

Effects of cyclophosphamide combined with prednisone on TNF- α expression in treatment of patients with interstitial lung disease

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Abstract. Effects of cyclophosphamide combined with prednisone on TNF- α expression in the treatment of patients with interstitial lung disease (ILD), and its clinical significance were investigated. A prospective analysis was performed on 198 patients with ILD in Jinan Central Hospital Affiliated to Shandong University from January 2010 to December 2017. Among them, 101 patients treated with cyclophosphamide combined with prednisone were assigned in the combined treatment group, and 97 patients treated with prednisone alone in the control group. Patients in the two groups were compared in terms of lung function, St. George's Respiratory Questionnaire (SGRQ) score, clinical efficacy, adverse reactions and TNF- α expression levels before and after treatment. After treatment, the patients in the combined treatment group had significantly higher forced vital capacity (FVC) and forced expiratory volume in first second (FEV1) compared with the control group, but significantly lower diffusing capacity of lung for carbon monoxide (DLCO) and DLCO% ($P < 0.05$). In both groups, patients after treatment had higher FVC and FEV1, but lower DLCO and DLCO% ($P < 0.05$), compared with before treatment, while SGRQ score before treatment was higher than that after treatment ($P < 0.05$). Compared with control group, the combined treatment group had significantly more patients with complete remission (CR) and higher total effective rate, however less patients with stable disease (SD) ($P < 0.05$). Patients with adverse reactions in the combined treatment group were less than those in the control group ($P < 0.05$). After treatment, TNF- α expression level in the combined treatment group was significantly lower than that in the control group

($P < 0.05$), and TNF- α expression before treatment was higher than that after treatment in both groups ($P < 0.05$). In conclusion, cyclophosphamide combined with prednisone is effective and safe in the treatment of ILD without severe adverse reactions, reducing TNF- α expression level, and therefore is worthy of clinical application.

Introduction

Interstitial lung disease (ILD), also known as diffuse parenchymal lung disease, is common in the respiratory system accounting for 14-16% of respiratory diseases (1,2). The incidence rate of the disease has increased with industrialization (3), and the cause of this disease may be related to air pollution and viral infection, according to the study of Salisbury *et al* (4). With less obvious specific symptoms in the early stage, the disease is usually ignored by patients who therefore miss the best treatment time (5). Lesions of ILD with complex onset are mainly in the alveolar wall and the surrounding tissue of the alveoli, so patients may suffer from pulmonary fibrosis if not treated in time. Moreover, ILD even causes respiratory failure with disease progression, posing a serious threat to the patient's life (6,7). Therefore, it is important to choose an effective treatment plan with few adverse reactions.

At present, ILD is symptomatically treated with antibiotics and glucocorticoids (8). Prednisone inhibits the aggregation of macrophages and leukocytes, and has anti-inflammatory response and anti-stress reaction (9). Cyclophosphamide blocks B-cell proliferation and inhibits the antibody production, as well as complements immunoadsorption due to its long action time, thereby ensuring good efficacy (10). According to a study by Reece *et al* (11), prednisone alone improves renal function in the treatment of multiple myeloma, however its total effective rate is lower than that of prednisone combined with cyclophosphamide. As a tumor necrosis factor, widely present in alveoli and histocytes, and an important factor in immune mediation, TNF- α produced by macrophages and neutrophils is abundantly expressed in the presence of pneumonia and kills abnormal cells, which induces the release of other inflammatory factors (12).

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Currently, there are few studies on cyclophosphamide combined with hormones for the treatment of ILD. Therefore, in the present study, a retrospective analysis was performed on the medical records of patients with ILD, and prednisone alone was compared with cyclophosphamide combined with prednisone in terms of efficacy, adverse reactions and TNF- α expression levels, before and after treatment, in order to provide a reference for the clinical treatment of ILD.

Patients and methods

Clinical information. A prospective analysis was performed on 198 patients with ILD in Jinan Central Hospital Affiliated to Shandong University (Jinan, China) from January 2010 to December 2017. In total, 131 males and 67 females, aged 21-70 years, were included, with an average age of 57.34 ± 4.54 years. Among them, 101 patients treated with cyclophosphamide combined with prednisone were assigned in the combined treatment group, and 97 patients treated with prednisone alone in the control group. Inclusion criteria: Patients with early and intermediate stages of ILD who were diagnosed by chest imaging, pulmonary ventilation and diffusion functions, pathological biopsy; patients in the two groups with balanced severity; patients of ≤ 70 years of age; patients with complete medical records; patients who had not been diagnosed and treated in other hospitals. Exclusion criteria: Patients allergic to the drugs of the study; patients with other respiratory diseases; pregnant or lactating women; patients with acute gastrointestinal bleeding or other severe diseases; patients with communication or cognitive disorders. All patients and their families signed an informed consent form and cooperated with the medical staff to complete the relevant medical treatment. The study was approved by the Ethics Committee of Jinan Central Hospital Affiliated to Shandong University.

Methods. Patients in the control group were treated with prednisone, 10 mg/time and 3 times/day (Zhejiang Xianju Pharmaceutical Co., Ltd.; SFDA approval no. H33021207) for 4 consecutive weeks. After that, the dosage was gradually reduced according to the patient's condition. In the combined treatment group, the patients were intravenously dripped with cyclophosphamide for infusion, 4 mg/kg and 1 time/day (Jiangsu Hengrui Pharmaceutical Co., Ltd.; SFDA approval no. H32020856) for 3 consecutive weeks. After that, the dosage was gradually reduced according to the patient's condition. Both groups of patients were treated for 12 weeks.

Spirometer (Jaeger, Ltd.) was used to detect the forced vital capacity (FVC), the forced expiratory volume in first second (FEV1), the diffusing capacity of lung for carbon monoxide (DLCO) and DLCO% before and at 12 weeks after treatment. Fasting venous blood was extracted and centrifuged at $3,000 \times g$ for 15 min at 4°C on admission and at 12 weeks after treatment, in order to determine TNF- α with enzyme-linked immunosorbent assay (ELISA), following strictly the manufacturer's instructions of TNF- α kit (Shanghai Yuanmu Biological Technology Co., Ltd.; cat. no. YM-QP10200). The St. George's Respiratory Questionnaire (SGRQ) score was used to evaluate patients' quality of

life with a total score of 100 points. The higher the score, the better the activity was. Changes in indicator levels and the incidence rate of adverse reactions were recorded and compared between the two groups.

Criteria for efficacy evaluation. The clinical efficacy on ILD was evaluated based on chest CT before and after treatment, referring to relevant criteria (13). Complete remission (CR): Target lesions partially disappeared, and the pleural edge was regular. Partial remission (PR): Lesions had ground-glass opacities, with reduced stripes and reticular shadows. Stable disease (SD): No significant changes in target lesions. Progressive disease (PD): Lesions had ground-glass opacities, with increased stripes and reticular shadows, or lesions had honeycomb opacities. The clinical total effective rate = $(\text{CR} + \text{PR}) / (\text{total number of cases}) \times 100\%$.

Statistical analysis. SPSS 17.4 software (Beijing NDTimes Technology Co., Ltd.) was used for statistical analysis. Enumeration data were expressed as n (%) and tested by Chi-square test. Measurement data were expressed as the mean \pm standard deviation, and t-test was used for the differences between two groups. Paired t-test was used for comparison of the data before and after treatment. Data among multiple groups were compared with ANOVA and Dunnett's post hoc test. $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Comparison of clinical information. There were no significant differences between the two groups in terms of sex, age, dyspnea, mucopurulent sputum, anorexia, weakness, arthralgia in limbs, fever or alveolitis ($P > 0.05$). Thus, the groups were comparable (Table I).

Comparison of lung function indices before and after treatment. Before treatment, there were no statistically significant differences between the two groups in FVC, FEV1, DLCO or DLCO% ($P > 0.05$). After treatment, the patients in the combined treatment group had significantly higher FVC and FEV1 compared with the control group, however significantly lower DLCO and DLCO% ($P < 0.05$). In the combined treatment and control groups, the patients after treatment had higher FVC and FEV1, but lower DLCO and DLCO%, compared with before treatment ($P < 0.05$) (Table II and Fig. 1).

Comparison of SGRQ score before and after treatment. Before treatment, there was no statistically significant difference between the two groups in SGRQ score ($P > 0.05$). However, after treatment the SGRQ score in the combined treatment group was significantly higher than that in the control group ($P < 0.05$). In the combined treatment and control groups, SGRQ scores before treatment were higher than those after treatment ($P < 0.05$) (Table III).

Comparison of efficacy before and after treatment. There were no statistically significant differences in patients with PR or PD between the combined treatment and control groups

Table I. Basic patient information of the combined-treatment group and the control group [n (%)].

Characteristics	Combined treatment group (n=101)	Control group (n=97)	χ^2	P-value
Sex			0.125	0.724
Male	68 (67.33)	63 (64.95)		
Female	33 (32.67)	34 (35.05)		
Age (years)			0.061	0.805
<45	35 (34.65)	32 (32.99)		
≥45	66 (65.35)	65 (67.01)		
Dyspnea			0.432	0.511
Yes	78 (77.23)	71 (73.20)		
No	23 (22.77)	26 (26.80)		
Mucous purulent sputum			0.116	0.733
Yes	72 (71.29)	67 (69.07)		
No	29 (28.71)	30 (30.93)		
Anorexia			1.011	0.315
Yes	64 (63.37)	68 (70.10)		
No	37 (36.63)	29 (29.90)		
Weakness			0.322	0.980
Yes	73 (72.28)	76 (78.35)		
No	28 (27.72)	21 (21.65)		
Arthralgia in limbs			1.175	0.278
Yes	69 (68.32)	73 (75.26)		
No	32 (31.68)	24 (24.74)		
Fever			0.615	0.433
Yes	58 (57.43)	61 (62.89)		
No	43 (42.57)	36 (37.11)		
Cell type in alveolar structure			0.807	0.369
Neutrophil-type pulmonary fibrosis	54 (53.47)	58 (59.79)		
Lymphocyte-type pulmonary fibrosis	47 (46.53)	39 (40.21)		

Table II. Comparison of lung function before and after treatment between the combined treatment group and the control group.

Group	FVC (l)	FEV1 (l)	DLCO (l)	DLCO (%)
Combined treatment group (n=101)				
Before treatment	2.48±0.57	2.06±0.71	5.64±2.84	66.51±13.12
After treatment	2.83±1.25	2.64±1.06	3.57±1.15	46.67±7.34
t	2.560	4.569	6.790	13.260
P-value	0.011	<0.001	<0.001	<0.001
Control group (n=97)				
Before treatment	2.49±0.46 ^a	2.04±0.54 ^a	5.61±2.79 ^a	65.82±12.89 ^a
After treatment	2.62±0.42 ^b	2.31±0.92 ^b	4.22±1.53 ^b	56.25±11.63 ^b
t	2.055	2.493	4.302	4.294
P-value	0.041	0.014	<0.001	<0.001

^aP>0.05, not significant compared with the combined treatment group before treatment. ^bP<0.05, statistically significant compared with the combined treatment group after treatment. FVC, forced vital capacity; FEV1, forced expiratory volume in first second; DLCO, diffusing capacity of lung for carbon monoxide.

(both P>0.05). Compared with the control group, the combined treatment group had significantly more patients with CR and significantly higher total effective rate, but less patients with SD (P<0.05) (Table IV).

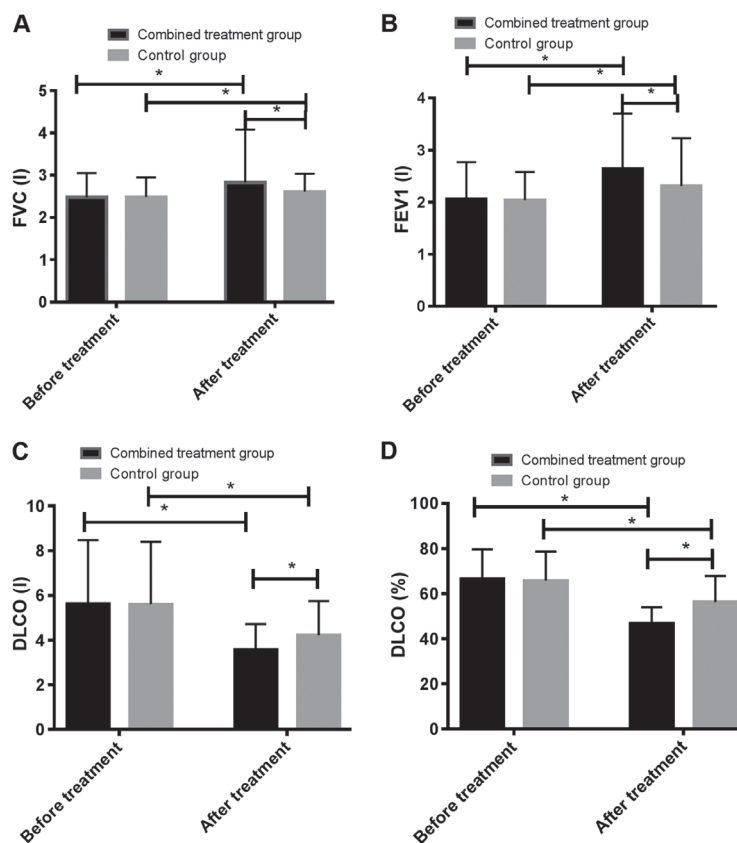


Figure 1. Comparison of lung function indicators before and after treatment in the combined treatment group and the control group. (A) After treatment, the FVC index of the combined treatment group was significantly higher than that of the control group, and the FVC index after treatment in the two groups was higher than that before treatment. (B) After treatment, the FEV1 index of the combined treatment group was significantly higher than that of the control group. In the two groups, the FEV1 index after treatment was higher than that before treatment. (C) After treatment, the DLCO index of the combined treatment group was significantly lower than that of the control group, and the DLCO index after treatment in the two groups was lower than that before treatment. (D) The DLCO% index of the combined treatment group was significantly lower than that of the control group, and the DLCO% index after treatment in the two groups was lower than before treatment. *P<0.05. FVC, forced vital capacity; FEV1, forced expiratory volume in first second; DLCO, diffusing capacity of lung for carbon monoxide

Table III. Comparison of SGRQ score before and after treatment between the combined treatment group and the control group.

Group	Combined treatment group (n=101)	Control group (n=97)	t	P-value
Before treatment	62.38±13.27	61.75±12.86	0.339	0.735
After treatment	46.84±11.81	35.51±9.57	7.399	<0.001
t	8.792	16.12		
P-value	<0.001	<0.001		

SGRQ, St. George's Respiratory Questionnaire.

Table IV. Comparison of treatment efficacy before and after treatment between the combined treatment group and the control group [n (%)].

Treatment outcome	Combined treatment group (n=101)	Control group (n=97)	χ^2	P-value
CR	51 (50.50)	35 (36.08)	4.183	0.041
PR	35 (34.65)	33 (34.02)	0.009	0.925
SD	14 (13.86)	25 (25.77)	4.439	0.035
PD	1 (1.0)	4 (4.12)	1.974	0.160
Total effective rate	86 (85.15)	68 (70.10)	6.480	0.011

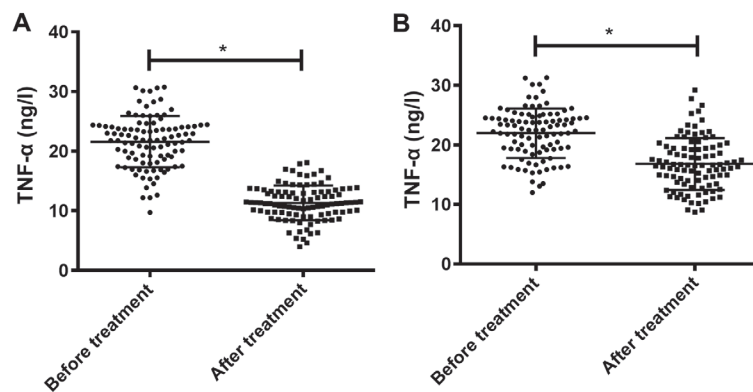
CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease.

Table V. Comparison of adverse reactions before and after treatment between the combined treatment group and the control group [n (%)].

Adverse reaction	Combined treatment group (n=101)	Control group (n=97)	χ^2	P-value
Gastrointestinal reaction	6 (5.94)	14 (14.43)	3.930	0.047
Elevated blood glucose	2 (1.98)	8 (8.25)	4.053	0.044
Chemical cystitis	1 (1.0)	6 (6.19)	3.916	0.048
Others	4 (3.96)	12 (12.37)	4.712	0.030

Table VI. Changes in blood TNF- α levels in patients before and after treatment in the combined treatment group and the control group (ng/l).

Group	Combined treatment group (n=101)	Control group (n=97)	t	P-value
Before treatment	21.83 \pm 4.22	22.14 \pm 4.53	0.498	0.619
After treatment	11.56 \pm 3.26	16.13 \pm 4.15	8.635	<0.001
t	4.079	4.264		
P-value	<0.001	<0.001		

Figure 2. Comparison of TNF- α expression level before and after treatment. TNF- α expression level was determined by ELISA. (A) The expression of TNF- α levels before treatment in the combined treatment group was higher than that after treatment. (B) The expression of TNF- α levels in the control group before treatment was higher than that after treatment. *P<0.05.

Comparison of adverse reactions before and after treatment.

The combined treatment group had less patients with gastrointestinal reactions, hyperglycemia and chemical cystitis than the control group (P<0.05) (Table V).

Comparison of TNF- α expression level before and after treatment.

In the combined treatment group, TNF- α expression levels before and after treatment were 21.83 \pm 4.22 and 11.56 \pm 3.26 ng/l, respectively, and in the control group were 22.14 \pm 4.53 and 16.13 \pm 4.15 ng/l, respectively. Before treatment, there was no statistically significant difference between the two groups in TNF- α expression level (P>0.05). However, the TNF- α expression in the combined treatment group after treatment was significantly lower than that in the control group (P<0.05). In the combined treatment and control groups, TNF- α expression levels before treatment were higher than those after treatment (P<0.05) (Table VI and Fig. 2).

Discussion

Heterogeneous ILD has complex causes, so its pathogenesis remains unclear (14). The disease has no special symptoms in the early stage, so it is diagnosed through etiology, pathological manifestations and imaging features. As a result, most patients are in the advanced stage of irreversible pulmonary fibrosis when diagnosed. In the advanced stage of ILD, inflammation spreads to blood vessels and the interstitium, destroys the lung tissue and leads to pulmonary fibrosis, which damages the lung function, increases the difficulty of treatment and causes patient death (15). With the advancement of modern medicine, ILD is controlled but difficult to cure, with high incidence and mortality rates and a long treatment cycle (16). Therefore, timely drug treatment is the key to control the deterioration of the disease. ILD is currently treated based on anti-pulmonary fibrosis and anti-inflammation.

In the present study, a prospective analysis was performed on 198 patients with ILD in Jinan Central Hospital Affiliated to Shandong University from January 2010 to December 2017. Patients in the combined treatment and control groups were compared in terms of efficacy, adverse reactions and TNF- α expression level, before and after treatment. The results of lung function tests, efficacy and SGRQ score before and after treatment in the combined treatment group were better than those in the control group. Anti-inflammatory and anti-allergic prednisone regulates protein biosynthesis and metabolism, reduces connective tissue proliferation and inflammatory exudation, and inhibits histamine formation and release (17). The inflammatory state of advanced ILD is less obvious, however, the lung becomes gradually fibrotic with disease progression, so anti-fibrotic therapy is necessary for the patients (18). According to a study (19), the efficacy of hormones is not significant on systemic sclerosis-associated ILD, so the disease is currently treated with prednisone combined with cyclophosphamide. Cyclophosphamide treats autoimmune diseases, and restricts the transformation of viruses into immunoblasts through non-specifically killing small lymphocytes (20,21). According to a study by Mok (22), cyclophosphamide combined with prednisone in the treatment of lupus nephritis was shown to have a high total effective rate, suggesting that the combination treatment improves the patient results of lung function tests and quality of life, which further supports the results of this study. In the present study, patients with gastrointestinal reactions, hyperglycemia and chemical cystitis in the combined treatment group were less than those in the control group. Prednisone leads to hyperglycemia through promoting protein to convert into sugar, and gastrointestinal reactions and other adverse reactions through promoting gastric secretion (23). Cyclophosphamide interferes with the production of DNA and RNA, and cross-links with the former, thereby inhibiting the immune response, proliferation and division of immune lymphocytes, and blocking immune complex deposition, so as to treat diseases. Due to fewer adverse reactions, cyclophosphamide has been widely used in the treatment of lymphatic systemic and autoimmune diseases (24). According to a study by Mulvenna *et al* (25), non-small cell lung cancer weakens lung function, and the high incidence rate of adverse reactions after treatment with prednisone reduces the immune function of the body, and therefore adverse reactions occur easily. In comparison of TNF- α expression levels before treatment, there was no statistically significant difference between the two groups, whereas after treatment, TNF- α expression level was significantly lower in the combined treatment group than that in the control group. TNF- α mediates the expression of inflammatory factors, aggravates inflammatory responses and proliferates fibroblasts. A large amount of collagen secretion causes the occurrence and development of pulmonary fibrosis, which plays a key role in respiratory diseases. Therefore, the combined treatment reduces TNF- α expression level (26).

In this investigation, due to the small number of patients with ILD in Jinan Central Hospital Affiliated to Shandong University, the sample size is small, so there may be contingency in the results. Therefore, a longer-term follow-up survey will be conducted in the future.

In conclusion, cyclophosphamide combined with prednisone is effective and safe in the treatment of ILD, without

severe adverse reactions and reducing the TNF- α expression level, and therefore is worthy of clinical promotion.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

JL performed ELISA and wrote the manuscript. XC and YQ collected and interpreted the general data of the patients and were responsible for the statistical analysis. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of Jinan Central Hospital Affiliated to Shandong University (Jinan, China). Patients who participated in this research, signed an informed consent and had complete clinical data.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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