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Original Article

Treatment of psoriasis by compound glycyrrhizin injection and its effects on peripheral blood Th17 cell proportion and IL-22 concentration

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Abstract: Objective: To observe the therapy efficacy of compound glycyrrhizin for psoriasis vulgaris and investigate peripheral blood Th17 cell proportion and IL-22 level changes, patients were evaluated before and after the treatment. Methods: One hundred patients with psoriasis vulgaris were recruited in our hospital from June 2015 to June 2016. Two groups (glycyrrhizin for compound glycyrrhizin plus standard treatment, standard for general treatment) were allocated randomly. Forty healthy people were selected as the control group (control). The therapy efficacy of compound glycyrrhizin was evaluated through changes of Psoriasis Area and Severity Index (PSAI) score. The safety of compound glycyrrhizin was expressed as changes in blood pressure, blood and urine routine, live and renal function parameters as well as electrolyte balance. Before and 4 weeks after the treatment, peripheral blood of each group was further collected to detect the percentage of Th17 cells and IL-22 expression concentrations. Results: Compound glycyrrhizin plus standard treatment showed higher effective rate for psoriasis vulgaris than standard treatment (87% vs. 62%, $P<0.05$). Patients with psoriasis vulgaris showed higher percentage of Th17 cells and increased IL-22 concentrations in the peripheral blood compared with healthy controls (both $P<0.05$). The decreasing of Th17 cell proportion and IL-22 level showed positive correlation with PSAI grade. Compound glycyrrhizin plus standard treatment resulted more decreases in peripheral blood Th17 cell proportion and IL-22 concentration compared with standard treatment ($P<0.05$). No significant changes were found for blood pressure, blood and urine routine, liver and renal function parameters as well as electrolyte balance during compound glycyrrhizin treatment (both $P>0.05$). Conclusion: Th17 and IL-22 may be related to the pathogenesis of psoriasis. The combination of compound glycyrrhizin and standard treatment showed good efficacy, which may be related with the decreasing of Th17 cell proportion and IL-22 levels.

Keywords: Psoriasis, compound glycyrrhizin, Th17 cell, IL-22

Introduction

Psoriasis is a chronic inflammatory autoimmune skin disease with an abnormal proliferation of keratinocytes. According to the clinical features, psoriasis can be divided into four types: vulgaris type, arthropathia type, pustule type and erythrodermia type. The most commonly type is the psoriasis vulgaris. The duration of psoriasis vulgaris is relatively long, which is not sensitive or tolerant to conventional drugs. Its pathogenesis and etiology are not fully understood until now [1]. The abnormal proliferation of $CD4^+$ T cells in patients may related to the pathogenesis of psoriasis in the previous studies [2, 3]. For a long time, researchers believed that Th1 cells are closely associated with the pathogenesis of psoriasis. However, as the Th17 cell was found several years ago, more and more studies revealed the important role of Th17 cell in many different autoimmune inflammatory diseases [4, 5].

IL-22 is an inflammatory factor which secreted by Th17 and Th22 cells. After companion with other proinflammatory factors, IL-22 could affect the changes of epidermis and the role of keratinocytes in psoriasis [6]. Compound glyc-

yrrhizin is extracted from licorice, which is a traditional Chinese medicine. Compound glycyrrhizin has several therapeutic functions, including anti-inflammatory, anti-allergies and suppressing the virus activity, protecting the liver cells, and immunomodulatory effects [7]. The previous studies showed that the compound glycyrrhizin can achieve immunomodulation by reducing capillary permeability, increasing INF-γ, activating NK cells and T cells and inhibiting complement response [8-10].

The aims of this study were to investigate the relationship between Th17 cell/IL-22 levels and psoriasis vulgaris severity. Moreover, the efficacy and safety of compound glycyrrhizin in treating psoriasis vulgaris and the effects of compound glycyrrhizin on Th17 cell /IL-22 levels were also evaluated.

Materials and methods

Patients

This study has got approval from local ethical committee. One hundred participants who suffered from psoriasis vulgaris were recruited in our hospital from June 2015 to June 2016. The inclusion criteria were consisted of (A) meeting the diagnostic criteria for psoriasis [11], (B) no use of glucocorticoids, immunosuppressive agents, immunomodulators and other drugs in the last month, (C) no formal systematic treatment been conducted in recent two months, (D) the patients and family members understanding and signing the informed consent. The exclusion criteria consisted of (A) concomitant with other skin diseases, infectious diseases, autoimmune diseases, (B) severe liver and kidney damage and other organic lesions, (C) allergic to compound glycyrrhizin, (D) women in gestation and lactation period.

One hundred patients including 54 male and 46 female, from 23 to 62 years old were involved. The duration of the disease was from 2 months to 15 years. The 100 patients were randomly and equally allocated to compound glycyrrhizin plus standard treatment (group A) and standard treatment only (group B). There was no significant difference between the two groups (P=0.325, P>0.05) for gender, age, course and staging of disease. In the control group (group C), 40 cases of healthy people were selected in our hospital, also showed no significant difference in gender and age between group C and medication groups (A and B).

Intervention

Combination treatment was employed in group A as follows: compound glycyrrhizin injection (Stronger Neo-Minophagen C, Minophagen pharmaceutical, Japan) 60 ml was added in 250 ml of 5% glucose liquid (ivgtt, once per day); acitretin capsule (Fangxi, Huabang pharmaceutical, China) 10 mg, 3 times per day (po) and calcipotriol ointment (Brightfuture pharmaceutical, China), 2 times per day for external use. The standard treatment group (group B) was only treated with acitretin capsule and carpodiol ointment.

The treatment period was 4 weeks with continuous follow-up. The efficacy was analyzed when medication was over.

Outcome measures

Therapy efficacy: The severity of psoriasis vulgaris and the clinical efficacy were evaluated by skin lesions according to the Psoriasis Area and Severity Index (PASI) scoring method [12]. The total score was 72, and the higher score indicates more serious of the disease. The efficacy was determined based on the curative effect index. Curative effect index = (PASI score - PASI score before treatment)/pretreatment PASI score *100%. Cleared: PASI score is greater than 90%, good: 60%< PASI score <90%, fair: 20%< PASI score <60%, slight and unchanged: PASI score <20%. Treatment effective rate = (cleared + good + fair)/total number *100%.

Safety: The two groups of patients were examined for liver and kidney function, routine blood and urine tests, blood pressure, heart rate, blood biochemical index before and after treatment. Side effects (including hypokalemia, hypertension, abdominal pain) and adverse reactions (including pseudo aldosteronism, and rhabdomyolysis, such as low muscle strength, muscle pain, limb spasm and paralysis) were recorded during the treatment. The patient who experienced serious adverse reaction was excluded for further treatment, and the efficacy were deemed as ineffective.

Th17 cell and IL-22 levels determination: The percentage of Th17 cells and the level of IL-22

Table 1. Participant's information of three groups

Item	Case	Gender		Average age	Average duration years of disease	Time to progression	Static period
		Male	Female				
Group A	50	28	22	35.2±5.7	5.2±1.2	32	18
Group B	50	26	24	36.5±4.2	5.8±1.1	26	24
Group C	40	25	25	36.8±3.9	-	-	-
P	-	0.576		0.624	0.376	0.662	

Note: Group A, compound glycyrrhizin plus standard treatment; Group B, standard treatment only; Group C, control group.

Table 2. Correlation between Th17/IL22 and PASI score

Item	Th17 cell		IL-22	
	r	P	r	P
Group A and B	0.75	0.002	0.82	0.001

Note: Group A, compound glycyrrhizin plus standard treatment; Group B, standard treatment only.

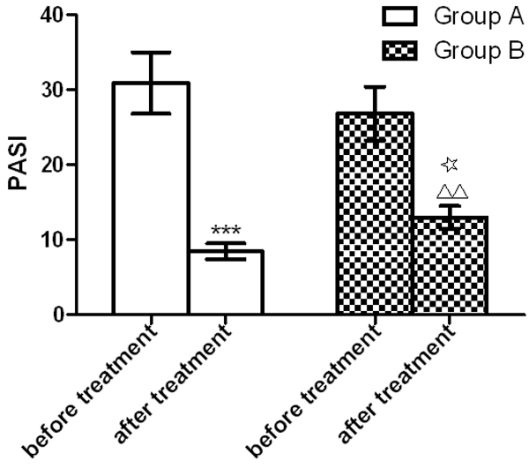

Figure 1. PASI scores of two groups before and after treatment. Group A, compound glycyrrhizin plus standard treatment; group B, standard treatment only. PASI scores were significantly different before and after treatment in group A, and the PASI score significantly decreased after treatment (***P<0.001). PASI scores were significantly different before and after treatment in group B, and the PASI score significantly decreased after treatment (△△P<0.01). The treatment of group A showed better efficacy than that in group B (☆P<0.05).

in peripheral blood were analyzed as follows. Peripheral venous blood (4 ml) of participants from each group was collected. The percentage of Th17 cell in peripheral blood was tested by flow cytometry. Anti-CD4-PE and anti-CD8-FITC antibodies were added to the whole blood, and incubated without light for 30 min. NH4Cl hemolysis reagent, fixative solution, hemolytic and membrane breaking solution were added in turn into the whole blood solution. Discarding supernatant after centrifuge and incubation without light were needed for each step. Finally, Anti-IL-17-PE antibody was added into the solution, and incubation without light before flow cytometry. Anti-IgG1-PE antibody was employed as negative control. For IL-22 level determination, specific ELISA kit was used for serum. The serum of each participant was collected through 30-min low speed centrifugation from whole blood. The relationship between the percentage of Th17 cell or IL-22 level and PASI score were further investigated.

Statistical analysis

SPSS17.0 software was employed for data analysis. The data was expressed by mean ± standard deviation (mean ± SD). The comparison between group A and B was conducted with independent sample t test. The comparison among group A, B and C was measured with One-Way ANOVA. The counting data was tested by χ^2. The relationship between the percentage of Th17 cells and the expression level of IL-22 and PASI score was analyzed by Pearson correlation analysis. P<0.05 indicated statistically significant difference.

Results

Participant's characteristics

Participant's characteristics are shown in **Table 1**. No differences in age or sex distribution were found among three groups. Patients in compound glycyrrhizin and standard treatment group were similar in the duration of disease and disease phase.

Correlation between Th17 cell proportion or IL-22 level and PASI score

Th17 cell proportion or IL-22 level and PASI score were collected for group A and B before and after treatment. Using Pearson correlation analysis, the positive correlation between Th17 or IL-22 levels and PASI score was confirmed. The higher proportion of Th17 cell or IL-22 level indicated the higher PASI score. The lower per-

Table 3. Comparison PASI scores of before and after treatments in two groups

Item	Case	PASI score		Effective rate (%)	P
		Before treatment	After treatment		
Group A	50	30.93±13.26	8.47±3.88	87	<0.001
Group B	50	26.87±13.44	13±5.66	62	0.0062
P	-	0.0956	0.0327	-	-

Note: Group A, compound glycyrrhizin plus standard treatment; Group B, standard treatment only.

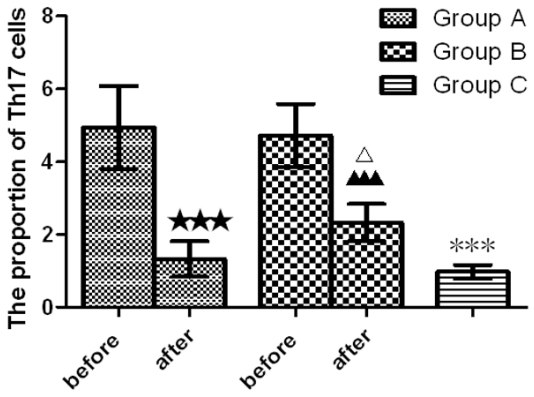

Figure 2. Th17 cell proportion before and after treatment. Group A, compound glycyrrhizin plus standard treatment; group B, standard treatment only; group C, the control group. The Th17 cell proportion in group A and B was significant higher than that of group C before treatment (***P<0.001). The proportion of Th17 cells in group A was decreased significantly after treatment (★★★P<0.001). The proportion of Th17 cells in group B was decreased after treatment (△P<0.05). Compared with group B after treatment, the proportion of Th17 cells in group A was decreased significantly (▲▲▲P<0.001).

centage of Th17 and IL-22, the lower PASI score was observed (**Table 2**).

Efficacy

Before the treatment, there was no significant difference in PASI scores between group A and B (P=0.0956, P>0.05). PASI scores of both groups decreased significantly after the treatment compared with the scores before treatment (both P<0.05). The effective rate of group A (87%) was significantly higher (P<0.05) than that of group B (62%, **Figure 1**, **Table 3**).

Th17 cell proportion in $CD4^+CD8^-$ lymphocytes in peripheral blood

Comparison with group C, two treated groups showed significantly higher Th17 cell proportion in peripheral blood (both P<0.05). The data showed no significant difference of Th17 cell proportion before treatment between group A and B (P=0.134, P>0.05). After treatment, Th17 cell proportion of group A and B all showed significant decrease when compared with pre-treatment (both P<0.05). Comparison with group B, Patients in group A showed significantly decreased proportion of Th17 cells after treatment (P<0.05, **Figure 2** and **Table 4**).

IL-22 level in peripheral blood

The IL-22 levels in the group A and B of patients were significantly higher than that in normal participants (both P<0.05). The IL-22 levels in serum in those two groups after treatment was decreased when compared with the levels before treatment. Moreover, IL-22 concentration was significantly decreased in group A (P<0.05) than that of group B after treatment. The data is shown on **Table 5** and **Figure 3**.

Adverse reactions

Three patients in group A developed hypokalemia symptoms, but recovered the normal level of potassium by oral supplement potassium. There were 5 patients in group B with lip dry scalp off, 1 patient with mild edema of both lower extremities. All symptoms disappeared after proper treatments. There was no significant difference between the two groups for the incidence of adverse reaction (P=0.0726, P>0.05).

Discussion

Many kinds of psoriasis are observed and investigated until now. The pathogenesis of psoriasis is complicated, including genetics, immune factors, environmental factors, the infection factors and other aspects. In recent years, researchers are focusing on the immunologic mechanism which is considered as important reason for psoriasis. According to the previous research, the abnormal activation of T cells and of a series of cytokines which released by T cells, played very important role in the pathogenesis and the development of the disease [13]. For example, the early study showed that $CD4^+$ T cells play a role in the occurrence and development of psoriasis [14]. The $CD4^+$ T cells are divided into helper T cells and regulatory T cells. Moreover, regulatory T

Table 4. Proportion of Th17 cell in peripheral blood before and after treatment

Item	Case	Before treatment (%)	After treatment (%)	P
Group A	50	4.94±1.1	1.33±0.47	<0.001
Group B	50	4.71±0.84	2.33±0.49	0.0265
Group C	40	0.98±0.18	-	-
P (group A and B)	-	0.134	<0.001	-

Note: Group A, compound glycyrrhizin plus standard treatment; Group B, standard treatment only; Group C, control group.

Table 5. IL-22 levels in each group before and after treatment

Item	Case	Before treatment (pg/mL)	After treatment (pg/mL)	P
Group A	50	50.19±14.94	16.36±3.90	<0.001
Group B	50	49.95±12.58	25.65±4.25	0.0036
Group C	40	11.75±3.24	-	-
P (group A and B)	-	0.782	<0.001	-

Note: Group A, compound glycyrrhizin plus standard treatment; Group B, standard treatment only; Group C, control group.

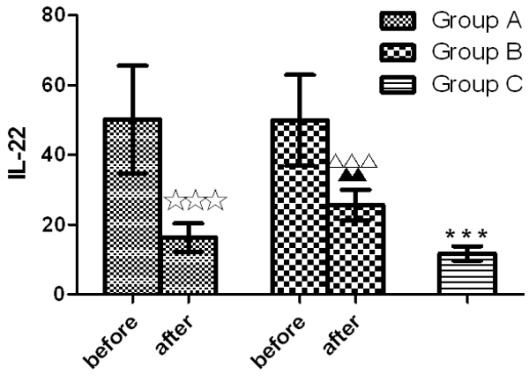

Figure 3. IL-22 levels in each group before and after treatment. Group A, compound glycyrrhizin plus standard treatment; group B, standard treatment only; group C, the control group. IL-22 levels in group A and group B were significantly higher than that in group C before treatment (***P<0.001). IL-22 level was significantly decreased after treatment in group A (☆☆☆P<0.001). IL-22 level was significantly decreased after treatment in group B (▲▲P<0.01). Compared with group B after treatment, IL-22 level in group A was decreased significantly (△△△P<0.001).

cells consisted of type 1 and type 2 cells [15]. IFN-γ, TNF-β and IL-12 cytokines which mediate cellular immunity were produced in Th1 cells, whereas IL-4, IL-5, IL-6, IL-13 and other cytokines which mediate humoral immunity were secreted by Th2 cells [16, 17].

For a long time, researchers believed that the psoriasis is induced by the imbalance between Th1 and Th2 cells [18-20]. However, more and more studies showed that this could not fully explain the pathogenesis of psoriasis. In recent years, a new type of T lymphocyte was found which can produce IL-17 and the name of Th17 cell was given to this new type of T cell [21]. Th17 is a completely different type cell when comparison with Th1 and Th2. It has unique immuno-regulation mechanism. The main feature of Th17 cell is the production of IL-17 and IL-22, but not IL-4 and IFN-α [22]. The differentiation in human body mainly depends on the IL-23 and IL-1β. IL-23 is an important cytokine for maintaining Th17 cell stable and mature. The recent studies shown that the IL-23/Th17 shaft played an important role in the development of psoriasis [23-25].

In this study, we found that Th17 cell was associated with the pathogenesis of psoriasis, and its proportion was positively correlated with disease severity. These results further confirmed the role of Th17 cell in the development of psoriasis. We also found that IL-22 (secretory factor of Th17 cell) level in patients were significantly higher than that in healthy people. The results also showed positive correlation between severity of psoriasis and IL-22 in patients. Thus, it suggests that the IL-22 may also participate in the development of psoriasis.

IL-22 exerts its biological function mainly through the specificity binding with receptor *in vivo*. The target cells are mainly epithelial cell. IL-22 binds with several different types of receptors to induce cell to produce cytokines, acute reactive protein, chemokines, and other inflammatory factors or antimicrobial peptides [26]. Then the downstream signals will participate in the inflammatory response. The previous study showed that IL-22 down-regulated keratinocyte differentiation related gene and protein expression levels, and inhibited differentiation of keratinocyte. Then it induced the skin lesions which were typical symptoms of psoriasis [27]. Meanwhile, other studies confirmed that IL-22 expression level in the skin tissues with psoriasis is higher than normal skin [28-30].

In this study, the results confirmed the viewpoints in previous studies, and showed that Th17 and IL-22 play an important role in the development of psoriasis. However, this study is limited to Th17 cell and IL-22, and IL-22 is not only secreted by Th17 cell, but also by Th22 cell, which is the main source of IL-22. Thus, more research was need to be performed to investigate that the changes of IL-22 level were caused by Th17 cell only, or other regulation factors such as Th22 cell. Moreover, other secretory factors of Th17 cell whether affect the development of psoriasis are also needed to be evaluated.

Compound glycyrrhizin is a kind of compound preparations, commonly used in the treatment of various skin allergic diseases in dermatological department. It also has been shown immunomodulatory effect *in vitro*, including the effect on T cells, NK cells, IFN-γ, and so on. Therefore, compound glycyrrhizin can be used for the treatment of psoriasis theologically. This study showed the efficacy and adverse reaction of compound glycyrrhizin combined with acitretin capsule and calcipotriol ointment significantly better than that without compound glycyrrhizin. This research provided new sights and approaches for treatment of psoriasis. Acitretin capsule is a classic first-line drug for the treatment of psoriasis, but its side effects, adverse reaction had been noticed. Thus, this combination method could reduce the dose and duration, also adverse reaction of acitretin capsule. There were limited time and participants in this study, so large number of adverse reactions did not occur. This paper also confirmed that the proportion of Th17 cell and IL-22 expression level decreased significantly in compound glycyrrhizin combined treatment group than the treatment group without compound glycyrrhizin. The result showed that lower proportion of Th17 cells and IL-22 expression level may benefit the compound glycyrrhizin treatment of psoriasis. Then it regulates the Th17 and IL-22 mediated inflammatory response, which may be one of the mechanisms of compound glycyrrhizin treatment in psoriasis. But the certain mechanism of compound glycyrrhizin for down-regulation of Th17 cell and IL-22 is still not clear, and need to be investigated in the future studies.

Disclosure of conflict of interest

None.

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