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Original Article

The effect of prednisone acetate combined with cyclophosphamide on systemic lupus erythematosus and serum IL-4, IL-6, and IL-10 expressions

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Abstract: Objective: To investigate the efficacy of prednisone acetate combined with cyclophosphamide for the treatment of systemic lupus erythematosus and their effects on serum interleukin (IL)-4, IL-6, and IL-10. Methods: A total of 90 patients with systemic lupus erythematosus were randomly assigned into a control group and an observation group. The control group was treated with prednisone (n=45), while the observation group was given an additional cyclophosphamide (n=45). The serum levels of IL-4, IL-6, and IL-10 were measured by ELISA after 28 days of treatment. The changes in the IL-4, IL-6, and IL-10 expressions, efficacy and adverse reactions after treatment were compared between the two groups. According to the efficacy after 90 days of treatment, the patients were divided into two subgroups, the favorable efficacy subgroup (patients of markedly effective efficacy) and the poor efficacy subgroup (patients of effective and ineffective efficacy). The expressions of IL-4, IL-6, and IL-10 were compared between the two subgroups. A receiver operating characteristic curve was plotted to observe the predictive value of each indicator for efficacy. Results: There were no statistical differences in the baseline data between the two groups (all P>0.05). After treatment, the expressions of serum IL-4, IL-6, and IL-10 in the observation group were significantly lower than they were in the control group (all P<0.05). The total incidence of adverse reactions between the two groups was not significant (P>0.05). The clinical outcomes between the two groups were significantly different (P<0.05). The expressions of serum IL-4, IL-6, and IL-10 in the patients with favorable efficacy were significantly lower than those in the patients with poor efficacy (all P<0.05). The receiver operating characteristic curve analysis showed that the areas under the curve of IL-4, IL-6, and IL-10 were 0.703, 0.782, and 0.670, respectively. Conclusion: Prednisone acetate combined with cyclophosphamide can effectively improve the conditions of patients with systemic lupus erythematosus, and the expressions of IL-4, IL-6, and IL-10 in the serum can be used as potential indicators for the prediction of clinical efficacy.

Keywords: Cyclophosphamide, prednisone acetate, systemic lupus erythematosus, clinical efficacy, cytokines

Introduction

Systemic lupus erythematosus (SLE) is a kind of autoimmune connective tissue disease involving multiple organs and systems. Patients with SLE have various kinds of autoantibodies in the serum, showing pathological manifestations of complex pathogenic autoantibody responses and an accumulation of immune complex [1, 2]. In a survey of SLE in Asia by Osio-Salido et al., the incidence of SLE in 24 countries is usually 30-50/100,000, and it is significantly higher in women than in men, and most of them were young and middle-aged [3]. To date, the cause of SLE is not clear yet, but studies have confirmed that the causes of SLE include the neuroendocrine system, infections, genetics, immunological abnormalities, etc. [4-6].

Patients with serious SLE may have renal damage and neurological diseases, which seriously

affect the quality of life and the survival of patients [7]. Therefore, the treatment for SLE is particularly important. With the improvement of medical understanding and the deepening of scientific research, the treatment for SLE has been continuously improved. Prednisone acetate, a glucocorticoid drug, can reduce the amount of capillary exudation and inhibit the phagocytosis of leukocytes by increasing the vascular tension in the early stage, so as to inhibit the inflammatory reaction and immune response [8]. As a bifunctional alkylating nitrogen mustard agent, cyclophosphamide inhibits T and B cells so as to inhibit cell proliferation at various stages, and it also inhibits complement activity and reduces renal damage in patients [9]. A clinical study showed that prednisone acetate combined with cyclophosphamide significantly improved the condition of SLE patients [10]. But there are few diagnostic indicators for the efficacy of SLE treatment. In recent years, studies have shown that IL-4, IL-6, and IL-10 are differentially expressed in the serum of SLE patients [11]. However, whether they can be used as predictive indicators for the efficacy of treatment for SLE has not been reported. Therefore, we enrolled 90 patients with SLE in a randomized, controlled trial and hope to provide a reference for clinical treatment.

Materials and methods

Clinical data

In this study, we enrolled 90 patients with SLE who were treated at The Second Hospital of Shandong University as the subjects. The patients were randomly assigned into an observation group or a control group, with 45 patients in each group. Another 40 healthy subjects who underwent physical examinations were enrolled in the normal group. This study was approved by the Medical Ethics Committee of The Second Hospital of Shandong University, and an informed consent was obtained from each of the subjects.

Inclusion criteria & exclusion criteria

Patients were eligible for the study if they: met the SLE classification standard revised by the American College of Rheumatology in 1997 [12]; were treated for the first time; were aged 14-60 years old; had a SLEDAI score of 5-14 points; had a predictive survival of the whole treatment period; had complete clinical data.

Patients were excluded if they had other malignant tumors, autoimmune diseases other than SLE, coronary heart disease, hypertension, or digestive system disease; had allergies or contraindications to the experimental drugs; had poor compliance with treatment; were pregnant or lactating; had refractory SLE.

Materials

The ELISA kits for detecting IL-4, IL-6, and IL-10 were obtained from Shanghai Beyotime, China. The prednisone acetate tablets were obtained from Tianjin Lisheng, China. The cyclophosphamide for injection was obtained from Jiangsu Shengdi, China.

Therapeutic regimen

The control group and the observation group were treated with single treatment and combined treatment, respectively. The control group was treated with oral prednisone acetate tablets 0.2 mg/kg in the morning for 6 continuous weeks. The dosage was reduced according to their improvement in condition (generally decreasing at a rate of 5 mg per week), and then maintained at 5-10 mg/d. Patients in the observation group were given cyclophosphamide on the basis of the control group. Cyclophosphamide 500 mg was dissolved in 250 mL of 0.9% NaCl for intravenous injection, 14 days/time for the first 3 times, and 28 days/time for the remaining period of the course (90 days per course).

Detection of IL-4, IL-6, and IL-10

Five milliliters of fasting venous blood were collected before treatment, and after 28 days of treatment, held at room temperature for 30 min, centrifuged at 1,509.3 g for 10 min, and then the serum was collected for the subsequent experiments. The collected serum was added into blank wells with 50 μL of standard solution at different concentrations. 50 μL of distilled water and 50 μL of the antibody were added into the blank control wells; 40 μL of the sample and 10 μL of the biotin-labeled antibody were added into the other wells. Subsequently, the plate was incubated at 37°C for 30 min. When washing the plate, we ensured each

Table 1. Evaluation of efficacy

Efficacy	Manifestation
Markedly effective	The clinical symptoms of the patients completely disappeared or significantly improved, and the relevant laboratory indicators returned to normal or significantly improved.
Effective	The patient's clinical symptoms recovered to a certain level, and the laboratory indicators were improved.
Ineffective	The patient's clinical symptoms remained or were aggravated, and the laboratory indicators were not improved.

well was full of the washing solution but without overflowing, for 30 seconds, and then the plate was patted dry. After being washed five times, 50 μL of the enzyme standard solution was added to each well to seal the plate again for 60 min incubation at 37°C. Again, the plate was washed 5 times and patted dry thoroughly after the last time with the use of absorbent paper. Horseradish peroxidase of 100 μL/well was added and incubated at 37°C for 15 min in the dark. Then, the color substrate TMB at 100 μL/well was added and incubated at room temperature for 20 min in the dark. At last, a stop buffer of 50 μL/well was added. The determination of the maximum absorption wavelength of 450 nm was performed using a microplate reader within 15 min. In this experiment, 3 duplicate wells were set, and the experiment was repeated 3 times.

Outcome measures

The main outcome measures were the changes in the IL-4, IL-6, and IL-10 expressions after 28 days of treatment, and the therapeutic effects after treatment. See **Table 1** for the evaluation criteria.

The secondary outcome measure was the adverse events during treatment.

According to the treatment efficacy, the patients were divided into a favorable efficacy subgroup (patients of markedly effective efficacy), and a poor efficacy subgroup (patients of effective and ineffective efficacy). The expressions of IL-4, IL-6, and IL-10 were compared after the treatment in the two subgroups. The receiver operating characteristic (ROC) curve was plotted to observe the predictive value of IL-4, IL-6, and IL-10 for efficacy.

Statistical analysis

The collected data were statistically analyzed using the SPSS 20.0 software package. The data were plotted using GraphPad Prism 7. The count data were expressed as the rate (%), and processed using chi-squared test, denoted as χ^2. The ranked data were processed using a non-parametric test, denoted by Z. The distribution of the measurement data was analyzed using a K-S test. The measurement data in accordance with the normal distribution was expressed as the mean ± standard deviation (mean ± sd), and compared between the two groups using an independent sample *t* test, denoted by *t*. The ROC curve was used to evaluate the predictive value of IL-4, IL-6, and IL-10 for the post-treatment efficacy. There was a statistical difference between two groups when $P<0.05$.

Results

Comparison of the clinical data

There were no statistical differences in gender, age, BMI, duration of disease, past medical history, smoking history, alcohol abuse history, systemic lupus erythematosus disease activity index (SLEDAI) score, cause of disease, C3, or C4 between the two groups (all $P>0.05$). See **Table 2**.

Expressions of IL-4, IL-6, and IL-10

The expressions of serum IL-4, IL-6, and IL-10 after 28 days in the observation group were significantly lower than they were in the control group, with significant differences (all $P<0.05$). The differences between before and after treatment in the observation group were more significant as compared with the differences in the control group (all $P<0.05$). See **Tables 3**-**5**.

Adverse reactions and evaluation of clinical efficacy

The adverse reactions in the two groups were recorded. In the observation group, there were 2 case of intestinal reactions, 2 cases of menstrual disorders, 3 cases of nausea and vomiting, and 2 cases of hypertension, with a total

Table 2. Clinical data

	Control group (n=45)	Observation group (n=45)	t/χ^2	P
Sex				
Male	9 (20.00)	7 (15.56)	0.304	0.581
Female	36 (80.00)	38 (84.44)		
Age (year)	31.9±7.0	32.3±6.0	0.291	0.771
BMI (kg/m^2)	23.51±1.80	22.80±1.59	1.983	0.051
Duration of disease	3.29±0.69	3.11±0.76	1.176	0.243
Past medical history				
Diabetes	8 (17.78)	6 (13.33)	0.338	0.561
Hypertension	9 (20.00)	10 (22.22)	0.067	0.796
COPD	2 (4.44)	3 (6.67)	0.212	0.645
Hyperlipidemia	6 (13.33)	8 (17.78)	0.338	0.561
Smoking history			0.207	0.649
Yes	15 (33.33)	13 (28.89)		
No	30 (66.67)	32 (71.11)		
Alcohol abuse			0.549	0.459
Yes	3 (6.67)	5 (11.11)		
No	42 (93.33)	40 (88.89)		
SLEDAI			0.227	0.634
Moderate	34 (75.56)	32 (71.11)		
Severe	11 (24.44)	13 (28.89)		
Cause of disease			1.586	0.811
Genetic	8 (17.78)	10 (22.22)		
Virus infection	12 (26.67)	8 (17.78)		
Drug	3 (6.67)	3 (6.67)		
Abnormal sex hormone levels	15 (33.33)	14 (31.11)		
No obvious cause	7 (15.56)	10 (22.22)		
C3 (g/L)	0.38±0.08*	0.40±0.06*	1.342	0.183
C4 (g/L)	0.10±0.03*	0.11±0.03*	1.581	0.117

Note: BMI: body mass index, COPD: chronic obstructive pulmonary disease, SLEDAI: systemic lupus erythematosus disease activity index, C3: complement C3, C4: complement C4. Compared with the control group, *P<0.05.

incidence of 20.00%. In the control group, there were 3 cases of intestinal reactions, 2 cases of menstrual disorders, 3 cases of nausea and vomiting, and 3 cases of hypertension, with a total incidence of 24.44%. There was no statistical difference in the total incidence of adverse reactions between the two groups (X^2=0.257, P=0.612).

The clinical efficacy of the two groups was evaluated after one course of treatment. The control group had 17 patients of markedly effective, 18 patients of effective, and 10 patients of ineffective, while the observation group had 28 patients of markedly effective, 13 patients of effective, and 4 patients of ineffective, and there was a significant difference in clinical efficacy between the two groups (P<0.05). See **Table 6**.

Expressions of serum IL-4, IL-6, and IL-10 in the favorable and poor efficacy subgroups

According to the clinical efficacy after one course of treatment, the patients were divided into a favorable efficacy subgroup (patients of markedly effective efficacy, n=45), and a poor efficacy subgroup (patients of effective and ineffective efficacy, n=45). The expressions of serum IL-4, IL-6, and IL-10 were found to be significantly lower in the favorable efficacy subgroup than they were in the poor efficacy subgroup (all P<0.05). See **Table 7** and **Figure 1**.

Predictive value of serum IL-4, IL-6, and IL-10 for clinical efficacy

According to the expression of IL-4, IL-6, and IL-10 in the favorable and poor efficacy subgroups, an ROC curve was plotted to observe the predictive value of each indicator for clinical efficacy. The results showed that the area under the IL-4 curve was 0.703, 95% CI: 0.589-0.816; the area under the IL-6 curve was 0.782, 95% CI: 0.685-0.879; the area under the IL-10 curve was 0.670, 95% CI: 0.558-0.782. See **Table 8** and **Figure 2**.

Discussion

SLE mostly develops in young and middle-aged women, with a small proportion in children and the elderly, showing an n-shaped distribution. As an autoimmune disease, SLE affects multiple organs and tissues of the patients and seriously harms their lives and health [13]. How-

Table 3. Changes in IL-4 expression

Group	IL-4 (g/mL)		t	P	Difference value
	Before treatment	After 28 d of treatment			
Control group (n=45)	35.17±10.32*	26.60±5.15	3.400	0.001	8.58±5.57
Observation group (n=45)	34.72±10.60*	21.57±4.54	9.647	<0.001	13.14±6.28
t	0.204	4.915			3.644
P	0.838	<0.001			<0.001

Note: Compared with the control group, *P<0.05.

Table 4. Changes in IL-6 expression

Group	IL-6 (g/mL)		t	P	Difference value
	Before treatment	After 28 d of treatment			
Control group (n=45)	9.30±3.03*	6.86±2.02	3.022	0.004	2.45±1.23
Observation group (n=45)	8.97±2.55*	5.16±2.55	7.087	<0.001	3.81±2.94
t	0.559	3.506			2.862
P	0.578	<0.001			0.005

Note: Compared with the control group, *P<0.05.

Table 5. Changes in IL-10 expression

Group	IL-10 (g/mL)		t	P	Difference value
	Before treatment	After 28 d of treatment			
Control group (n=45)	49.49±16.16*	31.57±9.54	7.792	<0.001	17.68±7.13
Observation group (n=45)	48.59±19.21*	24.97±7.55	7.072	<0.001	23.63±11.91
t	0.240	3.639			2.875
P	0.810	<0.001			0.005

Note: Compared with the control group, *P<0.05.

Table 6. Evaluation of clinical efficacy

Group	Markedly effective	Effective	Ineffective	Z	P
Control group (n=45)	17 (37.78)	18 (40.00)	10 (22.22)	-2.448	0.014
Observation group (n=45)	28 (62.22)	13 (28.89)	4 (8.89)		

Table 7. Expression of serum IL-4, IL-6, and IL-10 in the favorable and poor efficacy subgroups

Group	IL-4 (pg/mL)	IL-6 (pg/mL)	IL-10 (pg/mL)
Favorable efficacy subgroup (n=45)	21.32±6.39	4.78±1.80	24.29±8.08
Poor efficacy subgroup (n=45)	25.29±4.55	6.71±1.79	29.67±8.23
t	3.395	5.100	3.129
P	0.001	<0.001	0.002

ever, the pathogenesis of SLE has not been thoroughly studied at present, but the factors related to the disease at present are genetics, the environment, viral infections, and autoimmune defects [14]. The common treatments for SLE in clinical practice are corticosteroids and immunological agents. Cyclophosphamide is a common clinical inhibitor of B lymphocyte alkylation, which can effectively improve the abnormal proliferation of B lymphocytes *in vivo*, so as to reduce the expression of immunoglobulin in patients [15]. As a glucocorticoid, prednisone has considerable therapeutic effects on inflammation and allergies, which reduces the capillary permeability and the production of toxic substances *in vivo* by inhibiting the abnormal proliferation of connective tissue in SLE patients [16].

In the present study, we observed the clinical efficacy of two drugs for the treatment of SLE.

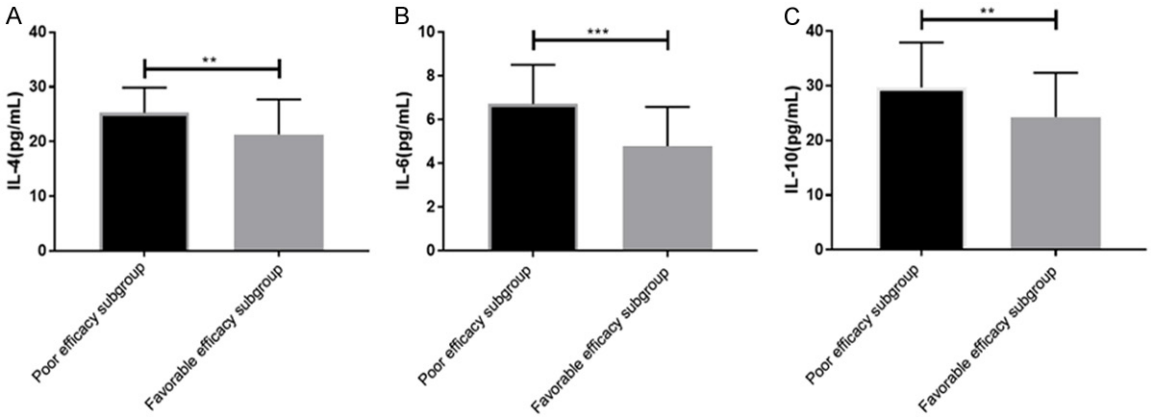

Figure 1. Expressions of serum IL-4, IL-6, and IL-10 in the favorable and poor efficacy subgroups. A. The expression of serum IL-4 in the favorable efficacy subgroup was significantly lower than it was in the poor efficacy subgroup (**P<0.01). B. The expression of serum IL-6 in the favorable efficacy subgroup was significantly lower than it was in the poor efficacy subgroup (***P<0.001). C. The expression of serum IL-10 in the favorable efficacy subgroup was significantly lower than it was in the poor efficacy subgroup (**P<0.01).

Table 8. Receiver operating characteristic curves of serum IL-4, IL-6, and IL-10

Index	AUC	95% CI	Sensitivity (%)	Specificity (%)	Youden's index (%)	Cut-off (pg/mL)
IL-4	0.703	0.589-0.816	68.89	82.22	51.11	<22.565
IL-6	0.782	0.685-0.879	68.89	80.00	48.89	<5.760
IL-10	0.670	0.558-0.782	46.67	86.67	33.33	<23.075

Note: AUC: area under the curve; 95% CI: 95% confidence interval.

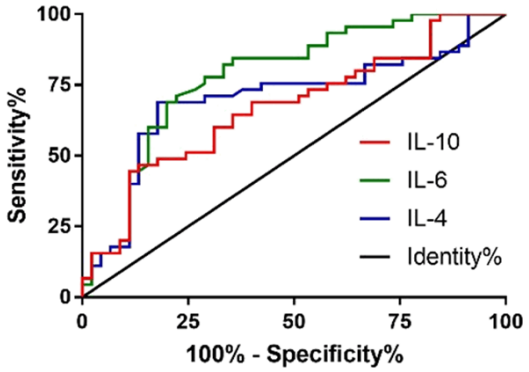

Figure 2. Receiver operating characteristic curve of serum IL-4, IL-6, and IL-10.

The clinical efficacy of the control group, treated with a single drug, was significantly less promising than that of the observation group, treated with a combination of two drugs. In a study by An et al., 77.60% of SLE patients treated with cyclophosphamide combined with prednisone showed a markedly effective outcome, which is basically consistent with our study [17]. This result suggests that we can improve the recovery and conditions of patients by this combination. Moreover, we also compared the occurrence of adverse reactions during the treatment, and found that there was no difference in the incidence of adverse reactions between the two groups, indicating that the combination of the two drugs does not increase the adverse reactions in patients.

In recent years, with the deepening of research on the mechanism of SLE, increasing biological indicators have been found to be closely related to the development of SLE. As an important Th2 cytokine, IL-4 can promote the transformation of Th0 cells into Th2 cells, and can also promote the proliferation of B cells to produce a large number of antibodies, which can increase the expressions of IgE and IgG *in vivo* [18]. Studies have shown that IL-4 can induce Th2 cell differentiation, and Th2 cell differentiation can increase the expression of IL-4. The interaction between the two can promote the autoimmune response of SLE patients, resulting in the aggravation of SLE [19]. IL-6 can stimulate the maturation of B cells, inducing B cell differentiation to become a mature immunoglobulin, thereby secreting plasma cells [20]. In the studies of Eilertsen and Umare et al., the expression of IL-6 in the peripheral blood and

urine of patients with SLE was significantly higher its expression in normal subjects, and the IL-6 expression in patients was significantly reduced after treatment [21, 22]. As an anti-inflammatory factor, IL-10 has its inhibitory effect in a variety of cells. The main function of anti-inflammatory factors is to inhibit tissue damage caused by specific and non-specific immune responses, and to enhance the immune function of patients, similar to the role of a "scavenger" [23]. In the present study, the serum levels of IL-4, IL-6, and IL-10 in the normal subjects were significantly lower than those in the SLE patients, indicating that the expressions of serum IL-4, IL-6, and IL-10 were increased in patients who developed SLE. In the studies of Guimarães and Wong et al., the expressions of IL-4, IL-6, and IL-10 in the peripheral blood of patients with SLE were higher than those in the normal group, which is consistent with our study [24, 25]. However, the expressions of the indicators in SLE patients after treatment, and whether they can be used as efficacy indicators for the treatment of SLE are not clear yet. Therefore, we further tested the serum IL-4, IL-6, and IL-10 in patients after treatment. The results showed that the expressions of IL-4, IL-6 and IL-10 in the serum of the two groups after treatment were significantly lower than they were before treatment. Also, the different values before and after treatment were smaller in the control group than they were in the observation group, suggesting that the combination of the two drugs was better at decreasing the expressions of serum IL-4, IL-6, and IL-10 than the single drug. We speculate that this may be because cyclophosphamide can not only kill the lymphocytes in the proliferating phase, but it also has a certain effect on the cells in the quiescent phase, thus reducing the number of circulating B lymphocytes and T cells, thereby inhibiting the production of IL-4, IL- 6, and IL-10, so that the level of the indicators in the body can return to a normal level.

At the end of the study, we divided the patients into a favorable efficacy subgroup and a poor efficacy subgroup, and found that the expressions of serum IL-4, IL-6, and IL-10 in the favorable efficacy subgroup were significantly lower than they were in the poor efficacy subgroup. The ROC curve was plotted according to the expressions. It was found that the areas under the IL-4, IL-6, and IL-10 curves were 0.703, 0.782, and 0.670, respectively, suggesting that IL-4, IL-6, and IL-10 have a good predictive value for the clinical efficacy of patients and are expected to be potential indicators for therapeutic effects in patients with SLE.

However, there are still some limitations in this study. Firstly, this clinical trial did not clarify the mechanism of prednisone acetate combined with cyclophosphamide affecting the expressions of IL-4, IL-6, and IL-10 in the serum of patients with SLE. Secondly, we only studied the indicators in a single center. So, it is unclear whether there are differences between different regions and ethnic groups. Lastly, we did not observe the combined predictive value of the indicators for the clinical outcomes. Therefore, we will carry out further experiments with larger sample sizes to verify the results of this study.

In summary, prednisone acetate combined with cyclophosphamide can effectively improve the condition of patients with SLE, and the expressions of IL-4, IL-6, and IL-10 in the serum can be used as potential indicators to predict the clinical efficacy.

Disclosure of conflict of interest

None.

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