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Original Article

Efficacy and mechanism of Liangxue Xiaoyin decoction for blood-heat type psoriasis

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Abstract: Objective: To evaluate the clinical efficacy and mechanism of Liangxue Xiaoyin decoction in treating blood-heat type psoriasis. Methods: Clinical data from 136 patients with blood-heat type psoriasis were retrospectively analyzed. Patients treated with Liangxue Xiaoyin decoction were included in the study group and patients treated with Avi A capsules were in the control group; 68 cases were studied in each group. Tumor necrosis factor-α (TNF-α) and interleukin-8 (IL-8) concentration in the serum were detected before and after treatment by an enzyme-linked immunosorbent assay (ELISA), and the clinical efficacy and adverse reactions of the two groups were observed after treatment. Results: The pre-treatment psoriasis area and severity index (PASI), pruritus degree score, and serum TNF-α and IL-8 levels of the test group were not significantly different from those of the control group ($P>0.05$); The total effective rate in the study group was significantly higher than that in the control group ($P<0.05$), but the adverse reaction rate in the study group was not significantly different from that in the control group ($P>0.05$). Conclusion: Liangxue Xiaoyin decoction is clinically effective for the treatment of blood-heat type psoriasis and enables the reduction of psoriasis area, relief of pruritus degree, and improvement of the clinical symptoms of patients. Liangxue Xiaoyin decoction may achieve its therapeutic effect through the inhibition of serum TNF-α and IL-8 levels and the regulation of the inflammatory reactions and immune responses of human body.

Keywords: Liangxue Xiaoyin decoction, blood-heat type psoriasis, TNF-α, IL-8

Introduction

Psoriasis, a common relapsing chronic inflammatory skin disease presenting erythema scales as the principal clinical feature, mainly invades the skin and joints of the body, with multiple layers of silvery-white scales covering the surface of the skin. The condition is divided based on its clinical features into erythrodermic psoriasis, psoriasis pustuleux, psoriasis vulgaris, and psoriasis arthropathy [1]. Relapses of psoriasis frequently occur and recovery is difficult, with a long course of the disease and opting for non-standard therapy aggravating the disease condition [2]. The incidence of psoriasis has increased over the years, and the long-term lack of recovery and repeated attacks of the disease condition exert severe adverse effects on the quality of life of the patients [3]. The pathogenesis of psoriasis is complicated; an effective prevention and treatment method is not found yet in clinical practice, and, at present, most therapies only achieve short-term clinical efficacy [2]. Therefore, the prevention and treatment of psoriasis is a focus for scholars in the field of dermatology, and it is particularly important to find drugs with greater safety and better curative effect for the prevention and treatment of psoriasis.

The pathogenesis of psoriasis has not yet been clarified and most scholars believe that the generation and progression of the disease are closely associated with immunity, metabolism, environment, gene, infection, and individual factors [4]. Immune-mediated therapy is an important focus of research on psoriasis and it has been previously established that patients with psoriasis have abnormal immune functions: cytokines function as immune-regulators in inflammation reactions and immune responses and cellular immunity play important roles in the development and progression of the disease [4, 5]. Psoriasis is similar to the "white

crust" condition recorded in traditional Chinese medicine, which was believed to be induced by the loss of nourishment in skin owing to overheating of the body, improper diet, etc. [6]. Psoriasis is classified into three types traditionally: blood dryness, blood stasis, and blood heat; it is mainly treated by adopting blood circulation, blood nourishment, and heat-clearing methods, with the blood-heat type psoriasis being the most commonly-encountered in clinical practice [7]. The initial stages of psoriasis are treated mainly by cold relief, and dampness elimination, followed by rehydration, reduction of body temperature, and cooling of blood, which involves treatment with the Chinese herbal medicines having cooling and detoxifying effects [8]. The Liangxue Xiaoyin decoction is effective in eliminating heat, cooling blood, providing relief from swelling, and detoxifying, and its components are known to exert anti-inflammatory, immune regulatory and antiviral effects [6].

Currently, the efficacy of applying Liangxue Xiaoyin decoction to treat blood-heat psoriasis and its influence on cytokines have rarely been studied or reported. In this study, patients with blood-heat type psoriasis were treated with Liangxue Xiaoyin decoction and the changes in serum tumor necrosis factor-α (TNF-α) and interleukin-8 (IL-8) expression before and after the treatment were observed, to evaluate the mechanism of Liangxue Xiaoyin decoction in the treatment of blood-heat psoriasis and to provide a reference for the clinical treatment of psoriasis.

Materials and methods

General information

Clinical data from 136 patients with blood-heat type psoriasis admitted to the Dongying People's hospital was retrospectively analyzed. Patients treated with Liangxue Xiaoyin decoction were included in the study group, whereas patients treated with Avi A capsules were in the control group with 68 cases in each group. The study group comprised 38 men and 30 women between 21 and 56 years of age with a mean age of 38.4±5.7 years. The disease courses of the patients were between 3 months to 19 years, with a mean disease course of 7.8±1.5 years. The lesion types of the patients were coin shape (18 cases), map shape (5 cases), plaque shape (8 cases), droplet shape (24 cases), and mixed shape (13 cases). The control group included 35 men and 33 women aged between 20 and 54 years of age with a mean age of 37.5±5.9 years. The disease courses of the patients varied from 5 months to 17 years with a mean disease course of 7.6±1.3 years. The lesion types of the patients were coin shape (19 cases), map shape (7 cases), plaque shape (5 cases), droplet shape (22 cases), and mixed shape (15 cases). This study has been approved by the Ethics Committee of Dongying People's hospital. All study participants had given their written informed consent before participating in the study.

Inclusion and exclusion criteria

The following inclusion criteria were applied: the patients complied with the diagnostic criteria for blood-heat type psoriasis developed in Clinical Dermatology [9] and the clinical data of the patients was complete. Patients with one or more of the following conditions were excluded: patients with severe liver and kidney disease, malignant tumors, neurological diseases, cardiovascular and cerebrovascular diseases; other skin diseases; pregnant or breast-feeding women; and patients who had taken Avi A or other drugs within the 3 months prior to enrolment in the study. This study was approved by the Ethics Committee of the Dongying People's hospital. The enrolling patients and their families were all informed of the study design and they provided informed consent.

Treatment method

The study group comprised patients treated with Liangxue Xiaoyin decoction, which has the following composition [10]: scrophulariae, 9 g; gypsum, 30 g; rehmannia root, 30 g; rhizoma imperatae, 30 g; nepeta, 9 g; anemarrhenae, 9 g; white peony, 12 g; burdock, 9 g; cohosh, 3 g; honeysuckle, 15 g; radix sileris, 9 g; and licorice, 6 g. The components were soaked for 10 min, boiled for 20 min over a high heat, and filtered twice. Approximately 450 mL of the drug liquid was administered daily in the morning and in the evening. Patients in the control group were treated with 0.5 mg/(kg.day) Avi A capsule (Chongqing Huabang Pharmaceutical Co., Ltd., batch number: H20010126) once daily. The urine routine and liver and kidney functions of the patients in both groups were

Table 1. Baseline data for study and control groups (x ± sd/[n (%)])

Category	Research group (n=68)	Control group (n=68)	t/χ^2	P
Gender			0.266	0.731
Male	38 (55.88)	35 (51.47)		
Female	30 (44.12)	33 (48.53)		
Age	38.4±5.7	37.5±5.9	0.904	0.367
Course of disease (years)	7.8±1.5	7.6±1.3	0.830	0.407
Lesion type			1.282	0.863
Coin-like	18 (26.47)	19 (27.94)		
Map-like	5 (7.35)	7 (10.29)		
Plaque	8 (11.76)	5 (7.35)		
Droplet	24 (35.29)	22 (32.35)		
Mixed	13 (19.12)	15 (22.06)		
BMI (kg/m^2)	25.23±3.42	25.71±3.16	0.850	0.396
ALT (U/L)	18.25±5.74	19.01±6.15	0.745	0.457
AST (U/L)	15.52±6.79	16.47±7.15	0.794	0.428
Glu (mmol/L)	5.89±0.76	5.94±0.69	0.401	0.688
HDL (mmol/L)	1.52±0.34	1.59±0.47	0.995	0.321
LDL (mmol/L)	1.85±0.58	1.73±0.44	1.359	0.176
TG (mmol/L)	1.12±0.43	1.01±0.53	1.329	0.186

examined during the treatment, and drug application was to be discontinued in case of detection of any abnormality. The patients returned to the hospital for re-examination once every 2 weeks during drug administration and the efficacy evaluations were conducted after 10 weeks.

Observation indicators and efficacy determination

The psoriatic area and severity index (PASI) before and after treatment in the study group and the control group were rated [11]. For the PASI scoring criteria, the body surface area was measured. The body surface area is divided into four parts: head, upper extremities, main body and lower extremities, which account for 10%, 20%, 30%, 40% of the total body surface area respectively. PASI scores: 0 points, 1 point, 2 points, 3 points, 4 points, 5 points, 6 points are expressed as skin without rash, 10% or less, 10% to 29%, 30% to 49%, 50% to 69%, 70% to 89%, 90% to 100%. The severity of skin lesions was judged by three clinical manifestations of erythema (redness), induration (thickness) and desquamation (scaling). The PASI scores ranged from 0 (no disease) to 72 (maximal disease), with higher scores indicating worse conditions. Severity parameters are measured on a scale of 0 to 4, from none to maximum. The sum of all three severity parameters is then calculated for each section of skin, multiplied by the area score for that area and multiplied by weight of respective section (0.1 for head, 0.2 for arms, 0.3 for body and 0.4 for legs). The degree of pruritus was scored as follows [12]: mild pruritus not affecting the patient's life, 2; paroxysmal pruritus affecting the patient's life, 4; violent pruritus severely affecting the patient's life, 6. The clinical efficacy after treatment in the study group and the control group was observed in reference to the Guidelines on the Clinical Studies of New Chinese Medicines [13]: an efficacy index of <95% with complete disappearance of clinical symptoms represented recovery; an efficacy index between 70% and 95% with the relief of clinical symptoms represented excellence; an efficacy index between 30% and 70% with an improvement in clinical symptoms represented effectiveness; an efficacy index <30% with non-improvement or aggravation of clinical symptoms represented ineffectiveness. The percentage of subjects with an index representing recovery, excellence, or effectiveness formed the total effective rate. Adverse reactions recorded in the study group and the control groups were nausea and retching, elevated blood lipids, edema, desquamation, headache, dizziness, and diarrhea. The percentage of the total population with adverse reactions was the incidence of adverse reactions.

Sample collection and detection

Five milliliters of venous blood was drawn from the subjects under fasting conditions, centrifuged to separate the serum, and preserved in a refrigerator at -20°C until use. The serum TNF-α and IL-8 concentrations were measured by the enzyme-linked immunosorbent assay (ELISA) [14] using a TNF-α ELISA kit (Guangdong TB Healthcare) and human IL-8 ELISA kit (Shanghai Renjie Biotechnology Co., Ltd.) in accordance with the manufacturers' instructions. The test sample and the reagent kit were

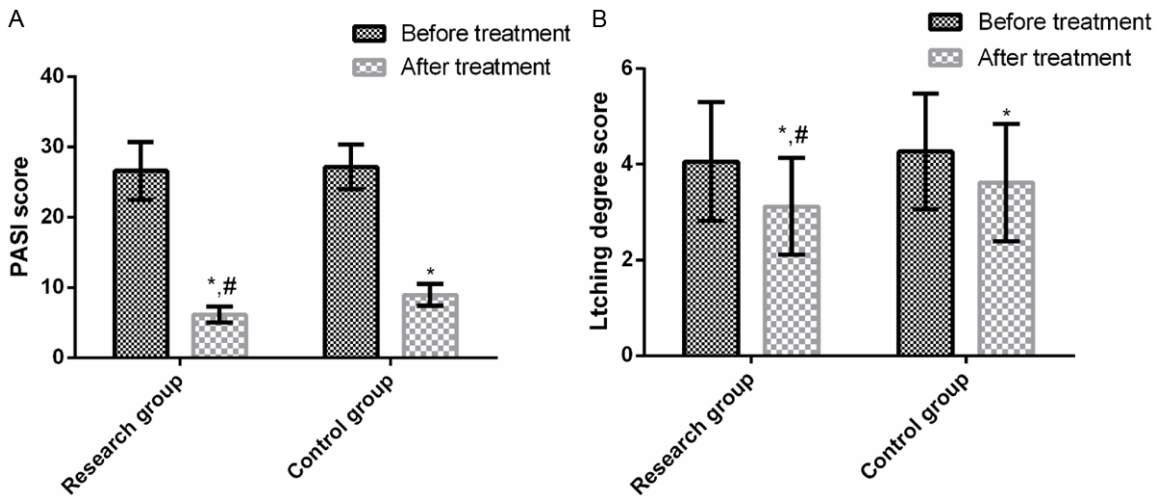

Figure 1. Comparison of PASI scores and pruritus scores before and after treatment in the study and control groups. The PASI scores of the study group and the control group before and after treatment were compared (A); the scores of the pruritus degree before and after the treatment in the study group and the control group were compared (B). Note: *P<0.05 compared with the control group; #P<0.05 compared with the control group after treatment.

removed from the refrigerator 45 min prior to equilibrate to 18°C-21°C; subsequently, the reagents were thoroughly mixed and the reaction wells, standard wells, and blank wells were established. No reagents were added to the blank wells, whereas 50 μl of the test samples and the diluted standards were added to each of the other wells. Subsequently, 50 μl of biotin-labelled antibody was added and the plates were covered and incubated for 1 h at 37°C. After incubation, the liquid in each well was discarded, the wells were dried and flushed three times, and 80 μl of streptavidin was added to each well, mixed, and incubated for 30 min at 37°C. Again, the liquid in each well was discarded and the well was dried and flushed three times; 50 μl of substrate A and working solution B were added to each well, mixed, and incubated at 37°C for 10 min, to prevent light from continuing to develop the chromatic reaction; then the plates were preserved at room temperature and 50 μl of stop solution was added to each well. Finally, the OD value of each well was measured at 450 nm by using a fully automated microplate reader (Beijing Perlong Technology Co., Ltd.) and the TNF-α and IL-8 concentrations were calculated.

Statistical method

SPASI17.0 (Yijun (Shanghai) Information Technology Co., Ltd.) was used for statistical analysis. The measurement data were expressed as the mean ± standard deviation (x ± SD); *t*-test was used for the comparison of measurement data between the groups and chi-square test was used for the comparison of enumeration data between the groups. *P* values of <0.05 were considered to indicate statistically significant differences.

Results

Baseline data

The general clinical baseline data, including the mean gender, age, course of disease, lesion type, body mass index (BMI), alanine transaminase (ALT), enzymes aspartate transaminase (AST), blood glucose (Glu), high density lipoprotein (HDL), low density lipoprotein (LDL), and total cholesterol (TG) were not significantly different between the study group and the control group (P>0.05) (**Table 1**).

PASI and pruritus scores before and after treatment in the study and control groups

The pre-treatment and post-treatment PASI scores in the study group were 26.57±4.12 and 6.13±1.13, respectively, and the pre-treatment and post-treatment pruritus degree scores in the study group were 4.06±1.24 and 3.12±1.01, respectively. The pre-treatment and post-treatment PASI scores in the control group were 27.16±3.15 and 8.94±1.57, respec-

Table 2. Comparison of clinical efficacy after treatment in study group and control group [n (%)]

Groups	n	Get well	Significantly	Effective	Invalid	Total efficiency (%)
Research group	68	14 (20.59)	41 (60.29)	6 (8.82)	7 (10.29)	61 (89.71)
Control group	68	5 (7.35)	28 (41.18)	14 (20.59)	21 (30.88)	47 (69.12)
χ^2	-	-	-	-	-	8.815
P	-	-	-	-	-	0.005

tively, and the pre-treatment and post-treatment pruritus degree scores in the control group were 4.27±1.21 and 3.62±1.23, respectively. The pre-treatment PASI scores and pruritus degree scores were not significantly different between the study group and the control group (P>0.05); the post-treatment PASI scores were significantly lower than the pre-treatment scores in both the study and control groups (*t*=39.450, P<0.001; *t*=42.690, P<0.001, respectively); the post-treatment PASI score in the study group was significantly lower than that in the control group (*t*=11.980, P<0.001); the post-treatment pruritus degree scores in the study and control groups were significantly lower than the respective pre-treatment scores (*t*=4.847, P<0.001; *t*=3.107, P=0.002); and the post-treatment pruritus degree scores of the study group was significantly lower than that of the control group (*t*=2.591, P=0.010; **Figure 1A** and **1B**).

Clinical efficacy in the study and control groups after treatment

In the study group, the efficacy results of recovery, excellence, effectiveness, and ineffectiveness were observed in 14 (20.59%), 41 (60.29%), 6 (8.82%), and 7 (10.29%) cases, respectively, with a total effective rate of 89.71%; in the control group, the results of recovery, excellence, effectiveness and ineffectiveness were found in 5 (7.35%), 28 (41.18%), 14 (20.59%), and 21 (30.88%) cases, with the total effective rate of 69.12%. The total effective rate of the study group was significantly higher than that of the control group (χ^2=8.815, P=0.005; **Table 2**).

Changes in serum TNF-α and IL-8 levels before and after treatment in the study and control groups

The pre-treatment and post-treatment serum TNF-α concentration in the study group were 36.45±6.89 pg/ml and 13.25±3.47 pg/ml, respectively, whereas the pre-treatment and post-treatment serum IL-8 levels in the study group were 86.25±9.03 pg/ml and 43.52±5.74 pg/ml, respectively. The pre-treatment and post-treatment serum TNF-α concentration in the control group was 37.25±7.01 pg/ml and 16.85±3.85 pg/ml, respectively, and the pre-treatment and post-treatment serum IL-8 concentration in the control group was 85.26±8.77 pg/ml and 50.14±6.42 pg/ml, respectively. There was no significant difference in the pre-treatment serum TNF-α and IL-8 concentrations between the study group and the control group (P>0.05); the post-treatment serum TNF-α concentrations in the study and control groups were significantly lower than the respective pre-treatment concentrations (*t*=24.800, P<0.001; *t*=21.030, P<0.001); the post-treatment serum TNF-α concentration in the study group was significantly lower than that in the control group (t=7.654, P<0.001); the post-treatment serum IL-8 concentrations in the study and control groups were significantly lower than their respective pre-treatment values (*t*=32.930, P<0.001; *t*=26.65, P<0.001); and the post-treatment serum IL-8 concentration in the study group was significantly lower than that in the control group (t=6.339, P<0.001; **Figure 2A** and **2B**).

Incidence of adverse reactions in the study and control groups

The principle adverse reactions in the study group and the control group included nausea, retching, edema, headache, dizziness, and diarrhea. The incidence of adverse reactions between the study group and the control group was not statistically different (P>0.05) (**Table 3**).

Discussion

Psoriasis is a clinically common chronic and relapsing erythematous scaly dermatosis with varying incidence worldwide. Patients with pso-

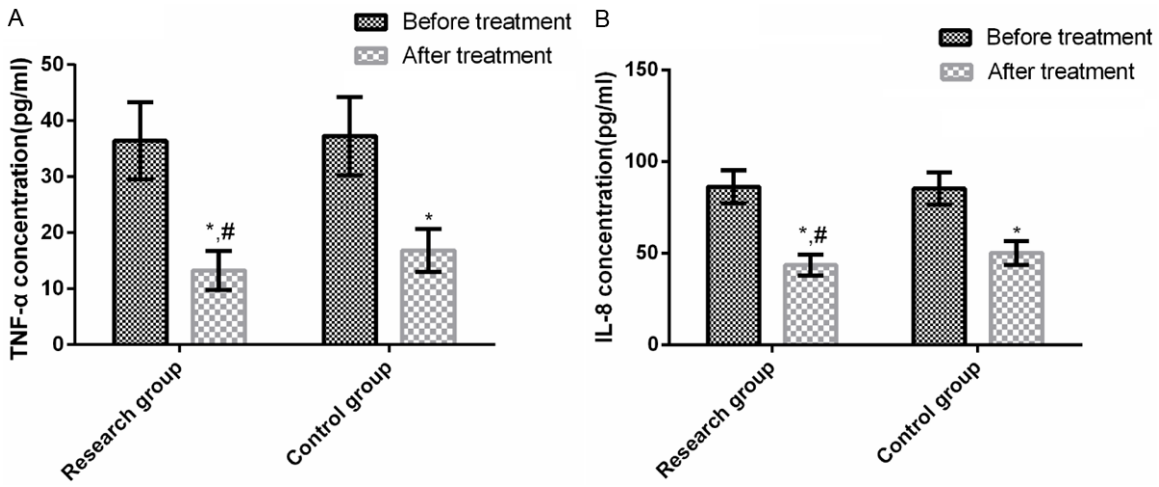

Figure 2. Comparison of serum TNF-α and IL-8 concentrations in the study and control groups before and after treatment. The serum TNF-α concentrations in the study and control groups were compared before and after treatment (A); the serum IL-8 concentrations in the study and control groups before and after treatment were compared (B). Note: *P<0.05 compared with the control group; #P<0.05 compared with the control group after treatment.

Table 3. Comparison of the incidence of adverse reactions in study and control groups [n (%)]

Groups	n	Nausea and retching	Edema	Headache dizziness	Diarrhea	Incidence of adverse reactions (%)
Research group	68	3 (4.41)	1 (1.47)	2 (2.94)	2 (2.94)	8 (11.76)
Control group	68	4 (5.88)	2 (2.94)	1 (1.47)	3 (4.41)	10 (14.71)
χ^2	-	-	-	-	-	0.256
P	-	-	-	-	-	0.801

riasis are predominantly young adults with chronic, long-lasting, and recurring disease, accompanied by severe desquamation, extensive skin lesions, and joint invasion, which adversely and severely affects patients' quality of life [15]. At present, the existing treatment of psoriasis can only achieve short-term therapeutic remedies and does not prevent recurrence, as there is no specialty drug for the treatment of psoriasis [16]. Therefore, it is of great significance to develop drugs with higher safety and better efficacy for the prevention and treatment of psoriasis.

The clinical course of psoriasis, known as "white crust" in traditional Chinese medicine, is divided into stationary, progressing, and recovery phases [17]. The principle manifestations of progressing psoriasis are the constant appearance of new rashes, extended skin lesions, thicker scales, inflammation infiltration, and severe itching. The blood-heat type psoriasis is usually treated superficially to relieve the symptoms and the condition will aggravate if the drug is applied improperly [18]. In clinical practice, retinoids, calcitriol, and other drugs are usually applied for the treatment, but the extent of these drugs is limited by the induction of a series of adverse reactions when used for the treatment of progressing psoriasis. Therefore, these drugs are globally recommended for the treatment of psoriasis with slow progression, mild symptoms, and fewer skin lesions [19]. The blood-heat type psoriasis is mainly caused by cold invasion hidden in the blood and the skin, which induces wind and blood-heat over a long time and is present on the surface of the skin; the traditional Chinese treatment for the disease is based on detoxification, cold expelling, blood cooling, and heat relief [20]. Liangxue Xiaoyin decoction originated from *Zhu Renkang's Clinical Experience Collection* [21], wherein the effective use of the herbs anemarrhena, honeysuckle, and raw gypsum to defuse the excessive heat in the qi system; the radix rehmanniae was applied for heat removal and blood cooling in combination with white peony, rhizoma imperatae, and scrophu-

lariaceae; the radix sileris and herba schizonepetae were indicated for symptoms and cold; the rhizoma, fructus arctii and licorice were, respectively, applied for detoxification, reducing heat, and reconciliation. The results of this study showed that the post-treatment PASI and pruritus degree scores in the study group and control group were significantly lower than the corresponding pre-treatment scores; moreover, the post-treatment PASI and pruritus degree scores in the study group were significantly lower than those in the control group. The total effective rate in the study group was also significantly higher than that of the control group, which suggested that Liangxue Xiaoyin decoction had greater clinical efficacy for the treatment of blood-heat type psoriasis and was more effective in reducing the skin lesion area, relieving the degree of itching, and improving the clinical symptoms of patients. The studies of Zhou et al. [22] showed that Liangxue Xiaoyin decoction had good efficacy in psoriasis for the improvement of the microcirculation of the patients, inhibition of epithelial cell division, and promotion of epidermal cell differentiation, which was similar to the result of this study.

At present, it is believed that psoriasis is a multigene hereditary disease with multiple interacting factors; the mechanism of occurrence is thought to be closely associated with immune function disorders. Most researchers are convinced that psoriasis is an autoimmune inflammatory disease, as the release of cytokines plays an important role in the onset and pathology maintenance of psoriasis and some pro-inflammatory cytokines, such as TNF-α and IL-8, are closely associated with the occurrence and development of psoriasis [23]. The multi-effector cytokine TNF-α is generated by macrophages and functions as an immunomodulatory and pro-inflammatory agent in addition to its suppressive or toxic effects on tumor cells [24]. TNF-α promotes the production of cytokines, regulates immune response, and triggers a severe inflammatory reaction through the induction of keratinocytes to increase intercellular adhesion molecule-1, thereby promoting skin infiltration by inflammatory cytokines [25]. IL-8 is a intensely biologically active inflammatory factor that is important in inflammation and immunopathology; it has a chemotactic effect on T cells and neutrophils and promotes the proliferation of keratinocytes and the generation of vessels, which results in an increasingly severe inflammatory response [26]. The studies of Arican et al. [27] showed that TNF-α and IL-8 were involved in the occurrence and development of active psoriasis and that the concentrations of both were relevant in the assessment of the severity of the disease; therefore, TNF-α and IL-8 may play an important role in the pathogenesis of blood-heat psoriasis. The results of this study showed that serum TNF-α and IL-8 concentrations in the study and the control groups after the treatment were significantly lower than those before the treatment and that the serum TNF-α and IL-8 concentrations in the study group after the treatment were significantly lower than those in the control group after treatment; these results implied that Liangxue Xiaoyin decoction may be used to treat patients with blood-heat type psoriasis, and that the effects were mediated through the inhibition of the serum concentration of TNF-α and IL-8 and the regulation of the inflammatory and immune responses.

The study was conducted in strict accordance with the inclusion criteria and exclusion criteria to screen subjects, and the study group and the control group were not significantly different in sex, age, disease course, lesion type, BMI, ALT, AST, Glu, HDL, LDL, and TG, which ensured the rigorousness and reliability of the study. In this study, some adverse reactions were reported by the patients after treatment and the specific regulation mechanisms of TNF-α and IL-8 in blood-heat psoriasis were not discussed. Therefore, the scope of this study was limited, and further studies shall explore an effective and safe therapy generating fewer adverse reactions and the mechanisms of TNF-α and IL-8 in the regulation of blood-heat type psoriasis.

In summary, Liangxue Xiaoyin decoction is clinically effective for the treatment of blood-heat type psoriasis owing to reduced skin lesion area, relief of the degree of itching, and improved clinical symptoms. Liangxue Xiaoyin decoction may function through the inhibition of serum TNF-α and IL-8 and the regulation of the inflammatory reaction and immune response in patients.

Disclosure of conflict of interest

None.

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