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The Effect of Pyrifenidone on Idiopathic Pulmonary Fibrosis

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Abstract:

System evaluation of pyrifenidone on idiopathic pulmonary fibrosis (IPF). From January 2018 and December 2019, 96 IPF patients were selected and divided into three groups: group A, only pyrifenidone used; group B, only acetylcysteine used; group C, pyrifenidone combined with acetylcysteine used. Meanwhile according to clinical features divided into mild-to-moderate IPF group and severe IPF group. And clinical curative effect, pulmonary function, HRCT score and adverse reactions were compared. Clinical curative effect, FEV1, FVC, DLCO, HRCT score were statistically significant different among three groups (P<0.05). Within mild-to-moderate group, group C was better than that of group A, group A was better than that of group B (P<0.05); Within severe group, group A and group C showed no statistical difference (P>0.05), but both were better than that of group B (P<0.05). Within mild-to-moderate group, adverse reactions had no statistical difference among three groups (P>0.05); within severe group, group C had the most adverse reactions. This experiment shows that: to mild-to-moderate patients, pyrifenidone combined with acetylcysteineis recommended overlooks the ketone with acetylcysteine therapy; to severe patients, pyrifenidone only is enough.

Keywords*: Data analysis, Fuzzy, CAD.*

I. INTRODUCTION

Idiopathic pulmonary fibrosis (IPF) is a common type of idiopathic interstitial pneumonia. The etiology is unclear, and the chronic progressive pulmonary disease with progressive dyspnea and respiratory function deterioration is unclear. The final stage of the disease is usually died of respiratory failure. The 5-year survival rate is only 20%. At present, it is considered that the imbalance of oxidation/oxidation plays an important role in the pathogenesis of idiopathic pulmonary fibrosis. Oxidative stress leads to the over-expression of Pro fibrogenic cytokines and the up regulation of pulmonary cathepsin, which leads to the deposition of extracellular matrix and pulmonary fibrosis. Pirfenidone (PFD) was listed as a qualified recommended drug in 2015. It has anti-inflammatory, anti fibrosis and anti-oxidation effects. It has been proved to have some effect on delaying the progress of fibrosis in phase III clinical trials [1]. The indications of pifenicone are light and moderate idiopathic pulmonary fibrosis patients. However, there are still some controversies on how to apply the drug to patients with severe idiopathic pulmonary fibrosis. There are still some controversies on the effect of single use or combination

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of other drugs. Based on this, the study systematically evaluated the effect of pifenicone on the treatment of idiopathic pulmonary fibrosis patients by taking 96 patients with idiopathic pulmonary fibrosis in our hospital as the research object, in order to provide reference for the clinical application of pifenicone in the treatment of idiopathic pulmonary fibrosis.

II. DATA AND METHODS

2.1 Case Selection

From January 2018 to December 2019, 96 patients with idiopathic pulmonary fibrosis in our hospital were selected as the research objects, including 48 males and 48 females. Inclusion criteria: (1) in accordance with the diagnostic criteria of "Chinese expert consensus on diagnosis and treatment of idiopathic pulmonary fibrosis (2016)" [2,3]; (2) Patients with the age of 18-75 years old; (3) Patients with clear consciousness, good cognitive function, can fully understand the content of this study, agree to participate in this study and sign the informed consent; (4) The treatment and follow-up compliance were good. Exclusion criteria: (1) patients who were intolerant to the drugs used in this study (such as pirfenidone and acetylcysteine; (2) Patients who took prednisone or other glucocorticoids more than 10 mg/D or used immunosuppressants, interferon and other anti fibrosis drugs one month before participating in this study; (3) Patients with severe pulmonary infection or malignant tumor; (4) Patients with severe systemic diseases or organ dysfunction; (5) Pregnant or lactating women.

Patients were randomly divided into three groups: group A was treated with pirfenidone alone, group B was treated with acetylcysteine alone, and group C was treated with pirfenidone combined with acetylcysteine, with 32 cases in each group. There was no significant difference in clinical data among the three groups ($P > 0.05$), as shown in table 1. This study was approved by the medical ethics committee of our college.

TABLE I. Comparison of clinical data among the three groups

	A group	B group	C group	F/χ^2 value	P value
Cases	32	32	32	0.105	0.802
Mild to moderate / severe	15/17	14/18	16/16	0.208	0.231
Age (years)	58.23±4.56	57.49±4.29	58.01±4.98	-0.234	0.306
Sex	17/15	15/17	16/16	1.234	0.109

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composition (male / female)					
Course of disease (months)	14.76±3.41	16.16±4.02	14.86±3.58	0.875	0.206
Occupational exposure history [n (%)	5(15.63)	6(18.75)	5(15.63)	-0.902	0.409
Smoking [n (%)	20(62.5)	18(56.25)	21(66.63)	0.287	0.542
Complications [n (%)]	24(75)	23(71.88)	26(81.25)	0.431	0.641

2.2 Therapeutic Method

All patients were given symptomatic support treatment according to the patient's condition after admission. On this basis, group A was given oral pirpiridone (Beijing Contini Pharmaceutical Co., Ltd., Chinese medicine H20133376100mg/ tablet) for 24 weeks, the initial dose was 200mg each time, adjusted to 400mg every 2 weeks, adjusted to 600mg every time after 3 weeks, 3 times a day, orally. The patients in group B were treated with acetaminophen effervescent tablets (Zhejiang Jinhua Kangenbei biopharmaceutical Co., Ltd., Guoyao Zhunzi h20057334600 mg / tablet), 1 tablet/time, 3 times/day; The patients in group C were treated the same with group B on the basis of group A.

At the same time, according to the literature [4], patients in each group were divided into mild to moderate and severe groups. Mild to moderate standard: cough frequency ≤ 20 times/D, light physical labor, asthma, fine moist wheezing when deep inspiration, X-ray showed nodules and reticular shadows in both middle and lower lung fields; Severe standard: cough more than 20 times/D, wheezing and calm breathing at rest, moist rales can be heard, X-ray showed that bilateral lungs were covered with grid, nodular shadow or honeycomb lung like changes1.3 Evaluation index. (1) Comparison of clinical efficacy: according to the improvement of clinical symptoms and CT examination results as the judgment condition. Effective: the clinical symptoms of the patients were basically disappeared or improved, and CT results showed that the influence of pulmonary fibrosis was improved; Invalid: the clinical symptoms and CT results of the patients were not significantly improved or aggravated. Effective rate=effective cases/total cases ×100%; (2) Pulmonary function: FEV1, FVC and DLCO were measured before and after treatment; (3) HRCT score of pulmonary fibrosis: referring to literature [5], HRCT of selected patients was divided into three lung regions, namely upper lung region, middle lung region and lower lung region, with aortic

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arch and right lower pulmonary vein as the boundary. The imaging features of each lung area were calculated. According to the percentage of lesion area in the total area of the selected slice, 0: no abnormal change; 1: cumulative range < 5%; 2 points: 6%-25%; 3 points: 26%-50%; 4 points: 51%-75%; 5 points: 76%-100%. According to the routine, the upper edge of aortic arch, tracheal carina and 1cm level above right diaphragm were selected as the representative levels for evaluation. The pulmonary fibrosis score was the sum of the scores of all the pathological changes in all the pre-selected levels of the six lung regions; (4) Adverse reactions: the occurrence, severity and treatment measures of adverse reactions were recorded.

2.4 Statistical Methods

SPSS 23.0 statistical software package was used to analyze the data ± Standard deviation ($\bar{x} \pm s$) F test was used to compare the three groups, t test was used to compare the two groups and the same group before and after treatment; The counting data were compared between groups $\chi 2$ inspection. $P<0.05$ was statistically significant.

III. RESULTS

3.1 Comparison of Clinical Efficacy

There was significant difference among the three groups ($P<0.05$). The effective rate of group C was higher than that of group A ($t=36.781$, $P<0.05$); The effective rate of group A was also higher than that of group B ($t=34.652$, $P<0.05$). There was significant difference among the three groups ($P<0.05$). There was no significant difference between group C and group A ($t=0.982$, $P>0.05$). But group C and group A were higher than group B ($t^1=29.462$, $P<0.05$); $t^2=21.212$, $P<0.05$). See Table 2 for details.

TABLE II. Comparison of clinical efficacy of three groups of patients

		Effectiveness	Invalidity	Efficiency (%)
Mild to moderate group	A group (15)	10	5	66.67
	B group (14)	6	8	42.86
	C group (16)	14	2	87.50
	χ^2 value			6.452
	P value			0.022
Severe group	A group (17)	11	6	64.71
	B group (18)	8	10	44.44

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C group (16)	10	6	62.5
χ^2 value			34.322
P value			0.001

3.2 Comparison of Lung Function

FEV1, FVC and DLCO were significantly different in the light and moderate group (P < 0.05). FEV1, FVC and DLCO in group C were higher than those in group A, and the difference was statistically significant (t1=14.232, P<0.05; t2=21.462, P<0.05; t3=20.651, P<0.05); FEV1, FVC and DLCO in group A were also higher than those in group B, and the difference was statistically significant (t1=18.022, P < 0.05; t2=24.098, P<0.05; t3=33.871, P<0.05). FEV1, FVC and DLCO were significantly different in the three groups (P<0.05). There was no significant difference between group C and group A (t1=2.312, P>0.05; t2=0.834, P>0.05; t3=2.983, P>0.05). But FEV1, FVC and DLCO in group C were higher than those in group B, and the difference was statistically significant (t1=18.762, P<0.05; t2=19.351, P<0.05; t3=22.381, P<0.05). Group B: t1=17.791, P<0.05; t2=21.623, P<0.05; t3=29.087, P<0.05). See Table 3 for details.

TABLE III. Comparison of FEV1, FVC and DLCO between the three groups

		FEV1 (L)		**FVC (L)**		**DLCO (%)**	
		Before treatment	**After treatment**	**Before treatment**	**After treatment**	**Before treatment**	**After treatment**
Mild to moderate group	A group (15)	1.68±0.32	2.11±0.35	1.91±0.41	2.69±0.34	60.59±3.35	75.24±6.33
	B group (14)	1.65±0.35	1.73±0.22	1.92±0.38	2.44±0.36	60.61±3.32	68.83±6.31
	C group (16)	1.69±0.37	2.74±0.36	1.89±0.39	2.92±0.43	2.58±0.37	77.46±0.46
	F value	3.509	18.346	2.509	9.346	0.598	19.324
	P value	0.546	0.018	0.902	0.013	0.478	0.009

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Severe group	A group (17)	1.28±0.36	1.86±0.42	1.72±0.46	2.35±0.42	60.34±3.37	76.13±6.29
	B group (18)	1.21±0.41	1.68±0.26	1.71±0.46	2.12±0.46	60.31±3.35	67.78±5.42
	C group (16)	1.29±0.47	1.84±0.39	1.68±0.47	2.32±0.41	60.28±3.32	76.04±5.38
	F value	4.201	21.432	2.091	12.362	1.201	31.235
	P value	0.408	0.009	0.306	0.011	0.362	0.002

3.3 Comparison of HRCT Scores

There was significant difference in HRCT scores among the three groups (P<0.05). The HRCT score of group C was higher than that of group A (t=17.251, P<0.05); The HRCT score of group A was also higher than that of group B (t=12.761, P<0.05).

HRCT scores of the three groups in the severe group were statistically significant (P<0.05). There was no significant difference between the HRCT scores of group C and group A (t=1.291, P>0.05). But HRCT scores of group C and group A were higher than those in group B, and the difference was statistically significant (t^1=9.028, P<0.05); t^2=11.292, P<0.05). See Table 4 for details.

TABLE IV. Comparison of HRCT scores of three groups

		Before treatment	**After treatment**
Mild to moderate group	A group (15)	26.14±13.57	19.81±12.47
	B group (14)	25.98±13.28	21.46±11.99
	C group (16)	25.48±12.67	18.04±11.17
	F value	0.405	6.453

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	P value	0.876	0.043
	A group (17)	42.24±17.88	24.43±15.54
	B group (18)	43.58±18.32	29.35±16.34
Severe group	C group (16)	43.24±17，43	25.07±14.56
	F value	0.309	17.467
	P value	0.784	0.006

3.4 Comparison of Adverse Reactions

There was no significant difference in the number of adverse reactions among the three groups (P>0.05). The number of adverse reactions in group C was higher than that in group A and group B (t1=12.021, P<0.05; t2=18.291, P<0.05).

In patients with gastrointestinal reactions, by changing the medication time to intrameal or using anti acid drugs, the symptoms were significantly improved or disappeared; Photosensitive reaction, it is recommended that patients do a good job in the sun protection work; Patients with elevated liver enzymes should be treated with liver protective drugs. All patients with adverse reactions through symptomatic treatment can be tolerated, no patients quit. See Table 5 for details.

TABLE V. Comparison of adverse reactions among the three groups

		Gastrointestinal reaction	**Photoallergy and rash**	**Elevated liver enzymes**	**Total**	**χ^2 value**	**P value**
Mild to moderate group	A group (15)	5	2	1	8		
	B group (14)	4	2	2	8	0.908	0.203
	C group (16)	4	3	1	8		
Severe group	A group (17)	8	3	3	14		
	B group (18)	9	3	3	15	21.892	0.008
	C group (16)	11	2	5	18		

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IV DISCUSSIONS

Pifenicone is the first drug that has been proved to have certain effect on idiopathic pulmonary fibrosis through clinical trials. Relevant study [6] shows that pifenicone can effectively improve FEV1 and FVC in patients with idiopathic pulmonary fibrosis. Similar conclusions can be drawn in this study. It is found that FEV1, FVC and DLCO have been improved to different degrees after treatment with pifenidone, the mechanism is that PFP can down regulate fibroblast growth factor, tumor necrosis factor, platelet derived growth factor and transforming growth factor ß. The production and expression of one of them can reduce the proliferation of fibroblasts and extracellular matrix deposition, thus achieving the aim of anti fibrosis [7].

The degree of lung function damage of idiopathic pulmonary fibrosis is related to HRCT signs. The bronchointerstitial, interlobular septum, the thickening of the interlobular stroma and the inflammatory exudation of the surrounding tissues were diffuse and distributed in HRCT. When the pulmonary fibrosis was reversed, the area and degree of the frosted glass shadow and the mesh shadow were gradually reduced on HRCT. The results showed that HRCT score could be decreased and there were statistical differences between the two groups. Acetylcysteine is also an antioxidant, by blocking NF-κB signal transduction pathway, free radical scavenging and leukocyte aggregation were inhibited to inhibit inflammatory response and alleviate the damage of inflammatory response to lung tissue [8]. However, the effect of levyrcysteine alone is not good, so it is not recommended to treat IPF alone, especially for severe IPF.

In this study, it was found that the combination of pifenicone or pifenicone alone and acetylcysteine was superior to that of the patients in the single acetylcysteine group in clinical efficacy, lung function index (FEV1, FVC and DLCO) and HRCT score improvement index. Among them, in the light and moderate groups, the use of PFP and acetylcysteine was better than that of the patients in the single group in clinical efficacy, lung function index (FEV1, FVC and DLCO) and HRCT score improvement index, but in the severe group, there was no significant difference in these three aspects. There are many reports on the treatment of idiopathic pulmonary fibrosis with pifenicone and acetylcysteine, but the results are different. Some studies have suggested that [9], for patients with idiopathic pulmonary fibrosis in the middle and late stage, the treatment of pifenicone and acetylcysteine is more obvious than that of single use. Some studies also believe that [10-11], the combination of pifenicone and acetylcysteine can not improve the tolerance of patients with idiopathic pulmonary fibrosis to pifenicone, and it is not even as good as the treatment with pifenone alone in clinical efficacy. The results are similar to this.

The common adverse reactions of pifenicone and acetylcysteine include gastrointestinal adverse reactions, skin photoallergy and liver enzyme rise, but the degree is usually light, the patients can tolerate it, and the adverse reactions can be eliminated after treatment. In light and moderate patients, the adverse reactions of the two groups were similar to those of the combination of pifenicone and acetylcysteine, so the combination of the two did not increase the adverse reactions. However, in the severe patients, the adverse reactions of pifenicone combined with acetylcysteine are much higher than that of the single use of

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pifenone. Therefore, in the case of close curative effect, there are more adverse reactions in combination. It is suggested to use pifenone alone.

In conclusion, it is suggested that the patients with idiopathic pulmonary fibrosis should be classified first. For light and moderate patients, it is suggested to use pifenicone and acetylcysteine to improve the pulmonary function index and symptoms of pulmonary fibrosis; For severe patients, only pifenicone was used; Pifenicone has curative effect on IPF in light, moderate and severe patients.

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