Am J Transl Res 2022;14(8):5660-5668
www.ajtr.org /ISSN:1943-8141/AJTR0143966

Original Article

Clinical efficacy and quality of life effect of acetylcysteine plus pirfenidone in patients with pulmonary fibrosis

Rong Zhang[1*], Zhanshuai Song[1*], Yan Guan[2], Juan Zhang[1], Jianfang Zou[1], Yingxin Sun[3], Hua Shao[1]

[1]*Occupational Diseases Branch, Shandong Academy of Occupational Health and Occupational Medicine, Shandong First Medical University & Shandong Academy of Medical Sciences, Jinan 250000, P. R. China;* [2]*Department of Internal Medicine, Shandong Tumor Hospital, Jinan 250000, P. R. China;* [3]*Laboratory of Traditional Chinese Medicine, Shandong University of Traditional Chinese Medicine, Jinan 250000, P. R. China.* [*]*Equal contributors.*

Received May 6, 2022; Accepted July 14, 2022; Epub August 15, 2022; Published August 30, 2022

Abstract: Objective: To study the clinical efficacy of acetylcysteine combined with pirfenidone in patients with pulmonary fibrosis (PF). Methods: A total of 114 PF patients admitted from January 2018 to January 2019 were retrospectively analyzed. Among them, 64 patients treated with acetylcysteine combined with pirfenidone were classified into a research group, and the other 50 treated with acetylcysteine combined with budesonide were assigned into a control group. The clinical efficacy and total effectiveness rate of the two groups were compared after 6 months of therapy. The quality of life (QoL) in the two groups before and after treatment was evaluatedusing Asthma Therapy Assessment Questionnaire for idiopathic pulmonary fibrosis patients (ATAQ-IPF). The 2-year survival of the two groups was compared. Additionally, the incidence of adverse reactions was compared between the two groups. The changes in forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), inflammatory factors, and PF markers were compared between the two groups before and after therapy. Results: There were no significant differences in clinical efficacy or total effectiveness rate (all $P > 0.05$), serum IL-4, INFγ or IL-6 expression (all $P > 0.05$), as well as FEV1 and FVC levels (all $P > 0.05$) after therapy between two groups. After therapy, the research group showed significantly lower PCIII and HA levels, lower ATAQ-IPF scores, and lower total incidence of adverse reactions than the control group (all $P < 0.05$). In addition, a higher 2-year survival rate was observed in the research group than in the control group ($P=0.025$). Conclusion: Acetylcysteine combined with pirfenidone can reduce adverse reactions and improve the QoL and survival time of patients.

Keywords: Acetylcysteine, pifenidone, budesonide, pulmonary fibrosis, prognosis

Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, and fatal lung disease characterized by irreversible loss of lung function [1]. Its prevalence is gradually increasing. The pathogenesis of IPF is the remodeling of lung tissues caused by alveolar epithelial dysfunction after repeated injury [2]. The persistent injury of alveolar cells will lead to the activation of α-smooth muscle actin in myofibroblasts, and the activated alveolar epithelial cells will release fibroblast growth factor, promote the migration and differentiation of myofibroblasts, and lead to excessive deposition of extracellular matrix and the destruction of lung structure, trigginga decrease in lung function and body resistance [3, 4]. In addition, the replacement of normal lung tissue by extracellular matrix may lead to destruction of alveolar structure, decrease in lung compliance, interruption of gas exchange, respiratory failure, and even death [5]. The prognosis of IPF varies from person to person, and the median survival time of IPF patients is about 3-5 years [6].

The incidence of IPF in North America and Europe is about 3-9 cases/100,000 people each year, which is higher than that of South America and East Asia (less than 4 cases/100,000 people each year) [7]. Reportedly, in the United States, the prevalence of IPF is

10-60 cases/100,000 people. In a study in 2011, the incidence of IPF among adults over 65 years old was 494 cases/100,000 people, which is twice that recorded 10 years ago [8]. The increasing hospitalization rate and mortality triggered by IPF also suggest a growing burden from the disease [9]. In spite of a short clinically stable period, the continuous progress of IPF is inevitable, and its prognosis is unfavorable, with 5-year survival similar to that of several cancers [10]. Therefore, it is urgent to select an effective treatment regimen to improve the clinical efficacy and.

Acetylcysteine possesses a strong mucolytic effect, and the contained sulfhydryl group (-SH) can break the disulfide bond (-S-S) of the glycoprotein polypeptide chain in sputum, reducing phlegm viscosity and liquefying it, thus making sputum easier to be coughed up and improving patients' lung function [11, 12]. Pifenidone, a small molecule compound popularin recent years, has a curative effect in resisting fibrosis of heart, liver and kidney, which can achieve the purposes of anti-inflammation, anti-fibrosis and anti-oxidation by adjusting transforming growth factor and fibroblasts [13]. Budesonide is an effective inhaled glucocorticoid, with strong local anti-inflammatory effect, strong fat solubility, strong affinity for its receptor, short half-life, quick inactivation *in vivo*, which is adopted through local atomization and has no accumulation because of rapid metabolism [14]. At present, acetylcysteine combined with pirfenidone and acetylcysteine combined with budesonide are both effective in treating IPF in clinical practice [15]. However, whether the two combined regimens have any difference in therapeutic effect is still controversial.

The present study retrospectively analyzed the clinical efficacy of the two regimens in in IPF patients, with the goal of providing a reference for the selection of treatment regimen.

Methods and data

Clinical data

Clinical data of 114 PF patients admitted from January 2018 to January 2019 were retrospectively analyzed. Among them, 64 patients were treated with acetylcysteine combined with pirfenidone as the research group, and the other 50 were treated with acetylcysteine combined with budesonide as the control group. This study was approved by the Medical Ethics Committee of our hospital, with ethnical approval number of SDZFY-EC-2018-09.

Inclusion and exclusion criteria

Inclusion criteria: Adults aged 18-75 years old who met the IPF diagnostic guidelines published by Chinese Medical Association; patients whose predicted forced vital capacity (FVC) was ≥ 50% of the predicted value and the diffusing capacity of the lung for carbon monoxide (DLCO) was ≥ 40%; and patients whose 6-minute walking distance (6 MWD) was ≥ 150 m.

Exclusion criteria: Patients who showed evidence of active infection within 1 month before screening; patients with severe obstructive respiratory dysfunction (FEV1/FVC ratio < 70% and FEV1 ratio < 50% of the expected value after bronchodilator inhaling); patients with oxygen supplementation demand at rest (to maintain oxygen saturation > 88%); patients with a history of myocardial infarction within 1 year before screening; patients with heart failure or arrhythmia requiring drug treatment within the first 3 years before screening; pregnant or lactating women; patients who took part in other IPF clinical trials; patients who smoked within 4 weeks after screening; patients diagnosed with other interstitial lung diseases by high-resolution CT/lung biopsy; patients with incomplete clinical data; or patients unable to complete this treatment.

Treatment regimen

The control group was treated with acetylcysteine combined with budesonide: Each patient was required to inhale budesonide 4 times a day, 2 sprays each time (200 μg/spray, 100 sprays a bottle) and also required to take acetylcysteine orally 3 times a day (Zambon Group, Italy, H20090620), 600 mg each time. The treatment lasted for 6 months.

The research group was treated with acetylcysteine combined with pirfenidone: Each patient was given acetylcysteine and pirfenidone (Beijing Continent Pharmaceuticals Co., Ltd., H20133376). The patient was given 600 mg acetylcysteine each time, 3 times a day, and 200 mg pirfenidone each time, 3 times a day. After two weeks of continuous administration, the dose of pirfenidone was adjusted to 400 mg, and after three weeks, it was adjusted to

Table 1. Comparison of baseline data

Items	Control group (n=50)	Research group (n=64)	χ^2	*P* value
Age			0.193	0.660
≥ 65 years old	34	41		
< 65 years old	16	23		
Gender			0.837	0.360
Male	27	40		
Female	23	24		
BMI			2.234	0.135
≥ 23 kg/m^2	32	32		
< 23 kg/m^2	18	32		
Course of disease			1.105	0.293
≥ 3 years	33	48		
< 3 years	17	16		
Past medical history				
Hypertension	22	31	1.753	0.185
Diabetes mellitus	18	24	0.027	0.869
Smoking history			0.373	0.542
Yes	34	40		
No	16	24		

Note: Body Mass Index (BMI).

600 mg, three times a day. The treatment also lasted for 6 months.

Observation indices

Serum interleukin (Il)-4 (PI618, Beyotime, Shanghai, China), interferon-γ (INF-γ, PI511, Beyotime, Shanghai, China), IL-6 (PI330, Beyotime, Shanghai, China), type III procollagen (PCIII, LZ-H93374, Shanghai Razybio Technology Co., Ltd. Shanghai, China) and hyaluronic acid (HA, LZ-E99896, Shanghai Razybio Technology Co., Ltd. Shanghai, China) were quantified through ELISA before and after therapy.

Outcome measures

Primary outcome measures: The clinical efficacy of the two groups was compared 6 months after therapy. Clinical effect: remarkably effective: symptoms such as cough and dyspnea disappeared without cyanosis and high-pitched popping sound in both lungs after therapy. Effective: With occasional paroxysmal cough, slight dyspnea in a quiet state, cyanosis after activity, and high-pitched popping sound at the bottom of both lungs. Ineffective: With frequent cough symptoms, obvious dyspnea in a quiet state, and cyanosis and high-pitched popping sound in both lungs at rest. Total effective rate = (remarkably effective cases + effective cases)/total cases ×100%. The quality of life (QoL) of IPF patients before and after therapy was assessed by Asthma Therapy Assessment Questionnaire for idiopathic pulmonary fibrosis patients (ATAQ-IPF) [16], which covered 13 dimensions, including 74 items and each item with a score of 1-5 points. A higher score indicates worse QoL. The Kaplan Meier (KM) survival curve was adopted to analyze the 2-year survival rate of the two groups of patients, with the death of the patient as the end event.

Secondary outcome measures: The baseline data of the two groups were compared. In addition, the incidence of adverse reactions was compared between the two groups. The changes in forced expiratory volume in 1 second (FEV1), FVC, inflammatory factors and PF markers were compared between the two groups before and after therapy.

Statistical analyses

GraphPad 8 was used for data analysis and figure rendering. Measured data were expressed as mean ± SD, and the inter-group comparison was conducted using independent sample T-test while intra-group analysis was conducted using paired T-test. Counted data (%) were analyzed using the chi-square test, and presented as χ^2. The difference in 2-year survival was analyzed by the Kaplan-Meier test. Cox regression was conducted to analyze factors affecting patients' prognosis. $P < 0.05$ implied a significant difference.

Results

Baseline data

According to comparison of the two groups in baseline data, there were no significant differences between the two groups in age, gender, body mass index (BMI), course of disease, past medical history or smoking history (all $P > 0.05$, **Table 1**).

Table 2. Clinical efficacy

Group	Markedly effective	Effective	Ineffective	Total effective rate
Control group (n=50)	15	27	8	42 (84.00%)
Research group (n=64)	26	24	14	50 (83.33%)
χ^2 value				0.622
P value				0.430

Table 3. Changes of inflammatory factors before and after therapy

Group	IL-4 (ng/L)		INFγ (ng/L)		IL-6 (pg/mL)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group (n=50)	283.20±20.47	358.85±24.96*	203.81±20.48	156.83±13.53*	184.27±17.56	111.31±13.56*
Research group (n=64)	279.99±24.55	355.60±19.84*	204.75±18.21	154.26±16.20*	179.02±20.12	108.42±13.87*
T value	0.743	0.775	0.795	0.369	1.459	1.115
P-value	0.459	0.440	0.259	0.902	0.147	0.267

Note: *P < 0.05 vs. Before therapy, Serum interleukin (Il), interferon-γ (INF-γ).

Table 4. Comparison of pulmonary function before and after therapy

Group	FEV1 (L)		FVC (L)	
	Before treatment	After treatment	Before treatment	After treatment
Control group (n=50)	1.54±0.25	2.49±0.19*	2.55±0.16	3.01±0.32*
Research group (n=64)	1.59±0.19	2.47±0.18*	2.52±0.20	2.92±0.30*
T value	1.028	0.788	0.799	0.136
P value	0.306	0.432	0.426	0.150

Note: *P < 0.05 vs. Before therapy, forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC).

Therapeutic effect

According to comparison of clinical efficacy between the two groups after therapy, the clinical efficacy of the two groups was not significantly different (P > 0.05, **Table 2**). In addition, the total effective rate of the two groups was similar (P > 0.05).

Changes in inflammatory factors before and after therapy

Serum IL-4, INFγ, and IL-6 in the two groups were quantified. According to the results, after therapy, serum IL-4 in the two groups increased significantly, while serum INFγ and IL-6 decreased significantly (all P < 0.05), but there were no significant differences between the two groups (all P > 0.05, **Table 3**).

Influence on lung function before and after therapy

After therapy, FEV1 and FVC of the two groups increased greatly (all P < 0.05), but no difference was observed in FEV1 and FVC levels between the two groups after therapy (all P > 0.05, **Table 4**).

Changes in PF markers before and after therapy

PCIII and HA levels before and after therapy of the two groups were compared. According to the results, after therapy, serum PCIII and HA levels of the two groups decreased significantly (P < 0.05). Further analysis revealed significantly lower PCIII and HA levels in the research group than those in the control group after therapy (all P < 0.05, **Table 5**).

Comparison of QoL

ATAQ-IPF was used to evaluate and compare the QoL of patients before and after therapy. After therapy, the research group got significantly lower ATAQ-IPF scores than the control group (P < 0.05, **Figure 1**), and ATAQ-IPF score of both groups decreased after therapy P < 0.05).

Table 5. Comparison of PF markers in patients before and after therapy

Group	PCIII (μg/L)		HA (μg/L)	
	Before treatment	After treatment	Before treatment	After treatment
Control group (n=50)	103.47±31.50	84.75±21.80*	154.96±33.68	123.41±27.75*
Research group (n=64)	92.54±35.54	70.73±20.24*	165.25±.38.97	92.24±25.16*
T value	1.711	3.548	1.483	6.271
P value	0.089	0.001	0.141	< 0.001

Note: *P < 0.05 vs. Before therapy, type III procollagen (PCIII) and hyaluronic acid (HA).

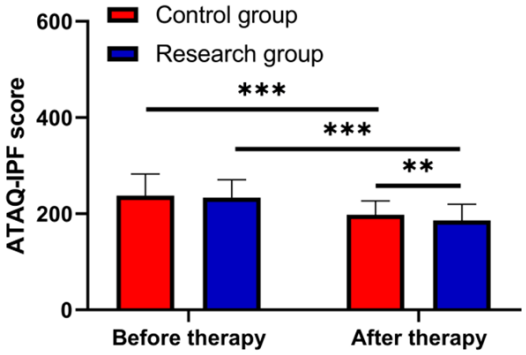

Figure 1. Changes in ATAQ-IPF score in patients after therapy. Notes: **P < 0.01, ***P < 0.001, a tool to assess quality of life in idiopathic pulmonary fibrosis (ATAQ-IPF).

Comparison of adverse reactions

According to comparison of adverse reactions between the two groups during therapy, no significant difference was found in the incidence of individual adverse reaction (P > 0.05), but a significantly higher total incidence of adverse reactions was found in the control group than in the research group (P < 0.05, **Table 6**).

Analysis of prognostic factors

The patients were followed up for 2 years. Among them, 28 patients died with an overall 2-year survival rate of 75.43%. The clinical data of patients were collected. Univariate Cox regression analysis showed that age, course of disease, treatment regimen, and IL-4 were tfactors impacting the prognosis of patients (**Figure 2**, P < 0.05). Further multivariate Cox regression analysis showed that the course of disease, treatment regimen, and IL-4 were independent factors affecting the prognosis of patients (**Table 7**, P < 0.05).

Discussion

Acetylcysteine is an important antioxidant drug that can strongly block NF-κB signal transduction by inhibiting the activity of INF-γ, thus inhibiting the inflammatory reaction of patients [17]. In addition, acetylcysteine plays a crucial role in scavenging free radicals, reducing oxygen free radicals, inhibiting the excessive release of reactive oxygen species by inflammatory cells, and enabling cells in a hypoxic-ischemic state to acquire antioxidant capacity and weaken cell damage [18]. However, long-term clinical practice has revealed that the effect of single drug therapy on IPF is not ideal, so it is suggested that combined drug therapy be used clinically. Budesonide is a macrolide antibiotic commonly used in clinical practice. It binds to the 50 S ribosome subunit of sensitive microorganisms, interferes with its protein synthesis, and thus possess a good killing or inhibiting effect on many pathogenic bacteria [19]. Pifenidone is a new type of cytokine inhibitor, which can inhibit the growth of fibroblasts by reducing excessive deposition of extracellular matrix and proliferation of fibroblasts [20, 21]. Currently, acetylcysteine combined with pirfenidone or budesonide are both frequently adopted clinically. However, both of them have the same effect on alleviating the disease condition of IPF patients; however, there had been no relevant research and analysis on whether there is any difference in curative effect between the two regimens. In the present study, both regimens delivered high clinical efficacy for IPF patients, and ameliorated the inflammatory response and improved lung function in patients, but no difference was found between the two regimens in terms of clinical efficacy, serum inflammatory factors or lung function. The results reveal that the two regimens can effectively treat IPF. However, in further comparisons, significantly higher levels of serum PCIII and HA levels were found in the research group than in the control group after therapy. PCIII and HA are crucial indices for the diagnosis of PF. PCIII mainly reflects the synthesis of type III collagen in the liver, and its serum con-

Table 6. Comparison of adverse reactions

Group	Metabolic disturbance	Nausea	Dyspepsia	Poor appetite	Hypoglycemia	Total incidence rate
Control group (n=50)	4	3	3	3	4	17 (34.00)
Research group (n=64)	1	1	2	1	2	8 (12.50)
χ^2 value						7.579
P value						0.006

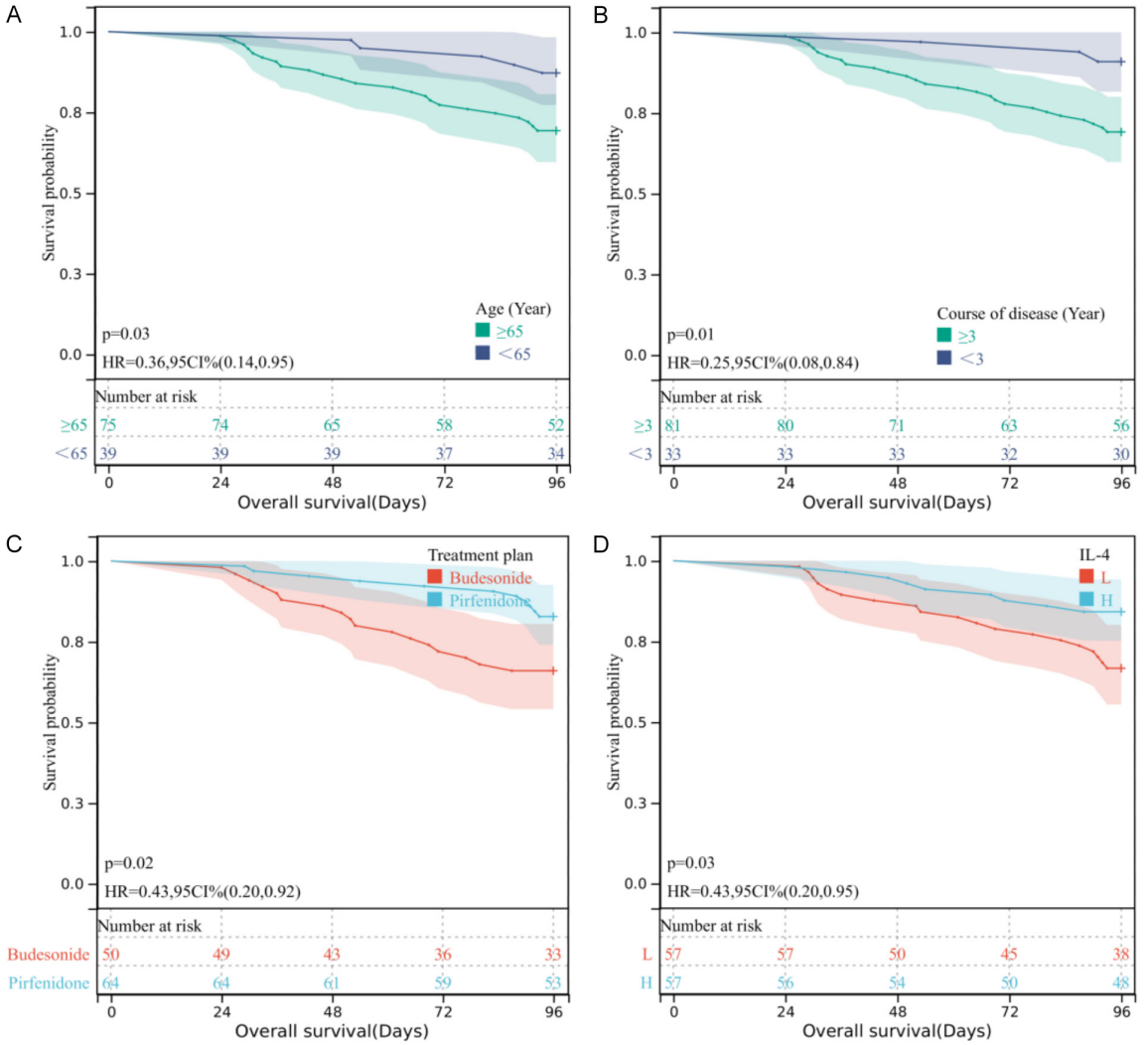

Figure 2. Univariate analysis and meaningful indicators of patients' survival. A. Relationship between age and patients' survival. B. Relationship between the course of disease and patients' survival. C. Relationship between treatment plan and patients' survival. D. Relationship between IL-4 and patients' survival. Note: Serum interleukin (Il).

tent is closely related to the degree of hepatic fibrosis. HA, which increases in the case of PF [22], is a matrix component synthesized by interstitial cells, that can adjust protein, balance extracellular space, and can thus exert a strong effect on promoting cell repair. The results suggest that acetylcysteine combined with pirfenidone is superior to acetylcysteine combined with budesonide in alleviating PF. The main reason is that pirfenidone can effectively fight against fibrosis, slow down the continuous increase of fibroblasts and tissues, and

Table 7. Analysis of prognostic factors

Factor	Univariate Cox			Multivariate Cox		
	P value	HR	95% CI	*P* value	HR	95% CI
Age	0.040	2.755	1.047-7.250	0.083	2.386	0.893-6.372
Gender	0.289	0.670	0.319-1.405			
BMI	0.802	0.910	0.433-1.912			
Course of disease	0.024	3.963	1.196-13.131	0.015	4.459	1.341-14.822
Hypertension	0.593	1.230	0.576-2.626			
Diabetes mellitus	0.490	0.768	0.363-1.624			
Smoking history	0.688	0.856	0.401-1.828			
Treatment regimen	0.029	2.326	1.089-4.971	0.008	2.882	1.322-6.284
IL-4	0.014	0.981	0.966-0.996	0.015	0.979	0.963-0.996
INF-γ	0.411	0.992	0.972-1.012			
IL-6	0.524	0.994	0.974-1.014			
FEV1	0.289	2.550	0.452-14.399			
FVC	0.573	1.757	0.247-12.476			
PCIII	0.326	1.005	0.995-1.016			
HA	0.953	1.000	0.990-1.010			

Notes: Hazard ratio: HR; 95% Confidence Interval (95% CI); Body Mass Index (BMI); Serum interleukin (II); interferon-γ (INF-γ); forced expiratory volume in 1 second (FEV1); forced vital capacity (FVC); type III procollagen (PCIII); hyaluronic acid (HA).

reduce pulmonary fibrosis [23, 24]. Moreover, a significantly higher incidence of adverse reactions was found in the control group than in the research group. This is primarily due to the strong immunosuppressive effect of glucocorticoids. Long-term use of glucocorticoids can easily affect patients' immune function and cause metabolic disorder [25].

Finally, the QoL and 2-year survival rate of patients after therapy was analyzed. ATAQ-IPF is a QoL score specially established for IPF patients, and its effectiveness has been verified in several clinical trials [26]. In the present study, the research group had significantly lower ATAQ-IPF scores than the control group after 6 months of therapy. The prognosis analysis found that the course of disease, treatment regimen, and IL-4 were closely correlated with prognosis. The above results show that acetylcysteine combined with pirfenidone can improve the QoL of IPF patients and prolong their survival. We believe that this is mainly because pirfenidone can improve the postoperative survival time and QoL of patients by inhibiting PF. Budesonide mainly alleviates the clinical symptoms of patients, but its inhibitory effect on PF is relatively weak, which leads to differences between the two schemes in improving the survival of IPF patients.

The study has some limitations. First of all, the study did not count the patients' progression time, but only collected the patient's death times, so it was impossible to analyze whether the two regimens impacted the patients' disease-free survival time. Secondly, the sample collection time of this study was short, and only the 2-year survival of two groups of patients were analyzed, so whether there is any difference between the two drugs on patients' long-term survival still needs further exploration. Finally, as a retrospective study, there may be some bias in sample collection and result analysis, and whether this affects the results of this study remains unclear. We hope to conduct a randomized controlled study in the future, with more patient samples and longer follow-up to further improve the research conclusions.

Thus, acetylcysteine combined with pirfenidone or budesonide can both deliver high clinical efficacy for IPF patients, but compared to budesonide, acetylcysteine combined with pirfenidone can better reduce adverse reactions, improve QoL, and prolong survival time.

Disclosure of conflict of interest

None.

Address correspondence to: Zhanshuai Song and Hua Shao, Occupational Diseases Branch, Shandong Academy of Occupational Health and Occupational Medicine, Shandong First Medical University & Shandong Academy of Medical Sciences, Jinan 250000, P. R. China. E-mail: szs067@163.com (ZSS); chinashaohua5888@163.com (HS); Yingxin Sun, Laboratory of Traditional Chinese Medicine, Shandong University of Traditional Chinese Medicine, Jinan 250000, P. R. China. E-mail: zj740117@126.com

References

[1] Xaubet A, Ancochea J and Molina-Molina M. Idiopathic pulmonary fibrosis. Med Clin (Barc) 2017; 148: 170-175.

[2] Shenderov K, Collins SL, Powell JD and Horton MR. Immune dysregulation as a driver of idiopathic pulmonary fibrosis. J Clin Invest 2021; 131: e143226.

[3] Luppi F, Kalluri M, Faverio P, Kreuter M and Ferrara G. Idiopathic pulmonary fibrosis beyond the lung: understanding disease mechanisms to improve diagnosis and management. Respir Res 2021; 22: 109.

[4] Wolters PJ, Blackwell TS, Eickelberg O, Loyd JE, Kaminski N, Jenkins G, Maher TM, Molina-Molina M, Noble PW, Raghu G, Richeldi L, Schwarz MI, Selman M, Wuyts WA and Schwartz DA. Time for a change: is idiopathic pulmonary fibrosis still idiopathic and only fibrotic? Lancet Respir Med 2018; 6: 154-160.

[5] Salisbury ML and Wijsenbeek MS. Management of idiopathic pulmonary fibrosis. Clin Chest Med 2021; 42: 275-285.

[6] Lynch JP 3rd, Huynh RH, Fishbein MC, Saggar R, Belperio JA and Weigt SS. Idiopathic pulmonary fibrosis: epidemiology, clinical features, prognosis, and management. Semin Respir Crit Care Med 2016; 37: 331-357.

[7] Wakwaya Y and Brown KK. Idiopathic pulmonary fibrosis: epidemiology, diagnosis andoutcomes. Am J Med Sci 2019; 357: 359-369.

[8] Schafer SC, Funke-Chambour M and Berezowska S. [Idiopathic pulmonary fibrosis-epidemiology, causes, and clinical course]. Pathologe 2020; 41: 46-51.

[9] Richeldi L, Collard HR and Jones MG. Idiopathic pulmonary fibrosis. Lancet 2017; 389: 1941-1952.

[10] Oldham JM and Vancheri C. Rethinking idiopathic pulmonary fibrosis. Clin Chest Med 2021; 42: 263-273.

[11] Smaga I, Frankowska M and Filip M. N-acetylcysteine as a new prominent approach for treating psychiatric disorders. Br J Pharmacol 2021; 178: 2569-2594.

[12] Deepmala, Slattery J, Kumar N, Delhey L, Berk M, Dean O, Spielholz C and Frye R. Clinical trials of N-acetylcysteine in psychiatry and neurology: a systematic review. Neurosci Biobehav Rev 2015; 55: 294-321.

[13] Ruwanpura SM, Thomas BJ and Bardin PG. Pirfenidone: molecular mechanisms and potential clinical applications in lung disease. Am J Respir Cell Mol Biol 2020; 62: 413-422.

[14] Chennakesavulu S, Mishra A, Sudheer A, Sowmya C, Suryaprakash Reddy C and Bhargav E. Pulmonary delivery of liposomal dry powder inhaler formulation for effective treatment of idiopathic pulmonary fibrosis. Asian J Pharm Sci 2018; 13: 91-100.

[15] O'Byrne PM, FitzGerald JM, Bateman ED, Barnes PJ, Zheng J, Gustafson P, Lamarca R, Puu M, Keen C, Alagappan VKT and Reddel HK. Effect of a single day of increased as-needed budesonide-formoterol use on short-term risk of severe exacerbations in patients with mild asthma: a post-hoc analysis of the SYGMA 1 study. Lancet Respir Med 2021; 9: 149-158.

[16] Swigris JJ, Wilson SR, Green KE, Sprunger DB, Brown KK and Wamboldt FS. Development of the ATAQ-IPF: a tool to assess quality of life in IPF. Health Qual Life Outcomes 2010; 8: 77.

[17] Minarini A, Ferrari S, Galletti M, Giambalvo N, Perrone D, Rioli G and Galeazzi GM. N-acetylcysteine in the treatment of psychiatric disorders: current status and future prospects. Expert Opin Drug Metab Toxicol 2017; 13: 279-292.

[18] Li F, Welling MC, Johnson JA, Coughlin C, Mulqueen J, Jakubovski E, Coury S, Landeros-Weisenberger A and Bloch MH. N-Acetylcysteine for pediatric obsessive-compulsive disorder: a small pilot study. J Child Adolesc Psychopharmacol 2020; 30: 32-37.

[19] Lopez-Sanroman A, Clofent J, Garcia-Planella E, Menchen L, Nos P, Rodriguez-Lago I and Domenech E. Reviewing the therapeutic role of budesonide in Crohn's disease. Gastroenterol Hepatol 2018; 41: 458-471.

[20] Taniguchi H, Ebina M, Kondoh Y, Ogura T, Azuma A, Suga M, Taguchi Y, Takahashi H, Nakata K, Sato A, Takeuchi M, Raghu G, Kudoh S, Nukiwa T; Pirfenidone Clinical Study Group in Japan. Pirfenidone in idiopathic pulmonary fibrosis. Eur Respir J 2010; 35: 821-829.

[21] Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D, King TE Jr, Lancaster L, Sahn SA, Szwarcberg J, Valeyre D, du Bois RM; CAPACITY Study Group. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet 2011; 377: 1760-1769.

[22] Ren W, Chen Y, Wang Y, Wang C, Tian M, Gu X and Lv W. Inhibitory effect of pirfenidone on

pulmonary fibrosis in patients with acute paraquat poisoning. Am J Transl Res 2021; 13: 13192-13199.

[23] Lancaster LH, de Andrade JA, Zibrak JD, Padilla ML, Albera C, Nathan SD, Wijsenbeek MS, Stauffer JL, Kirchgaessler KU and Costabel U. Pirfenidone safety and adverse event management in idiopathic pulmonary fibrosis. Eur Respir Rev 2017; 26: 170057.

[24] Maher TM, Corte TJ, Fischer A, Kreuter M, Lederer DJ, Molina-Molina M, Axmann J, Kirchgaessler KU, Samara K, Gilberg F and Cottin V. Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: a double-blind, randomised, placebo-controlled, phase 2 trial. Lancet Respir Med 2020; 8: 147-157.

[25] Qi M, Wang R, Liu S and Tang F. Meta-analysis of dose selection for budesonide in the treatment of Chinese patients with AECOPD. J Pak Med Assoc 2021; 71: 2018-2026.

[26] Yorke J, Spencer LG, Duck A, Ratcliffe S, Kwong GN, Longshaw MS, Belkin A and Swigris JJ. Cross-Atlantic modification and validation of the A Tool to Assess Quality of Life in Idiopathic Pulmonary Fibrosis (ATAQ-IPF-cA). BMJ Open Respir Res 2014; 1: e000024.