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TANAFFOS

Comparison of Longevity in Patients with Idiopathic Pulmonary Fibrosis Using Pirfenidone Versus Triple Therapy with Prednisolone, Azathioprine, and Acetylcysteine

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Background: The effect of the combination of prednisolone, azathioprine, and acetylcysteine for the treatment of Idiopathic pulmonary fibrosis (IPF) is minimal. We aimed to investigate the effect of these drugs in case of intolerance to new anti-fibrotic drugs.

Materials and Methods: This historical prospective study was performed on 91 patients with idiopathic pulmonary fibrosis who were referred to a pulmonologist in Mashhad during 2016-2020. Patients were divided into two groups, Pirfenidone which was prescribed for 46 subjects, and a combination of prednisolone, azathioprine, and acetylcysteine which was prescribed for 45 subjects. Patients were selected by convenience sampling and a life expectancy comparison between the two groups was performed by Cox regression.

Results: There were no statistically significant differences between age, gender, and drug type in the two groups at the beginning of treatment. The death rate per year in the triple-drug treatment group was 44.44% (n = 20) and in the Pirfenidone treatment group was 11.08% (n=2). Of the 65 recovered population, 49% (22 patients) were in the triple-drug treatment group, and 78% (36 patients) were in the Pirfenidone treatment group which indicated that Pirfenidone has a significant impact on reducing death rate compared to triple-drug treatment (p-value=0.003 <0.05). Pirfenidone decreased the risk of death, compared to triple therapy (0.23 when death was set up as one in the triple-therapy group).

Conclusion: Pirfenidone has a favorable effect on increasing life expectancy and triple therapy should be considered as short-term only in subjects intolerant to anti-fibrotic.

Keywords: Acetylcysteine; Azathioprine; Idiopathic pulmonary fibrosis; Longevity; Prednisolone; Pirfenidone

INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is the most common idiopathic interstitial pneumonia which provides the worst prognosis among these patients and the average survival range from 3 to 5 years (1). Epidemiological studies showed that men are more likely to be affected by this disease than women (10 out of 100,000 men and 7 out of 100,000 suffer from IPF) (2). Moreover, the prevalence of IPF increases with age since two-thirds of patients are over 60 years old (2). In the Middle East, Saudi Arabia, Kuwait, and Iran, the average age of the disease was reported lower than in the United States and Europe (range: 54.7 – 56.2

years) (2,3). If IPF is not diagnosed and treated at an appropriate time, it would lead to right heart failure and even the necessity for lung transplantation. Deterioration in respiratory function can start a gradual limitation of physical activity which can lead to a lower quality of life (4,5).

The use of glucocorticoids and immunosuppressive agents including azathioprine and N-acetyl cysteine (NAC) has become a standard treatment method for IPF in the past decade. Studies in this regimen showed improvement in physical activity including the 6-min walking distance test (6MWT) (6,7). Later, Pirfenidone was introduced with more success which proved to slow, not reverse, the respiratory deterioration. Pirfenidone exerts its beneficial effect via its antioxidant properties and decreases falling in forced vital capacity (FVC) (8,9). Moreover, Nintedanib is a novel anti-angiogenesis compound being investigated for the treatment of various cancers, but in patients with IPF, a randomized double-blind study showed its ability to reduce the decline in FVC, which is consistent with a slowing of disease progression (10,11).

Pirfenidone has shown a 25% per year increase in life expectancy (12). A study reported that the relative risk of death in patients treated with Pirfenidone was lower than placebo. This drug also has side effects that include: increased gastrointestinal function, nausea, indigestion, anorexia, as well as skin problems especially rashes and skin sensitivity to light (13). The combination use of prednisolone, azathioprine, and N-acetyl cysteine (triple drugs) has stopped because a double-blind randomized study showed that 8 of the 77 patients died, which led to the termination of that study (7). Unfortunately, this study was terminated prematurely which prevented the achievement of specific objectives, such as measuring the difference in survival rates between the triple-drug regimen and Pirfenidone (12). We believe that the study should be completed to compare the frequency of improved subjects with non-responder subjects.

Currently, there is not enough data to fully support the effectiveness and potential side effects of triple therapy. However, with the introduction of new anti-fibrotic drugs, it may not be necessary to consider triple therapy for any patients. In situations where there are severe side effects with Pirfenidone or difficulty obtaining Pirfenidone or Nintedanib, triple therapy could potentially be used as a temporary solution.

In this study, we aimed to compare life expectancy in patients with idiopathic pulmonary fibrosis using triple treatments of prednisolone, azathioprine, and N-acetyl cysteine (from our archive) compared to the new drug Pirfenidone, to determine the frequency of severe complications in case of necessity for using triple therapy.

MATERIALS AND METHODS

This historical prospective study reviewed the medical records of 91 eligible patients aged 18-19 years, with a diagnosis of IPF, recruited from a lung subspecialty clinic in Mashhad, between 2016 and 2020. Patients had a clinical diagnosis of IPF based on clinical symptoms, radiological high-resolution computed tomography (HRST) evaluation, and pulmonary function test. HRCT findings included definite criteria of usual interstitial pneumonia (UIP), including predominant basal, peripheral, and fine honeycomb with or without traction bronchiectasis. Pulmonary function tests included a forced vital capacity (FVC) of less than 80%, and a carbon monoxide diffusing capacity of the lungs (DLco) of less than 75%. Patients with a diagnosis of collagen vascular diseases, lymphoma, neoplasm, pulmonary arterial hypertension, bronchial asthma, sarcoidosis, bronchiectasis, severe or unstable concomitant disease, and a history of chronic exposure to an environmental agent considered as a risk factor for IPF and were excluded from the survey analysis.

The patients were split into two groups. The first group included 45 patients who were given triple therapy before Pirfenidone was available. These patients survived until the time of the study. The second group consisted of 46 patients who were given Pirfenidone after it became available. This group was similar in size to the triple therapy group. The average follow-up period was adjusted

to be 5 years. The first group (The Triple therapy group) received: 1-Prednisolone (Aburaihan Pharmaceutical Company, Tehran, Iran) 0.5 mg/kg PO divided three times a day after each meal for 3 months, and then the dosage was decreased to 10/kg mg after the breakfast, 2-Azathioprine (Ramofarmin Pharmaceutical company, Tehran, Iran) 1 mg/kg PO divided two times a day and 3-N-acetyl cysteine (Avicenna Pharmaceutical Company, Tehran, Iran) 600 mg PO controlled-release once daily. The second group received Pirfenidone (Cipla Pharmaceutical Company, Mumbai, India) two tablets of 200 mg, three times a day after the meals. The study collected patient data such as gender, age, type of medication, and mortality rate from their medical records and documented it in the checklist.

High-resolution chest CT imaging is considered a standard predictor, which provides crucial diagnostic and prognostic information on IPF. This method could evaluate and quantify several parenchymal abnormalities including the extent of ground-glass opacities, consolidation, reticulation, and honeycombing. Reticulation and honeycombing are often merged to generate an overall extent of fibrosis score. Besides, the overall pattern can be categorized by its consistency with the usual interstitial pneumonia (UIP) pattern. The primary endpoint was mortality rate (died patients per year); secondary endpoints included frequency of improvement reported by the patients and side effects in both groups.

Data analysis was performed by SPSS software (version 16). First, the normality of the quantitative variables was tested by Kolmogorov–Smirnov**.** Descriptive statistics indices including central tendencies and dispersion were calculated. T-test, Cox regression, and hazard ratio were utilized for data analysis. The Cox regression model was used to investigate the effect of drug type and gender, on patients' survival period. In this model, gender variables (women and men) and type of drug (triple therapy and Pirfenidone) were considered independent variables. The significance level in the tests was considered to be less than 0.05.

RESULTS

In this study, 91 Idiopathic Pulmonary Fibrosis (IPF) patients were evaluated. Women and men constituted 54.9% (50 patients) and 45.1% (41 patients) of the population, and the mean age them was 76.24±13.09 and 75.58±14.09 years, respectively. At the end of this 5-year follow-up, 26 patients died and 65 survived.

The mean age of the patients who consumed the triple-drug was 72.1± 1.2 years and the patients who received the Pirfenidone was 72.05±1.5 years. Comparison of the mean age of the two independent groups showed no sharp difference in the mean age, between females and males (t-value=0.017, p-value= 0.986 >0.05). There was no statistically significant relationship between age and drug type (t-value = 1.721, p-value = 0.0887> 0.05) (Figure 1).

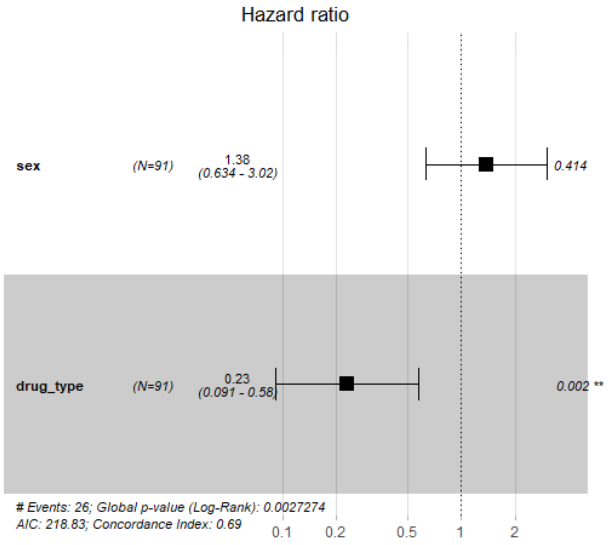

Figure 1. The risk ratio chart shows the Cox regression information. This diagram illustrates the risk ratio coefficient, the confidence distance for each independent variable with its significant P-value

The mean treatment duration for patients in the triple-drug treatment group was 22.04±22.71 months, and in the Pirfenidone treatment group was 15.5±11.94 months which revealed a significant difference between the two groups (t-value=1.715, p-value= 0.091 >0.05). The investigation of the survival rate in treatment groups indicates that the death rate per year in the triple-drug treatment group was 44.44% (n = 20) and in the Pirfenidone treatment group was 11.08% (n = 2). Of the 65 recovered population, 49% (22 patients) were in the triple-drug treatment group, and 78% (36 patients) were in the Pirfenidone

treatment group. The duration of surviving subjects, in the triple therapy group, was significantly more than Pirfenidone group (30±18 months in triple therapy compared to 13±6 months in the Pirfenidone group) (Table 1). However, they began their treatment 3 years before the Pirfenidone group; therefore, the death rate (frequency of death per year) was calculated (Table 3). As shown in Table 1, the death rate in the triple therapy group was 44±11 subjects per year, which was significantly higher than the Pirfenidone group (11±13).

Figure 1 shows the comparison of the risk of death between the Pirfenidone and the triple therapy group: Pirfenidone decreased the risk of death, compared to triple therapy (0.23 when death was set up as one in the triple-therapy group).

According to Table 2, the recovery rate was lower than 50% in triple therapy and more than 50% in the Pirfenidone group (z-value=-2.944, p-value=0.003 <0.05). This table also indicated that unlike the triple-drug, in which the majority of deaths occurred in the early years of the study, all patients taking Pirfenidone improved during the study period. In analyzing the survey of two groups, Figure 2 displays the Cox regression model. It indicates a higher survival rate in the Pirfenidone group. However, there was no significant correlation between the patient's condition and the mean duration of treatment (t-value = 1.882, p-value = 0.091).

Although Pirfenidone proved to be effective, three subjects had to switch from it to triple therapy due to gastric problems, vomiting, and an increase in disease severity as indicated by the CT scan. However, as triple therapy was found to be ineffective, Pirfenidone was prescribed to five patients instead.

A comparison of the frequency of death in males compared to females showed that the incidence of death in men is 1.38 times higher than in women; but, the results of the Cox regression model indicated that this difference is not statistically significant (Figure 2).

Table 1. Overall results of demographic and survey analysis between subjects suffering from IPF and receiving treatment with a triple of prednisolone, azathioprine, and acetylcysteine compared to single therapy with pirfenidone

	Triple therapy		Pirfendione		P value	
	Before	**After**	**Before**	**After**	**Before**	**After**
Female/Male	22/24	16/9	28/17	20/20	0.2	0.3
Age (year)	70±12	77±13	74±14	69±13	0.71	0.68
Improvement		22 (49%)		36 (78%)		
Incomplete improvement		3 (6%)		4 (8%)		0.004
Death		20 (45%)		6 (14%)		
Death rate (%Death/year)		44±11		11±13		0.06
Death age (year)		77±15		78±9		0.6
Survey (month)		30±18		13±6		0.001

Table 2. Frequency related to death and recovery rate by each year

		2016 Percent (n)	2017 Percent (n)	2018 Percent (n)	2019 Percent (n)	2020 Percent (n)
Total	Recovery	11	14	16	14	10
	Death	12	8	0	5	1
Recovery rate	Pirfenidone	-	-	1 (16)	0.74 (14)	0.91 (10)
	Triple-drug	0.48(11)	0.64(14)	-	-	-
Death rate	Pirfenidone	-	-	0	0.26(5)	0.09(1)
	Triple-drug	0.52(12)	0.36 (8)	-	-	-

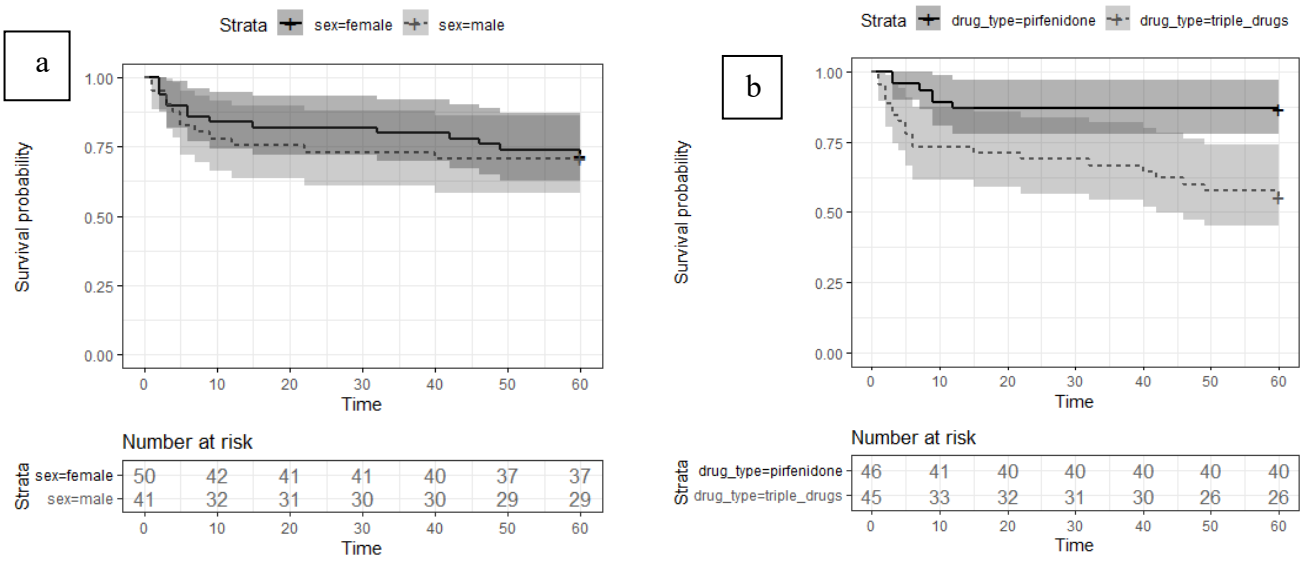

Figure 2. (a) The probability of survival rate based on gender; (b)drug type

DISCUSSION

This study showed that Pirfenidone is more effective in increasing the survival rate of patients with IPF compared to the previous treatment which consisted of prednisolone, azathioprine, and N-acetyl cysteine. Age and gender were not significant factors in the process of increasing patient survival.

In vitro studies have revealed that Pirfenidone exerts anti-inflammatory effects by suppressing TNF-α, interleukin-6 (IL6), IL-12, and IL-8. Pirfenidone's anti-fibrotic activity is believed to result principally by decreasing the synthesis and accumulation of collagen in lung tissue, downregulating the pulmonary growth factor transforming growth factor-β1, and preventing the expression of intracellular adhesion molecule-1 which is considered to play an important role in fibrosis by communicating with fibroblasts and lymphocytes (14). A study by Raghu et al. (7) found that the number of deaths in the triple-drug group was high and did not have much effect on increasing the survival of patients (p-value=0.01). In this double-blind clinical trial study, in contrast to our study, patients in the triple-drug group reported at least one complication with these drugs. Since our study was retrospective, we were not able to evaluate the precise drug side effects.

Hui Huang et al. studied the HRCT findings and categorized them as definite or probable UIP patterns. They found that Pirfenidone had a better effect on the recovery process of patients than placebo (p-value=0.02) (15). In this double-blind trial study, laboratory tests such as a 6-minute walk test, urine analysis, and arterial blood gas test were also evaluated from the patients (15). Hashemi Sadri et al. (2), demonstrated that the mean age of men and women is not significantly different (similar to this study). In this study, the mean age at the time of IPF diagnosis was 56.6 years compared to 76.03 years in the present study (not similar to this study) (2). This discrepancy could be attributed to the fact that the age range in our study was between 18 and 94 years, but in Hashemi Sadri's study it was between 9 and 90 years (2). This low mean age indicates the occurrence of IPF at a young age.

Due to the COVID-19 pandemic, there has been a noticeable rise in cases of organizing pneumonia, leading to late-stage fibrosis. Several subjects who were unresponsive to corticosteroids were observed. Many

physicians tried to use Pirfenidone to suppress the progression of fibrosis in these subjects.

There is a shortage of clinical studies on the effects of triple therapy in current literature because of the higher mortality rates, as reported by the IPFCR network. In this regard, further studies about triple therapy were stopped. As a result, the decision regarding the potential risks associated with this treatment was not strong enough to prevent its use, even in cases where there were serious side effects related to anti-fibrotic. This study used the remaining data about the effect of triple therapy, before the complete removal of triple therapy, and compared it with Pirfenidone.

We believe that this study can confirm, the current knowledge, about the potential effect of triple therapy if anti-fibrotics were not tolerated. Based on the findings of the current study, which indicated a higher risk of mortality in the early stages of triple therapy, it is advised that patients who experience intolerance to anti-fibrotic medication or accidental use of triple therapy should consider lung transplantation as a potential treatment option.

One major limitation of our study was its retrospective design. Gathering data from the system proved challenging due to some inaccuracies in the recorded data or patients' inability to recall certain information.

CONCLUSION

Based on the studies conducted and the results obtained from our study, Pirfenidone has been found to have a more positive impact on life expectancy. This indicates that patients suffering from IPF can use this drug with greater confidence. It is suggested that triple therapy may be used for a brief period if drugs are not available in certain regions, or for a longer period if lung transplantation is not an option.

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Conflict of Interest

The authors declare that there is no conflict of interest in this study.

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