Int J Clin Exp Med 2019;12(9):11675-11683
www.ijcem.com /ISSN:1940-5901/IJCEM0097567

Original Article

Clinical efficacy of levocetirizine combined with ebastine in the treatment of chronic urticaria and their effect on serum cytokines

Sheng Wang[1], Yang Liu[2], Jing Wang[3], Jing Zhang[1]

[1]Department of Dermatology, Tangshan Gongren Hospital, Tangshan 063000, Hebei Province, China; [2]Department of Anesthesiology, Kailuan General Hospital, Tangshan, Hebei Province, China; [3]Department of Dermatology, North China University of Science and Technology Affiliated Hospital, Tangshan, Hebei Province, China

Received May 27, 2019; Accepted August 6, 2019; Epub September 15, 2019; Published September 30, 2019

Abstract: Objective: To investigate the clinical efficacy of levocetirizine combined with ebastine in the treatment of chronic urticaria and their effect on serum cytokines. Methods: In total, 234 patients with chronic urticaria were selected as the study subjects and divided into the control group and the experimental group, with 117 patients in each group. The experimental group was treated with levocetirizine combined with ebastine, and the control group was treated with levocetirizine. The clinical efficacy and the incidence of adverse reactions were observed after treatment. The levels of serum tumor necrosis factor (TNF)-α, interleukin (IL)-6 and IL-10 were detected by enzyme-linked immunosorbent assay (ELISA). Patients were divided into group A (126 patients, cure) and group B (108 patients, markedly effective, effective and ineffective) according to clinical efficacy, and the serum levels of TNF-α, IL-6 and IL-10 were compared between the two groups. The receiver operating characteristic (ROC) curve was used to analyze the value of TNF-α, IL-6 and IL-10 in evaluating the clinical efficacy after treatment for patients with chronic urticaria. Spearman correlation analysis was used to analyze the correlation between each index and clinical efficacy. The clinical data of the two groups were compared. Results: There was no difference in clinical data between the experimental group and the control group ($P > 0.05$). After treatment, the expression of all indexes in the serum of the 2 groups were significantly lower than those before treatment ($P < 0.05$). The changes of all indexes in the experimental group were significantly lower than those in the control group ($P < 0.05$), and the clinical efficacy of the experimental group was significantly better than that of the control group ($P < 0.05$). The serum levels of TNF-α, IL-6 and IL-10 in group A were significantly lower than those in group B ($P < 0.05$). Spearman correlation analysis showed that the lower the value of each index, the better the clinical efficacy was, and there was a positive correlation between them ($r = 0.526$, $r = 0.518$, $r = 0.480$, $P < 0.001$). The ROC curve showed that the area under the curve of TNF-α, IL-6, and IL-10 were 0.801, 0.797, and 0.767, respectively. There was no statistical difference in the incidence of adverse reactions between the experimental group and the control group ($P > 0.05$). Conclusion: TNF-α, IL-6 and IL-10 can be used as potential indicators of clinical efficacy after treatment for patients with chronic urticaria. Levocetirizine combined with ebastine can effectively improve the condition of chronic urticaria patients.

Keywords: Chronic urticaria, levocetirizine, ebastine, clinical efficacy

Introduction

As a clinically common skin disease, urticaria is a local edematous allergic disease [1]. It is mainly caused by the expansion and leakage of skin or mucosal capillaries, and the common symptoms are wheal with skin itching [2]. According to the onset of the disease, it can be divided into acute and chronic urticaria, in which the former can disappear in a short time, but the latter can occur twice in a week and last for more than six weeks or even longer [3]. Studies have shown that the incidence of chronic urticaria in European and North American countries is 0.1% to 0.3% [4], but in the study of Ma et al., everyone can have chronic urticaria at any age, and the course of disease may vary [5]. The incidence of chronic urticaria in women is significantly higher than in men, and the proportion of patients with disease duration of over 5 years is more than 17.6%. Although chronic urticaria is not a severe malignant dis-

ease, it is a severe allergic disease, which can affect quality of life, as well as reduce work and learning efficiency.

At present, the main treatment for chronic urticaria is drug therapy. Levocetirizine is part of a new generation of highly effective non-sedating antihistamines, which are commonly used in clinical practice. It mainly inhibits the release of inflammatory mediators in allergic reactions by antagonizing histamine [6]. A study has shown that levocetirizine can easily pass through the blood-brain barrier and will not accumulate in the body; it has a long half-life (7.9 ± 1.9 hours) and is highly safe [7]. Another study has shown that levocetirizine has considerable effectiveness in the treatment of chronic urticaria [8]. Ebastine is a novel H1 receptor antagonist, as well as a benzylamino piperidine derivative, which has a better effect as a second-generation histamine antagonist, and it is easily absorbed orally [9]. Similarly, a study has shown that ebastine has excellent performance in the treatment of chronic urticaria [10]. The aim of this study was to investigate whether there is a difference in the therapeutic efficacy and safety between the two drugs.

In addition, tumor necrosis factor (TNF)-α is a common inflammatory factor produced by macrophages and fat cells in adipose tissue, which will significantly increase in the body when inflammation, tumors, and infections occur [11]. Interleukin (IL)-6 and IL-10 are interleukins, which are differentially expressed in the body when inflammation and tumors are present [12, 13]. Studies have shown that TNF-α, IL-6 and IL-10 are differentially expressed in the presence of chronic urticaria [14, 15]; but whether there will be changes after treatment and whether changes in post-treatment indicators can predict clinical efficacy have not been shown in related studies. Therefore, this study aims to observe the changes of TNF-α, IL-6 and IL-10 in patients with chronic urticaria treated with levocetirizine combined with ebastine, to explore the value of each index in evaluating the clinical efficacy of patients and provide references for clinicians.

Materials and methods

Clinical data

In this study, 234 patients with chronic urticaria admitted to our hospital from April 2015 to August 2017 were enrolled. The patients were divided into an experimental group and a control group by random number table method, with 117 patients in each group. In the experimental group, there were 59 males and 58 females with an average age of 38.5 ± 11.3 years. In the control group, there were 65 males and 52 females with an average age of 36.8 ± 10.9 years. This study was approved by the Medical Ethics Committee of Tangshan Gongren Hospital.

Inclusion and exclusion criteria

Inclusion criteria: all men and women were eligible for Guidelines for the diagnosis and treatment of urticaria (2007 edition), Department of Dermatology and Venereology, Chinese Medical Association [16] and the EAACI/GA 2 LEN/EDF/WAO Guideline for the definition, classification, diagnosis and management of urticaria (the 2013 revision and update) [17]. The clinical manifestations of patients were mainly wheal and itching, and the courses of the urticaria lasted for more than 2 months. Both the patients and their families knew the purpose of the study, and the patients signed the informed consent form.

Exclusion criteria: pregnant women; patients with congenital or severe primary disease of the heart, liver, kidney, or lung; patients with corticosteroid usage 1 week before the experiment; patient's life at risk after admission; patients with cognitive dysfunction or neurological disorders; patients with allergies to this drug or those who meet drug contraindications.

Main drugs and kits

Levocetirizine (5 mg * 15 tablets, Chongqing Huabang Pharmaceutical Co., Ltd., China); Ebastine (10 mg * 10 tablets, Emerald Medical Pharmaceutical Industry Co., Ltd., Spain); TNF-α, IL-6 and IL-10 ELISA Kits (PT518, PI330, PI528, Shanghai Beyotime Biotechnology, China).

Treatment programs

The control group was treated with levocetirizine tablets after diagnosis of chronic urticaria (1 tablet/time, 1 time/day). The experimental group was treated with ebastine on the basis of the control group (1 tablet/time, 1 time/day).

Patients in the two groups were treated for a total of 4 weeks.

Detection of serum levels of TNF-α, IL-6 and IL-10

The serum expression levels of TNF-α, IL-6 and IL-10 of patients were detected by ELISA kits. Five mL fasting venous blood from patients was taken on the morning of the next day after admission and 4 weeks after treatment, both samples were collected and centrifuged at 1509.3 xg for 10 minutes. The serum was collected for subsequent experiments. The ELISA test was performed as follows according to the instruction of kit. Fifty μL of the collected sera was added to each blank well of the ELISA plates containing different concentrations of standard solution. Fifty μL of distilled water and 50 μL of the antibody were added to the blank control wells. Forty μL of the sample and 10 μL of biotinylated antibody were added to the remaining wells, then the plates were sealed and incubated at 37°C for 30 minutes. The solution in the ELISA plates was discarded and the plate was washed 5 times and patted dry, ensuring that the washing solution of each well was full without overflowing for 30 seconds. Fifty μL of the enzyme standard solution was added to each well, the plate was sealed again and incubated at 37°C for 60 minutes, the plate was washed again 5 times and patted dry. One hundred μL of horseradish peroxidase label was added to each well, the plate was sealed and incubated at 37°C for 15 minutes in the dark. One hundred μL of chromogenic substrate TMB was added to each well and incubated at room temperature for 20 minutes in the dark. Finally, 50 μL of reaction stop solution was added to each well, and a microplate reader (SpectraMax M5, Silicon Valley, USA) was used for detection of the maximum absorption wavelength at 450 nm within 15 minutes. Three sets of duplicate wells were used and the experiment was repeated 3 times.

Outcome measurements

Main outcome measurements: the serum levels of TNF-α, IL-6 and IL-10 before and after treatment in the two groups were observed. The symptom score reduction index (SSRI) was used as the standard for evaluating the clinical efficacy of patients [18]. According to the clinical efficacy, patients were divided into group A with good curative effect (cure) and group B with poor curative effect (markedly effective, effective and ineffective), and the expression levels of TNF-α, IL-6 and IL-10 were observed in the two groups. The receiver operating characteristic (ROC) curves were used to analyze the value of using TNF-α, IL-6 and IL-10 in evaluating the clinical efficacy for patients with chronic urticaria after treatment.

Secondary outcome measurements: adverse reactions during the treatment and clinical data of patients in the two groups were observed.

Symptom score reduce index (SSRI)

Cure: SSRI ≥ 90%; markedly effective: SSRI = 60%-89%; effective: SSRI = 20%-59%; ineffective: SSRI < 20%. SSRI = (pre-treatment symptom score-post-treatment symptom score)/pre-treatment symptom score * 100%

Statistical analysis

In this study, statistical software SPSS 22.0 was used to analyze the data. GraphPad 7.0 software was used to draw required images. K-S test was used to analyze the dose data distribution. Normally distributed data were expressed as mean ± standard deviation ($\overline{x}$ ± sd). Comparison between groups was performed by independent sample t-test, and intra-group comparison was analyzed by paired t-test. Non-normally distributed data were represented by quartiles (Meas (P_{25}-P_{75})) and analyzed by nonparametric test, denoted by Z. The enumeration data were expressed as percentage (%) and analyzed by chi-square test, denoted by x^2. Ranked data were analyzed by the rank sum test, denoted by Z. The ROC was used to analyze the value of TNF-α, IL-6 and IL-10 in evaluating clinical efficacy after treatment. Spearman correlation analysis was used to study the relationship between TNF-α, IL-6, IL-10 and clinical efficacy. $P < 0.05$ was considered statistically significant.

Results

Clinical data

Comparing the clinical data between the control group and the experimental group, no difference was found in gender, age, body mass index, course of disease, past medical history,

Table 1. Comparison of clinical data between the two groups (n, %)

Factors	Control group (n = 117)	Experimental group (n = 117)	t/x^2	P
Gender			0.618	0.432
Male	65 (55.56)	59 (50.43)		
Female	52 (44.44)	58 (49.57)		
Age	36.80 ± 10.90	38.5 ± 11.2	1.230	0.220
BMI (kg/m^2)	22.58 ± 1.88	22.75 ± 1.62	0.741	0.460
Course of disease (months)	7.58 ± 1. 52	7.91 ± 1.66	1.586	0.114
Past medical history				
Hypertension	30 (25.64)	25 (21.37)	0.594	0.441
Diabetes	12 (10.26)	15 (12.82)	0.377	0.539
Hyperlipidemia	18 (15.38)	20 (17.09)	0.126	0.723
COPD	10 (8.55)	8 (6.84)	0.241	0.624
Smoking history			0.072	0.789
Yes	72 (61.54)	70 (59.83)		
No	45 (38.46)	47 (40.17)		
Alcohol history			1.120	0.290
Yes	15 (12.82)	10 (8.55)		
No	102 (87.18)	107 (91.45)		
Place of residence			0.842	0.359
City	66 (56.41)	59 (50.43)		
Rural area	51 (43.59)	58 (49.57)		
Education background			0.446	0.504
≥ University degree	49 (41.88)	44 (37.61)		
< University degree	68 (58.12)	73 (62.39)		
Histamine (nmol/L)	4.55 ± 2.11	4.39 ± 2.05	0.588	0.557
IgE (g/L)	125.22 ± 15.99	128.19 ± 18.36	1.320	0.188
C3 (g/L)	0.86 ± 0.12	0.88 ± 0.13	1.223	0.223
C4 (g/L)	0.35 ± 0.10	0.37 ± 0.09	1.608	0.109

Note: COPD: chronic obstructive pulmonary disease; BMI: body mass index; C3: complement 3; C4: complement 4; IgE: immunoglobulin E.

smoking history, alcohol history, place of residence, al background, histamine, IgE, complement 3, nor complement 4 (all P > 0.05), as shown in **Table 1**.

Serum levels of TNF-α, IL-6 and IL-10 before and after treatment

The serum levels of TNF-α, IL-6 and IL-10 were detected by ELISA in both groups. The results showed that there was no significant difference in levels of TNF-α, IL-6 and IL-10 before treatment between the two groups (P > 0.05). However, the level of each index in the serum of the two groups was significantly lower than that before treatment (P < 0.05). Comparing the indexes of the two groups after treatment, it was found that the indexes of the experimental group were significantly lower than those of the control group, and the change of the indexes in the experimental group during the treatment was significantly higher than that in the control group (P < 0.05), as shown in **Table 2**.

Comparison of clinical efficacy

The clinical efficacy in the two groups was compared. In the control group, 55 patients were cured, 40 patients were markedly effective, 17 patients were effective, and 5 patients were ineffective. In the experimental group, 71 patients were cured, 37 patients were markedly effective, 8 patients were effective, and 1 patient was ineffective. The clinical efficacy of treatment for patients in the experimental group was significantly better than that in the control group (P < 0.05), as shown in **Table 3**.

Adverse reactions during the treatment

Adverse reactions during the treatment between the two groups were compared. In the control group, there were 5 patients with sleepiness, 3 patients who were thirsty and 2 patients with dizziness. In the experimental group, there were 3 patients with sleepiness, 2 patients who were thirsty and 2 patients with dizziness. There was no significant difference in the incidence of adverse reactions between the two groups (P > 0.05), as shown in **Table 4**.

Correlation between the expression levels of TNF-α, IL-6 and IL-10 in serum and clinical efficacy

According to the clinical efficacy after treatment, patients were divided into group A (126 patients, cure) and group B (108 patients, markedly effective + effective + ineffective).

Table 2. Comparison of serum levels of TNF-α, IL-6 and IL-10 before and after treatment

	Control group (n = 117)	Experimental group (n = 117)	t	P
TNF-α (pg/mL)				
Before treatment	45.84 ± 11.17	44.29 ± 10.22	1.107	0.269
After treatment	29.35 ± 8.57*	21.33 ± 7.22*		
Change	16.49 ± 6.75	22.96 ± 9.35	6.069	< 0.001
IL-6 (pg/mL)				
Before treatment	16.25 ± 3.66	16.05 ± 3.05	0.454	0.650
After treatment	8.35 ± 2.33*	5.84 ± 2.71*		
Change	7.89 ± 3.52	10.21 ± 4.11	4.637	< 0.001
IL-10 (pg/mL)				
Before treatment	7.38 ± 1.88	7.11 ± 1.52	0.228	1.208
After treatment	4.77 ± 1.09*	2.58 ± 1.15*		
Change	2.61 ± 1.50	4.53 ± 2.33	7.495	< 0.001

Note: TNF-α: tumor necrosis factor-α; IL-6: interleukin -6; IL-10: interleukin-10. Compared with "before treatment", *P < 0.05.

The serum levels of TNF-α, IL-6 and IL-10 in group A were significantly lower than those in group B (P < 0.05). Subsequently, Spearman correlation analysis was used to analyze the correlation between each index and clinical efficacy. The results showed that the lower the indexes, the better the clinical efficacy was, and that there was a positive correlation between them (r = 0.526, r = 0.518, r = 0.480, P < 0.001; **Table 5** and **Figure 1**).

Evaluation value of serum TNF-α, IL-6 and IL-10 levels as a measure of clinical efficacy

According to the serum levels of TNF-α, IL-6 and IL-10 in group A and group B, the ROC curves were drawn. The results showed that the area under the TNF-α curve was 0.801 (95% confidence interval (CI): 0.743-0.859). The area under the IL-6 curve was 0.797 (95 CI%: 0.737-0.856). The area under the IL-10 curve was 0.767 (95 CI%: 0.705-0.829). See **Table 6** and **Figure 2**.

Discussion

Urticaria is a clinically common skin disease that can be caused by physical factors, food factors, animal and plant factors, and intestinal diseases [19]. The main manifestations were wheal, erythema and severe itching. Clinically, chronic urticaria is a condition that lasts for more than 6 weeks with at least 2 episodes per week [20]. Although chronic urticaria is less harmful than other malignant diseases, the itching caused by the disease has a serious impact on the quality of daily life and mood of patients. Therefore, the treatment of chronic urticaria is important.

The current clinical treatment of chronic urticaria is mainly through second-generation-non-sedating antihistamines. A study by Nettis et al. found that levocetirizine alone significantly improved the condition of patients with chronic urticaria [21]; while the results of a study by Godse et al. [22] showed that a high dose (20 mg/tablet) of ebastine alone is also effective and even more effective than normal doses (10 mg/tablet) of ebastine and levocetirizine. In this study, we used levocetirizine in combination with ebastine to treat patients, both of which are common second-generation non-sedating antihistamines for the treatment of chronic urticaria. In this 4-week treatment, we observed that the treatment efficiency of the two groups reached 99.14% and 95.73%, respectively, indicating that both regimens have considerable effects on chronic urticaria. By comparing the clinical efficacy of the two groups, we found that the clinical efficacy of the experimental group was significantly better than the control group, which also suggested that the combination of drugs could increase the cure rate of patients and improve the efficacy. This was mainly due to the fact that levocetirizine is a left-handed body of cetirizine, which has a stronger inhibitory effect on histamine activity and inhibits a variety of allergic inflammatory reactions. Ebastine also acts as an H1 receptor antagonist, which has the characteristics of high selectivity and long duration of anti-inflammatory antihistamine. Although both drugs cannot pass the blood-brain barrier, the combination of the two drugs could increase the anti-histamine and anti-inflammatory effects by superimposing pharmacological effects. The combination of the two drugs had a significant effect on the improvement of the patient's condition [23, 24]. The results of Potter et al. [25] showed that no significant adverse reactions appeared after 6 weeks of levocetirizine treatment with 5 mg per day, and the most common adverse

Table 3. Comparison of clinical efficacy (n, %)

Groups	Cure	Markedly effective	Effective	Ineffective	Z	P
Control group (n = 117)	55 (47.01)	40 (34.19)	17 (14.53)	5 (4.27)	-2.525	0.012
Experimental group (n = 117)	71 (60.68)	37 (31.62)	8 (6.84)	1 (0.86)		

Table 4. Incidence of adverse reactions (n, %)

Groups	Sleepiness	Thirsty	Dizziness	Total incidence
Control group (n = 117)	5 (4.27)	3 (2.56)	2 (1.71)	10 (8.55)
Experimental group (n = 117)	3 (2.56)	2 (1.71)	2 (1.71)	7 (5.98)
x^2	0.129	0	0.254	0.571
P	0.719	> 0.999	0.614	0.450

Table 5. Comparison of serum levels of TNF-α, IL-6 and IL-10 in patients with different clinical efficacy

Groups	TNF-α (pg/mL)	IL-6 (pg/mL)	IL-10 (pg/mL)
Group A (n = 126)	20.89 ± 6.82	6.17 ± 2.15	3.05 ± 1.30
Group B (n = 108)	30.82 ± 9.13	8.83 ± 2.56	4.49 ± 1.50
t	9.422	8.591	7.825
P	< 0.001	< 0.001	< 0.001

Note: TNF-α: tumor necrosis factor-α; IL-6: interleukin -6; IL-10: interleukin-10.

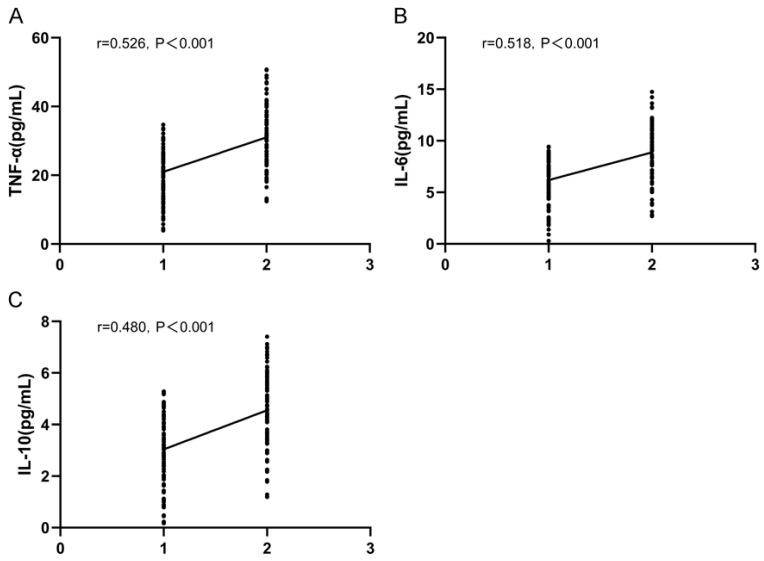

Figure 1. Relationship between serum TNF-α, IL-6 and IL-10 levels and clinical efficacy after treatment. A: The relationship between serum TNF-α level and clinical efficacy. The lower the serum TNF-α level, the better the clinical efficacy was. B: The relationship between serum IL-6 level and clinical efficacy. The lower the serum IL-6 level, the better the clinical efficacy was. C: The relationship between serum IL-10 level and clinical efficacy. The lower the serum IL-10 level, the better the clinical efficacy was. 1 = cure, 2 = markedly effective, effective, ineffective. TNF-α: tumor necrosis factor-α; IL-6: interleukin -6; IL-10: interleukin-10.

reactions were headache and lethargy, which were similar to our results. In our study, we found that the incidence of adverse reactions in the experimental group was significantly lower than that in the control group, suggesting that the adverse reactions could be reduced during treatment by combining levocetirizine with ebastine. We speculate that this was mainly due to the inability of ebastine to pass the blood-brain barrier, so it had only a slight sedative effect on the central nervous system, thus reducing the patients' severe sleepiness [26].

As an allergic disease, chronic urticaria is accompanied by an inflammatory reaction that secretes a large amount of inflammatory factors. TNF-α, IL-6 and IL-10 are important inflammatory factors, all of which will change to varying degrees after having an inflammatory response [27]. In this study, we examined these indicators in each group before and after treatment. We found that the indexes after treatment were significantly lower than those before treatment, and the changes of the indicators in the experimental group were significantly greater than those in the control group. This showed that the combination of levocetirizine and ebastine could significantly reduce the expression of inflammatory factors in patients. A study by Inaloz et al. reported that the expression of TNF-α in patients with chronic urticaria was significantly decreased after treatment [28]. A study by Papadopoulos et al. reported

Table 6. ROC parameters

Indicators	TNF-α	IL-6	IL-10
AUC	0.801	0.797	0.767
95% CI	0.743-0.859	0.737-0.856	0.705-0.829
Std. Error	0.029	0.030	0.032
Sensitivity	67.31%	76.92%	78.85%
Specificity	83.33%	73.02%	64.29%
Yoden index	50.64%	49.94%	43.13%
Cut off value	26.784 pg/mL	7.605 pg/mL	3.345 pg/mL

Note: AUC: area under the curve; 95% CI: 95% confidence interval; Std. Error: standard error; ROC: receiver operating characteristic; TNF-α: tumor necrosis factor-α; IL-6: interleukin -6; IL-10: interleukin-10.

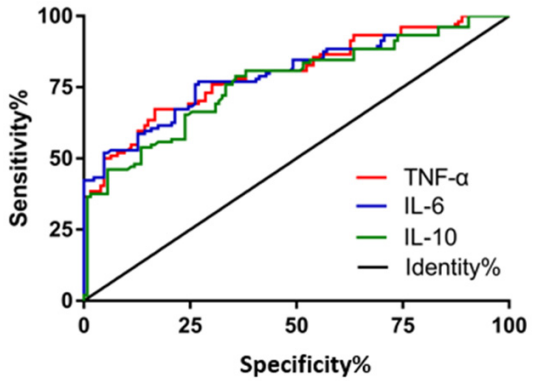

Figure 2. ROC curves of TNF-α, IL-6 and IL-10. ROC: receiver operating characteristic; TNF-α: tumor necrosis factor-α; IL-6: interleukin -6; IL-10: interleukin-10.

that after the treatment of betamethasone acetate and betamethasone phosphate for 2 weeks, the serum levels of IL-6 and IL-10 in patients with chronic urticaria were significantly reduced [27], which was consistent with our results. However, whether TNF-α, IL-6 and IL-10 can be used as indicators for the effectiveness of treatment of chronic urticaria has not been studied. Therefore, we further analyzed the difference of the serum expression levels of TNF-α, IL-6 and IL-10 between the cured patients (group A) and the markedly effective, effective and ineffective patients (group B). We found that the serum levels of TNF-α, IL-6 and IL-10 in group A were significantly lower than those in group B. Furthermore, the results of Spearman correlation analysis also showed that the lower the indicators, the better the clinical efficacy was, and that there was a positive correlation between them, indicating that these indicators can be used as potential observational indicators of chronic urticaria improvement. We finally mapped the ROC curves of TNF-α, IL-6 and IL-10 of patients after treatment in group A and group B. The results showed that the areas under the curve of TNF-α, IL-6 and IL-10 were 0.801, 0.797 and 0.767, respectively, suggesting that TNF-α, IL-6 and IL-10 can be used as potential indicators of post-treatment efficacy in patients with chronic urticaria.

In this study, it was found that levocetirizine combined with ebastine can effectively improve the condition of patients with chronic urticaria; and we found that TNF-α, IL-6 and IL-10 can be used as potential observational indicators of clinical efficacy in patients with chronic urticaria. However, there are still some shortcomings in this study. First, our study did not conduct long-term follow-up on patients, and any recurrences were not further investigated. Secondly, this study did not analyze the risk factors of clinical efficacy for patients, and it was unclear which factors had an impact on the clinical efficacy for patients. Finally, the mechanism by which the two drugs work in combination to reduce the expression of inflammatory factors has not been studied in depth. Therefore, to supplement the results of this study and confirm the correctness of the results, we will improve the follow-up of patients in future research, further analyze the risk factors affecting the treatment of chronic urticaria, and explore the mechanisms by which levocetirizine and ebastine affect the expression of inflammatory factors in patients.

In summary, TNF-α, IL-6 and IL-10 can be used as potential indicators of clinical efficacy after treatment in patients with chronic urticaria, and levocetirizine combined with ebastine can effectively improve the condition of patients with chronic urticaria.

Disclosure of conflict of interest

None.

Address correspondence to: Sheng Wang, Department of Dermatology, Tangshan Gongren Hospital, No.27 Wenhua Road, Lubei District, Tangshan 063000, Hebei Province, China. Tel: +86-0315-3722053; Fax: +86-0315-3722053; E-mail: wangsheng90q@163.com

References

[1] Zuberbier T, Aberer W, Asero R, Abdul Latiff AH, Baker D, Ballmer-Weber B, Bernstein JA, Bindslev-Jensen C, Brzoza Z, Buense Bedrikow R, Canonica GW, Church MK, Craig T, Danilycheva IV, Dressler C, Ensina LF, Gimenez-Arnau A, Godse K, Goncalo M, Grattan C, Hebert J, Hide M, Kaplan A, Kapp A, Katelaris CH, Kocaturk E, Kulthanan K, Larenas-Linnemann D, Leslie TA, Magerl M, Mathelier-Fusade P, Meshkova RY, Metz M, Nast A, Nettis E, Oude-Elberink H, Rosumeck S, Saini SS, Sanchez-Borges M, Schmid-Grendelmeier P, Staubach P, Sussman G, Toubi E, Vena GA, Vestergaard C, Wedi B, Werner RN, Zhao Z and Maurer M; Endorsed by the following societies: AAAAI, AAD, AAIITO, ACAAI, AEDV, APAAACI, ASBAI, ASCIA, BAD, BSACI, CDA, CMICA, CSACI, DDG, DDS, DGAKI, DSA, DST, EAACI, EIAS, EDF, EMBRN, ESCD, GA²LEN, IAACI, IADVL, JDA, NVvA, MSAI, ÖGDV, PSA, RAACI, SBD, SFD, SGAI, SGDV, SIAAIC, SIDeMaST, SPDV, TSD, UNBB, UNEV and WAO. The EAACI/GA (2) LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria. Allergy 2018; 73: 1393-1414.

[2] Antia C, Baquerizo K, Korman A, Bernstein JA and Alikhan A. Urticaria: a comprehensive review: epidemiology, diagnosis, and work-up. J Am Acad Dermatol 2018; 79: 599-614.

[3] Godse K, De A, Zawar V, Shah B, Girdhar M, Rajagopalan M, Krupashankar DS. Consensus statement for the diagnosis and treatment of Urticaria: a 2017 update. Indian J Dermatol 2018; 63: 2-15.

[4] Abd El-Azim M and Abd El-Azim S. Chronic autoimmune urticaria: frequency and association with immunological markers. J Investig Allergol Clin Immunol 2011; 21: 546-550.

[5] Ma CH. Clinical Epidemiological study of chronic urticaria. Chinese Journal of Practical Medicine 2014; 233-234.

[6] Liao S, Fan L, Liao H. Treatment of 40 cases of facial recurrent dermatitis with snti-allergy and snti-inflammatory lotion combined with levocetirizine hydrochloride. Herald of Medicine 2017; 36: 1374-1376.

[7] Ekiz F, Yuksel I, Ekiz O, Coban S, Basar O and Yuksel O. Levocetirizine induced hepatotoxicity in a patient with chronic urticaria. Ann Hepatol 2011; 10: 237-238.

[8] Sharma VK, Gupta V, Pathak M and Ramam M. An open-label prospective clinical study to assess the efficacy of increasing levocetirizine dose up to four times in chronic spontaneous urticaria not controlled with standard dose. J Dermatolog Treat 2017; 28: 539-543.

[9] Goyal V, Gupta A, Gupta O, Lal D and Gill M. Comparative efficacy and safety of ebastine 20 mg, ebastine 10 mg and levocetirizine 5 mg in acute urticaria. J Clin Diagn Res 2017; 11: Wc06-wc09.

[10] Godse K, Bhattar P, Patil S, Nadkarni N and Gautam M. Updosing of nonsedating anti-histamines in recalcitrant chronic urticaria. Indian J Dermatol 2016; 61: 273-278.

[11] Puxeddu I, Pratesi F, Ribatti D and Migliorini P. Mediators of inflammation and angiogenesis in chronic spontaneous urticaria: are they potential biomarkers of the disease? Mediators Inflamm 2017; 2017: 4123694.

[12] Godse K, De A, Zawar V, Shah B, Girdhar M, Rajagopalan M, Krupashankar DS. Consensus statement for the diagnosis and treatment of urticaria: a 2017 update. Indian J Dermatol 2018; 63: 2-15.

[13] Chen Q, Zhong H, Chen WC, Zhai Z, Zhou Z, Song Z and Hao F. Different expression patterns of plasma Th1-, Th2-, Th17- and Th22-related cytokines correlate with serum autoreactivity and allergen sensitivity in chronic spontaneous urticaria. J Eur Acad Dermatol Venereol 2018; 32: 441-448.

[14] Volker-Touw CM, de Koning HD, Giltay JC, de Kovel CG, van Kempen TS, Oberndorff KM4, Boes ML, van Steensel MA, van Well GT, Blokx WA, Schalkwijk J, Simon A, Frenkel J, van Gijn ME. Erythematous nodes, urticarial rash and arthralgias in a large pedigree with NLRC4-related autoinflammatory disease, expansion of the phenotype. Br J Dermatol 2017; 176: 244-248.

[15] Atwa MA, Emara AS, Youssef N and Bayoumy NM. Serum concentration of IL-17, IL-23 and TNF-α among patients with chronic spontaneous urticaria: association with disease activity and autologous serum skin test. J Eur Acad Dermatol Venereol 2014; 28: 469-74.

[16] Department of Dermatology and Venereology, Chinese Medical Association. Guidelines for the diagnosis and treatment of urticaria (2007 edition). Chinese Journal of Dermatology 2007; 40: 591-593.

[17] Zuberbier T, Aberer W, Asero R, Bindslev-Jensen C, Brzoza Z, Canonica GW, Church MK, Ensina LF, Giménez-Arnau A, Godse K, Gonçalo M, Grattan C, Hebert J, Hide M, Kaplan A, Kapp A, Abdul Latiff AH, Mathelier-Fusade P, Metz M, Nast A, Saini SS, Sánchez-Borges M, Schmid-Grendelmeier P, Simons FE, Staubach P, Sussman G, Toubi E, Vena GA, Wedi B, Zhu XJ, Maurer M; European Academy of Allergy and Clinical Immunology; Global Allergy and Asthma European Network; European Dermatology Forum; World Allergy Organization. The EAACI/GA (2) LEN/EDF/WAO Guideline for the definition, classification, diagnosis, and management of urticaria: the 2013 revision and update. Allergy 2014; 69: 868-887.

[18] Kowalski ML, Woessner K and Sanak M. Approaches to the diagnosis and management of patients with a history of nonsteroidal anti-inflammatory drug-related urticaria and angioedema. J Allergy Clin Immunol 2015; 136: 245-251.
[19] Saini S, Rosen KE, Hsieh HJ, Wong DA, Conner E, Kaplan A, Spector S and Maurer M. A randomized, placebo-controlled, dose-ranging study of single-dose omalizumab in patients with H1-antihistamine-refractory chronic idiopathic urticaria. J Allergy Clin Immunol 2011; 128: 567-573, e561.
[20] Maurer M, Metz M, Brehler R, Hillen U, Jakob T, Mahler V, Pföhler C, Staubach P, Treudler R, Wedi B, Magerl M. Omalizumab treatment in chronic inducible urticaria a systematic review of published evidence. J Allergy Clin Immunol 2018; 141: 638-649.
[21] Nettis E, Colanardi MC, Barra L, Ferrannini A, Vacca A and Tursi A. Levocetirizine in the treatment of chronic idiopathic urticaria: a randomized, double-blind, placebo-controlled study. Br J Dermatol 2006; 154: 533-538.
[22] Godse KV. Ebastine in chronic spontaneous urticaria in higher doses. Indian J Dermatol 2011; 56: 597-598.
[23] Asero R, Tedeschi A and Cugno M. Treatment of chronic urticaria. Immunol Allergy Clin North Am 2014; 34: 105-116.
[24] Antia C, Baquerizo K, Korman A, Alikhan A and Bernstein JA. Urticaria: a comprehensive review: treatment of chronic urticaria, special populations, and disease outcomes. J Am Acad Dermatol 2018; 79: 617-633.
[25] Potter PC. Levocetirizine is effective for symptom relief including nasal congestion in adolescent and adult (PAR) sensitized to house dust mites. Allergy 2003; 58: 893-899.
[26] Frare RG and Singh AK. A critical review of physicochemical properties and analytical methods applied to quantitative determination of ebastine. Crit Rev Anal Chem 2018; 48: 102-109.
[27] Papadopoulos J, Karpouzis A, Tentes J and Kouskoukis C. Assessment of interleukins IL-4, IL-6, IL-8, IL-10 in acute urticaria. J Clin Med Res 2014; 6: 133-137.
[28] Serhat Inaloz H, Ozturk S, Akcali C, Kirtak N and Tarakcioglu M. Low-dose and short-term cyclosporine treatment in patients with chronic idiopathic urticaria: a clinical and immunological evaluation. J Dermatol 2008; 35: 276-282.