of aspartate transaminase (AST) and alanine transaminase (ALT) etc. [28-31]

MATERIALS AND METHODS

A prospective observational study was conducted in Department of Pulmonology, Krishna Institute of Medical Sciences (KIMS) for a period of 6 months. Twenty five patients diagnosed with IPF were included in the study after explaining them about study and gaining their consent

Inclusion Criteria: Patients with IDIOPATHIC PULMONARY FIBROSIS (outpatients), Patients of age above 40 years, Patient with Forced Vital Capacity (%FVC) ≤ 40% at screening.

Exclusion Criteria: Pregnant and lactating women, Patients with history of chronic obstructive pulmonary disease

TOOLS USED: Assessment of X- ray, Pulmonary Function Test(FVC), Questionnaire

STATISTICAL ANALYSIS PAIRED T TEST: - was done to compare the observed values of pre and post treatment and P value was calculated using Graph pad software – Quick Calcs.

RESULTS

DEMOGRAPHIC DISTRIBUTION OF PATIENTS

Out of 25 patients, 5 patients were below 50 years and 20 patients were above 50 years

Table no. 1 Demographic Distribution of Patients

Gender	Age < 50 years of age	Age > 50 years of age
Male	3	12
Female	2	8

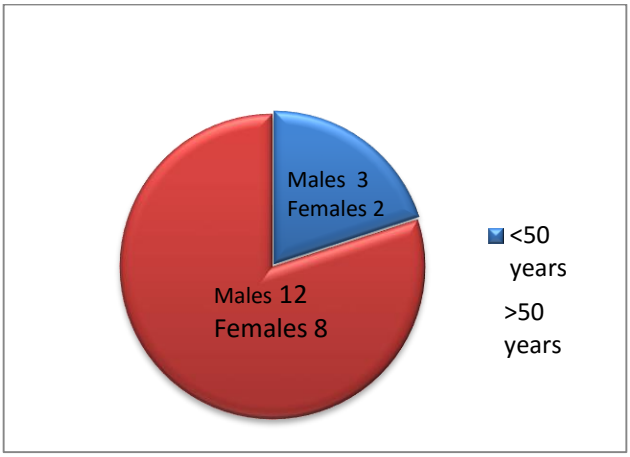


Fig 1 Demographic Distribution of Patients

AGE DISTRIBUTION OF PATIENTS

Age distribution of patients was calculated to know which age group of patients are suffering more with IPF. The range of age group is from 40-80years.It was found that patients with IPF were more in the age group 51-60 years

Table no.2 Age Distribution of Patients

Age Range (years)	Number of Patients	Percentage
40 – 50	5	20%
51 – 60	10	40%
61 – 70	8	32%
71 – 80	2	08%

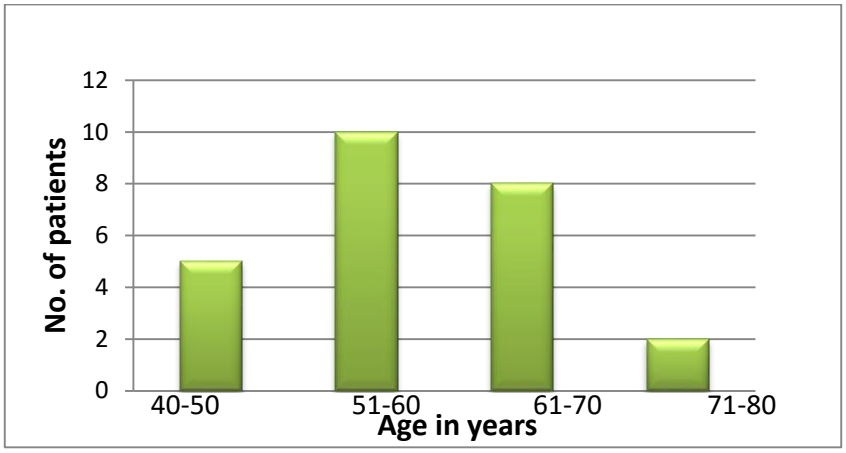


Fig no.2 Age Distribution of Patients

GENDER DISTRIBUTION OF PATIENTS

Among the total subjects, IPF was more commonly observed in men (60%) compared to women (40%).

Table no. 3 Gender Distribution of Patients

Gender	Male	Female
	15	10
Percentage	60%	40%

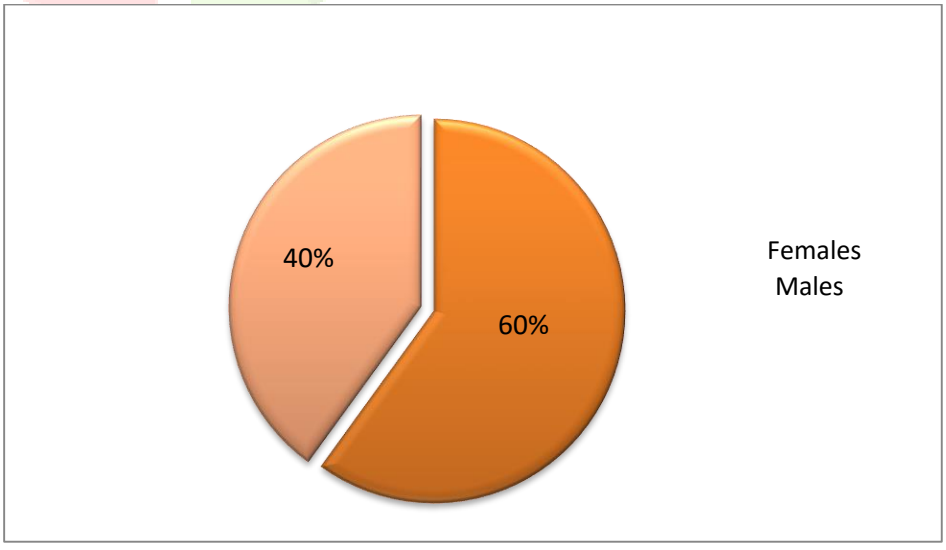


Fig no. 3 Gender Distribution of Patients

SMOKER AND NON-SMOKER [Male patients]

Smoking can worsen IPF. Out of 15 male patients 12 were

smokers(80%) and 3 were non-smokers(20%). There were no female smokers.

Table no. 4 Smoker and Non-Smoker Distribution

Case	No. of patients	Percentage
Smokers	12	80%
Non-smokers	03	20%

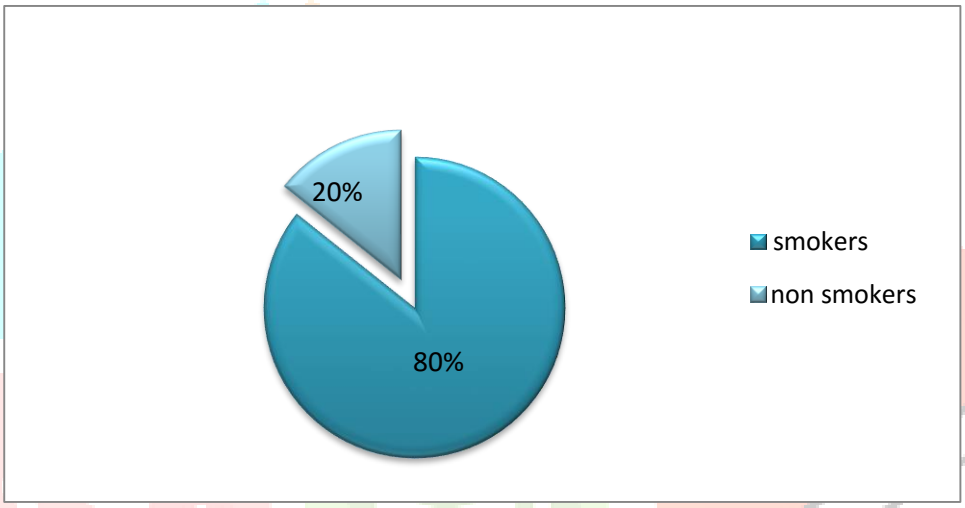


Fig no. 4 Smokers and Non-Smoker Distribution

SYMPTOMS OBSERVED IN IPF PATIENTS

Symptoms in IPF were categorised as shortness of breath, cough, clubbing of fingers and tiredness. The total no. of patients who experienced SOB were found to be 100% ,subjects who experienced cough were 92% ,subjects who had clubbing of fingers were 76% and people who experienced tiredness were 84%.

Table no. 5 Symptoms Categorization

S.No	Symptoms	No.of patients	Percentage
1	Shortness of breath	25	100%
2	Cough	23	92%
3	Clubbing of fingers	19	76%
4	Tiredness	21	84%

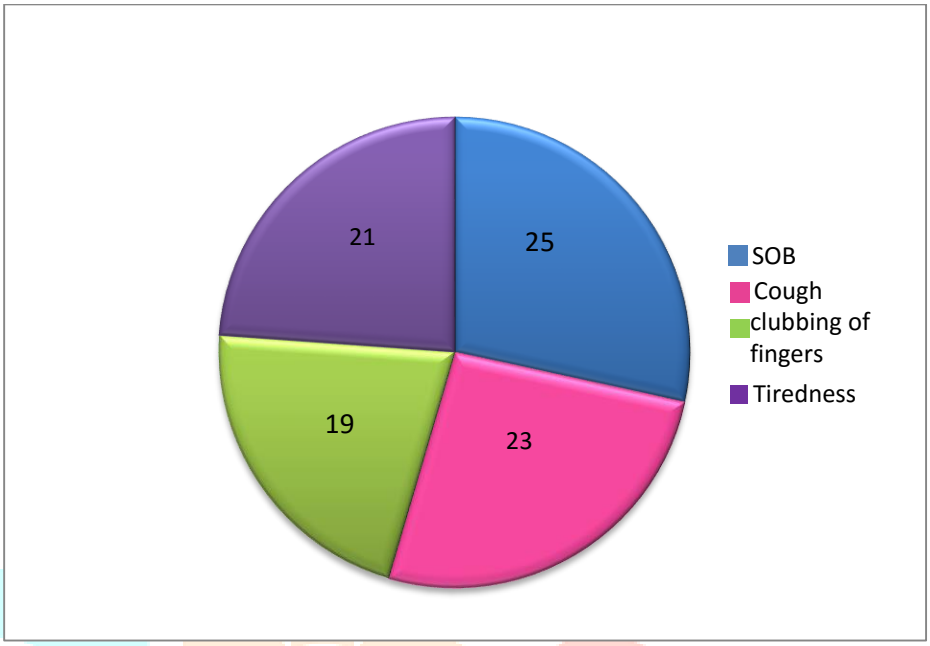


Fig no. 5 Symptoms Categorization

DISTRIBUTION OF PATIENTS BASED ON IPF QOL SCORE

Pre Medication

Based on scale and questionnaire used, IPF symptoms were categorized into mild, moderate and severe,of which 36% were grouped into mild condition, 32% were grouped into moderate and 32% were grouped into severe condition.

Table no. 6 (Pre-Medication)

Score Range (scale)	Number of Patients	Percentage
0 – 10 (mild)	9	36%
11 – 20 (moderate)	8	32%
21 – 30 (severe)	8	32%

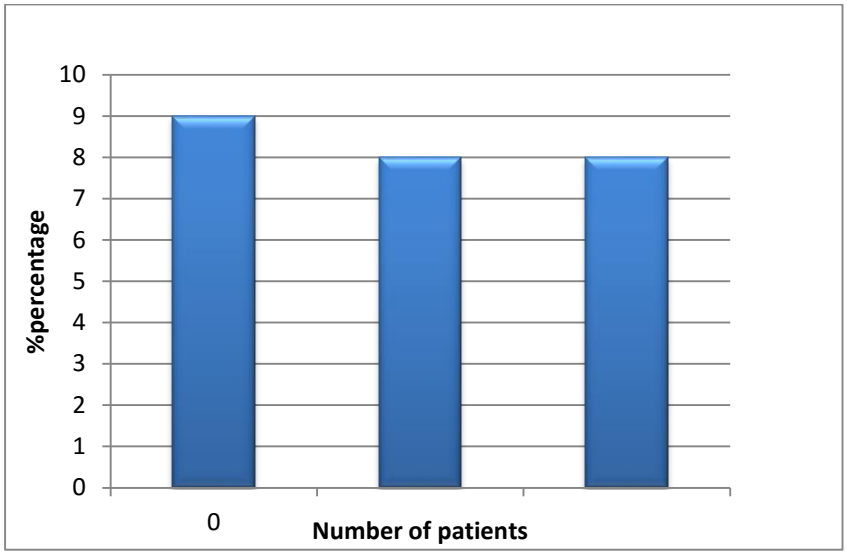


Fig no. 6 Pre-Medication %

Post Medication

After undergoing 1 month of treatment with pirfenidone, scores were again calculated and it was found that number of patients having moderate and severe IPF symptoms decreased when compared to pre-medication indicating the improvement of symptoms.

Table no. 7 (Post Medication - After 1 Month):

Score Range(scale)	Number of Patients	Percentage
0 – 10 (mild)	11	44%
11 – 20 (moderate)	10	40%
21 – 30 (severe)	4	16%

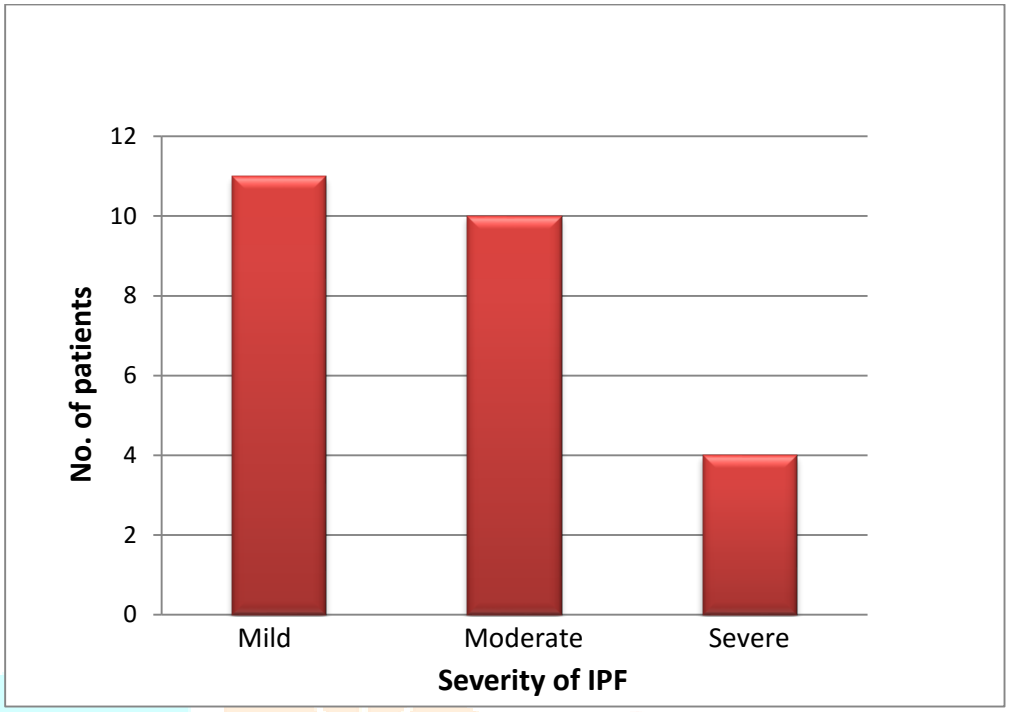


Fig 7:- Distribution of patients based on IPF QOL score(post medication)

COMPARISON OF SCORES BEFORE AND AFTER TREATMENT

It has been observed that after undergoing treatment with Pirfenidone, the no. of patients suffering with IPF has reduced to moderate and mild condition from severe condition, indicating the efficacy of the drug.

Table no. 8 Comparison of Scores Before And After Treatment

Score (scale)	Pre-medication	Post-medication
0 – 10 (Mild)	9	11
11 – 20 (Moderate)	8	10
21 – 30 (Severe)	8	4

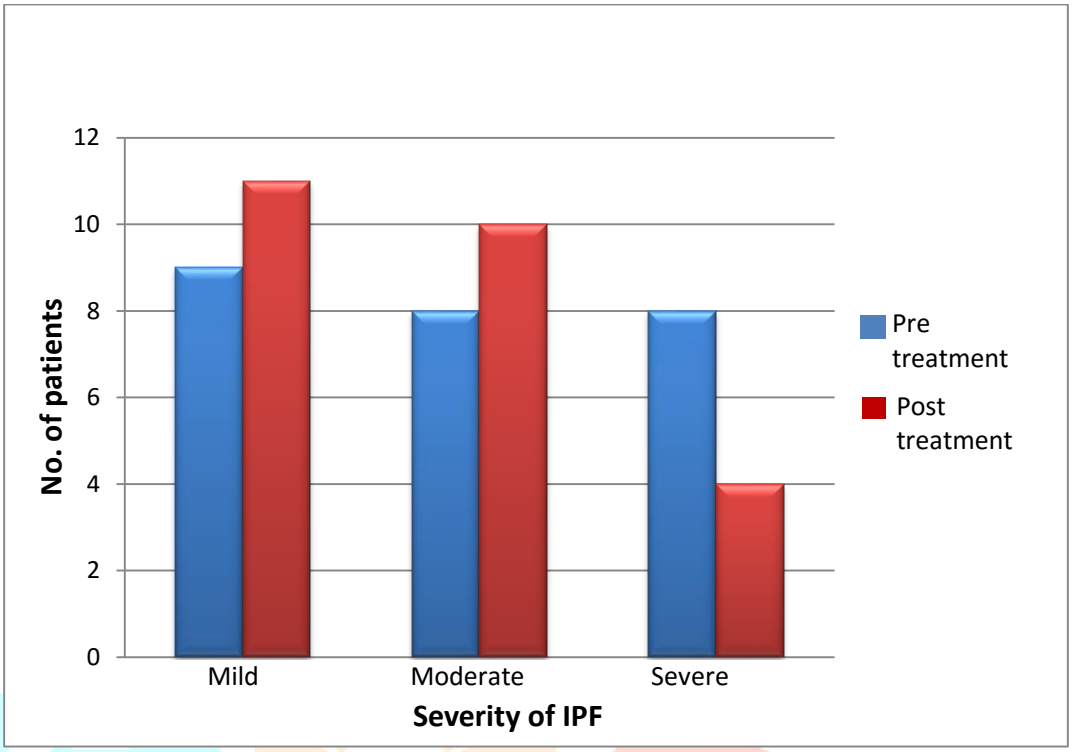


Fig 8 : Comparison of scores before and after Treatment

ADR'S OBSERVED IN PATIENTS AFTER GIVING PIRFENIDONE

Photosensitivity and LFT changes are two common ADR's of Pirfenidone.LFT changes were observed in more number of patients (76%).

Table no. 9 Adr's Observed In Patients After Giving Pirfenidone.

ADR's	No. Of patients	Percentage
Photosensitivity	03	12%
LFT changes	19	76%
Both photosensitivity and LFT changes	03	12%

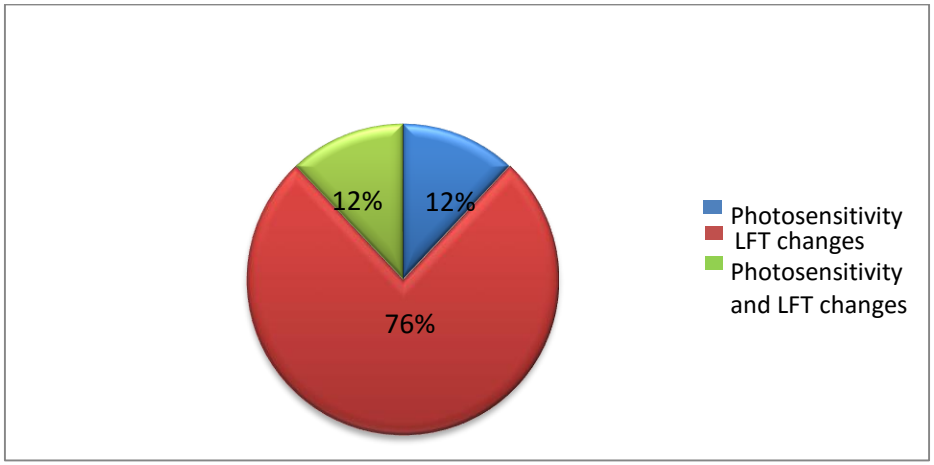


Fig :- 9 ADR's observed in patients after giving Pirfenidone

STATISTICAL ANALYSIS OF FVC VALUE

Table no.10

Statistical Value	FVC values	
	Pre treatment	Post treatment
Mean	36.08	41.72
P value	0.0001	

The difference between the mean of FVC values pre treatment and FVC values post treatment was **-5.64.**

P value was found to **be 0.0001.**

This indicates that improvement in FVC values was seen in patients, after giving Pirfenidone.

DISCUSSION

The current clinical research study conducted at KIMS, secunderabad in 25 subjects in patients with Idiopathic pulmonary Fibrosis was done to determine the efficacy and Safety of Pirfenidone, anti-fibrotic drug. In this prospective observational study, treatment with pirfenidone significantly reduced disease progression, as measured by changes in FVC and progression-free survival. The treatment effect on FVC emerged early and

increased during the course of the trial, resulting in an approximate halving in the rate of decline of disease progression. Inclusion Criteria:- Patients with Idiopathic Pulmonary Fibrosis (outpatients),Patients of age above 40 years, Patient with Forced Vital Capacity (%FVC) ≤ 40% at screening Exclusion Criteria were Pregnant and lactating women, Patients with history of chronic obstructive pulmonary disease. Treatment with pirfenidone was generally safe and had an acceptable side-effect profile. Reported clinically significant elevations in aminotransferase levels occurred more frequently; however, these elevations were reversible and did not have clinically significant consequences.

Therefore, the study concludes that "Pirfenidone is a promising new treatment for IPF which reduced disease progression, as reflected by lung function, exercise tolerance, and progression-free survival, in patients with idiopathic pulmonary fibrosis and the treatment was associated with an acceptable side-effect profile".

CONCLUSION

Treatment with pirfenidone significantly reduced disease progression, as measured by changes in FVC and progression-free survival. The treatment effect on FVC emerged early and increased during the course of the trial, resulting in an approximate halving in the rate of decline of disease progression. Treatment with Pirfenidone was generally safe and had an acceptable side-effect profile .There were no serious adverse events and deaths. Reported clinically significant elevations in aminotransferase levels occurred more frequently; however, these elevations were reversible and did not have clinically significant consequences.

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