

Original Article

The effects of acitretin on patients with psoriasis vulgaris

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Abstract: Objective: To study acitretin combined with narrow-band ultraviolet on patients with psoriasis vulgaris and to analyze the recurrence risk factors. Method: The patients in the control group (n = 75) were given narrow-band ultraviolet therapy, and those in the observation group (n = 75) received acitretin capsules in addition to the narrow-band ultraviolet therapy. The basically recovered patients and the significantly improved patients were categorized into the good curative effect group. The improved patients and ineffectual treatment patients were categorized into the poor curative effect group. Any recurrence within 1 year after the treatment was documented. The patients were divided into the recurrence group and the non-recurrence group based on their recurrence. The clinical data were collected for a single-factor analysis. The binary logistic regression method was adopted to analyze the independent risk factors for recurrence. Results: After the treatment, the expressions of IL-17 in the observation group were significantly lower than they were in the control group ($P < 0.05$). The clinical curative effect in the control group was significantly poorer than it was in the observation group ($P < 0.05$). The expressions of IL-17 in the good curative effect group were significantly lower than they were in the poor curative effect group ($P < 0.05$). The multi-factor logistic regression analysis showed that alcoholism, family history, infection, and irregular medication use were independent risk factors for recurrence. Conclusions: Compared with narrow-band ultraviolet alone, acitretin combined with narrow-band ultraviolet can effectively reduce the expression of IL-17 in the serum and can improve the patients' conditions, but alcoholism, family history, infections, and the irregular use of acitretin are the independent risk factors for recurrence.

Keywords: Acitretin, narrow-band ultraviolet, psoriasis vulgaris

Introduction

Psoriasis is a common dermatological inflammatory disease also known as serpedo. Its clinical manifestation is squamous plaques or erythema [1]. Studies have shown [2] that psoriasis is more common on the scalp and lower limbs. Keratoplasia and hyperkeratosis with parakeratosis can be observed in the focal area after onset. A study by Nair et al. [3] showed that the global incidence of psoriasis is about 0.1-5.0%, and the incidence varies by race and region. Psoriasis vulgaris occurs in more than 90% of patients with psoriasis and is more common in young adults. Psoriasis vulgaris is characterized by a longer course of the disease and frequent recurrence, and there is no effective radical treatment currently [4]. The pathogenesis has not been clearly demonstrated. However,

most studies have shown [5] that the pathogenesis is closely related to infection, heredity, and the environment.

As an inflammatory disease, psoriasis is mainly treated with anti-infectives and anti-inflammatories [6]. Acitretin is a common drug for the clinical treatment of psoriasis. A second-generation tretinoin, oral acitretin can regulate the mitosis of keratinocytes. Thus, the differentiation and proliferation of skin lesions return to normal as the drug inhibits the proliferation of collencytes and the generation of proteins. Meanwhile, acitretin has an anti-inflammatory effect [7]. In addition to the routine drug therapy, the patients can also receive physiotherapy. Among them, phototherapy is the most widely used treatment [8]. As the main phototherapy, narrow-band ultraviolet at 311 nm directly

induces the apoptosis of T cells. Thus, the proliferation of collencytes is inhibited. One study showed [9] that the skin lesions of patients with psoriasis are basically improved after phototherapy. IL-17 is an important member of the interleukin family. Another study showed [10] that IL-17 is involved in the occurrence and development of psoriasis, and the expression of IL-17 can be significantly improved after treatment. However, whether IL-17 can be used to predict treatment success has not been studied.

Therefore, acitretin combined with narrow-band ultraviolet in the treatment of patients with psoriasis vulgaris was investigated, and the expressions of IL-6 and IL-7 in serum were observed in this study. Meanwhile, the recurrence risk factors were analyzed. Thus, a reference was provided for clinicians.

Materials and methods

Clinical data

150 patients with psoriasis vulgaris were recruited as the study cohort from August 2017 to February 2019 at the First People's Hospital of Wenling. The patients were randomly divided into the control group ($n = 75$) and the observation group ($n = 75$). There were 41 males and 34 females in the control group, and they were 32.5 ± 4.2 years old on average. There were 45 males and 30 females in the observation group, and they were 33.1 ± 4.5 years old on average. This study was approved by the medical ethics committee of The First People's Hospital of Wenling. The patients and their family members were informed of the purpose of the study; the patients all signed an informed consent form. Inclusion criteria: Patients who met the diagnostic criteria for psoriasis vulgaris [11]; patients who had no other skin system diseases; patients who cooperated with the treatment; patients whose clinical data were complete. Exclusion criteria: Patients who were allergic to or unsuitable for the treatment; patients who had undergone systemic psoriasis treatment within the previous weeks; patients who had received glucocorticoids or formic acid immunosuppressants within the previous two weeks; patients who had congenital immunodeficiencies in addition to psoriasis.

Drugs and instruments

Acitretin capsules (Huapont Pharmaceutical Co., Ltd., GYZZ: H20010126), dermatologic therapeutic apparatus (Germany Waldmann uV).

Treatment regimen

The patients in both groups received narrow-band ultraviolet radiation therapy. The radiation was performed at the 311 nm wavelength for 30 min each time, 3 times per week. The surface irradiance was $1.8\text{--}3.2$ mW/cm². The initial dose was 0.2 J/cm², and it was gradually increased to 0.8 J/cm². The patients' response to the irradiation was closely monitored. The irradiation was immediately suspended if a patient had an adverse reaction, and it was continued after the patient's recovery. In addition to the radiation therapy, the patients in the observation group were given oral acitretin capsules. The initial dose was 30 mg/d. The dose gradually increased if the patients had no adverse reactions, but it was not more than 75 mg. The dose decreased to 20 mg/d if the skin lesions subsided.

The expressions of IL-17 before and after treatment

The expressions of IL-17 (USA R&D Company, D1700) was determined using the ELISA method. Fasting venous blood was collected on the next morning after admission to hospital. The blood was then centrifuged for 10 min at $1006.2 \times g$ after standing for 30 min. The supernatant was collected for subsequent analysis. 100 μ L of assay diluent RD1-36 and 100 μ L of serum were respectively added to each well, and 100 μ L of control substance was set. The incubation was performed for 3 h at room temperature after the plate was sealed. Finally, the plate was placed upside down on a clean tissue after being washed. Afterwards, 200 μ L of human IL-17 conjugate was added to each well. Incubation was performed for 1 h at room temperature after the plate was sealed. Then, 200 μ L of matrix was added. The incubation was performed in a dark room for 30 min. Finally, 50 μ L of stop buffer was added. A spectrophotometer was used for testing within 30 min. The experiment was repeated 3 times.

Table 1. Evaluation criteria for the clinical curative effect

Grade	Evaluation Criteria
Basic recovery	PASI score $\geq 90\%$
Significant improvement	PASI score 60%~90%
Improvement	PASI score 25%~59%
Inefficacy	PASI score <25%

Note: Curative effect index = (PASI score before treatment - PASI score after treatment) / PASI score before treatment * 100%.

Outcome measures

The Primary outcome measures: The PASI score was used to evaluate the clinical curative effect in the two groups of patients after two months of treatment. The expressions of IL-17 in the serum before and after treatment were observed. The basically recovered (PASI score reduction between 60% and 89%) patients and the significantly improved (PASI score reduction over than 90%) patients were categorized into the good curative effect group. The improved patients (PASI score reduction between 20% and 59%) and the ineffectual treatment patients (PASI score reduction less than 20%) were categorized as the poor curative effect group. The expression of IL-17 before the treatment was observed. A receiver operating characteristic (ROC) curve was plotted.

Secondary outcome measures: A recurrence within one year after the treatment was observed (The patients were notified to revisit the clinic by telephone). The patients were divided into the recurrence group and the non-recurrence group based on their recurrence. The clinical data were collected for a single-factor analysis. The factors with differences were assigned. The binary logistic regression method was adopted to analyze the independent recurrence risk factors (**Table 1**).

Statistical analysis

In this study, the collected data were statistically analyzed with SPSS 20.0, and the figures were plotted with GraphPad Prism 7. For the measurement data, the distribution of the data was analyzed with a K-S test. The normally distributed data were expressed as the mean \pm standard deviation (SD \pm means) and analyzed with t tests. Independent-sample t tests were

used for the comparisons among groups. The intra-group comparisons were analyzed with paired t tests and expressed with t. The non-normally distributed data were expressed with quartile P_{50} (P_{25} - P_{75}) and analyzed with non-parametric tests. The enumeration data utilization rate (%) was analyzed with chi-squared tests and expressed as χ^2 . The ranked data were analyzed with rank sum tests and expressed as U. The potential predictive value of IL-17 in psoriasis vulgaris before the treatment was analyzed by plotting an ROC curve. The recurrence was taken as a dependent variable, and the factors with statistical differences ($P < 0.05$) between two groups were taken as the independent variables. The risk factors of recurrence were analyzed using the binary logistic regression method.

Results

No differences in the baseline data

After the comparisons, the results showed that the gender, age, BMI, course of disease, PASI score, past medical history, smoking history, alcoholism history, and place of residence were not significantly different in the two groups ($P > 0.05$, **Table 2**).

The observation group showed greater changes in the IL-17 expressions

After measuring, we found that the expressions of IL-17 before the treatment were not statistically different in the two groups ($P > 0.05$). However, the expression of IL-17 was significantly reduced after the treatment. Meanwhile, the expression of IL-17 in the observation group was significantly lower than it was in the control group ($P < 0.05$). After the comparison, the results showed that the changes in IL-17 expression in the observation group were significantly greater than they were in the control group ($P < 0.05$) (**Table 3**).

The observation group showed better curative effects

The evaluation results of the clinical curative effect according to the PASI scores showed that there were 17 patients with a basic recovery, 21 with significant improvement, 27 with improvement, and 10 with inefficacy in the control group, and there were 30 patients with a

Table 2. Comparison of the clinical data [n (%)]

Factor		Control Group (n = 75)	Observation Group (n = 75)	t/ χ^2 Value	P Value
Gender	Male	41 (54.67)	45 (60.00)	0.436	0.509
	Female	34 (45.33)	30 (40.00)		
Age		32.5 \pm 4.2	33.1 \pm 4.5	0.844	0.400
BMI (kg/m ²)		23.45 \pm 1.84	23.74 \pm 1.69	1.005	0.316
Course of disease (year)		4.45 \pm 2.31	4.59 \pm 2.15	0.384	0.701
PASI score		17.54 \pm 4.32	17.20 \pm 3.84	0.509	0.611
Past medical history	Hypertension	15 (44.12)	19 (25.33)	0.609	0.435
	Diabetes mellitus	10 (13.33)	8 (10.67)	0.253	0.615
	COPD	3 (4.00)	5 (6.67)	0.528	0.467
Smoking history	Yes	44 (58.67)	47 (62.67)	0.251	0.616
	No	31 (41.33)	28 (37.33)		
Alcoholism history	Yes	11 (14.67)	14 (18.67)	0.432	0.511
	No	64 (85.33)	61 (81.33)		
Place of residence	City	51 (68.00)	45 (60.00)	1.042	0.307
	Country	24 (32.00)	30 (40.00)		

Table 3. Comparison of the changes

Group	IL-17 (ng/L)		
	Before treatment	After treatment	Difference
Control group (n = 75)	51.55 \pm 9.91	36.52 \pm 6.93	15.03 \pm 6.48
Observation group (n = 75)	52.45 \pm 9.53	27.57 \pm 4.74	24.87 \pm 10.42
t value	0.567	9.232	6.945
P value	0.572	<0.001	<0.001

Table 4. Comparison of the clinical curative effects [n (%)]

Group	Basic recovery	Significant improvement	Improvement	Inefficacy	Z Value	P Value
Control group (n = 75)	17.00 (22.67)	21.00 (28.00)	27.00 (36.00)	10.00 (13.33)	-3.240	0.001
Observation group (n = 75)	30.00 (40.00)	29.00 (38.67)	10.00 (13.33)	6.00 (8.00)		

basic recovery, 29 with significant improvement, 10 with improvement, and 6 with inefficacy in the observation group ($P < 0.05$) (**Table 4**).

The good curative effect group showed lower IL-17 expressions

The patients were grouped according to their clinical curative effect. The basically recovered patients and the significantly improved patients were categorized as the good curative effect group ($n = 97$), and the improved patients and the ineffectual treatment patients were categorized as the poor curative effect group ($n = 53$). The observation results showed that the IL-17

expressions in the good curative effect group before the treatment were significantly lower than they were in the poor curative effect group ($P < 0.05$, **Figure 1**) The ROC curve results showed that the area under the IL-17 curve was 0.846, but the ROC curve result in the control group was 0.5000 (**Figure 2**).

The risk factors related to recurrence were alcoholism, family history, infection and irregular medication use

The patients were followed up for 1 year after the treatment. The results showed that all the patients had a return visit after 1 year. Recurrence occurred in 80 (53.33%) patients,

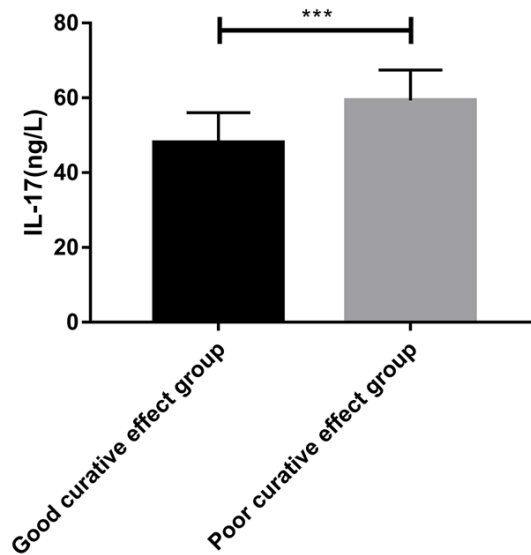


Figure 1. Expressions of IL-17 before treatment. The IL-17 expressions in the good curative effect group before the treatment was significantly lower than it was in the poor curative effect group. ***implied $P < 0.001$.

and non-recurrence occurred in 70 (46.67%) patients. The patients were divided into the recurrence group ($n = 80$) and the non-recurrence group ($n = 70$). The clinical data were collected for the single-factor analysis. The results showed that gender, age, BMI, course of the disease, past medical history, smoking history, and place of residence were not statistically different in the two groups ($P > 0.05$). However, alcoholism, family history, infections, and irregular medication use were significantly different ($P < 0.05$, **Table 5**). The factors with differences were assigned (**Table 6**). Recurrence was taken as a dependent variable, and the factors with differences were taken as independent variables. The independent risk factors of recurrence were analyzed using the binary logistic multi-factor regression method. The results showed that alcoholism, family history, infections, and irregular medication use were the independent recurrence risk factors (**Table 7**).

Discussion

Psoriasis is a chronic inflammatory skin disease, and many immune cells including T cells (predominant) are involved [12]. The occurrence of psoriasis vulgaris caused by psychological pressure and irregular diet is increasing [13]. The patients often have intractable and

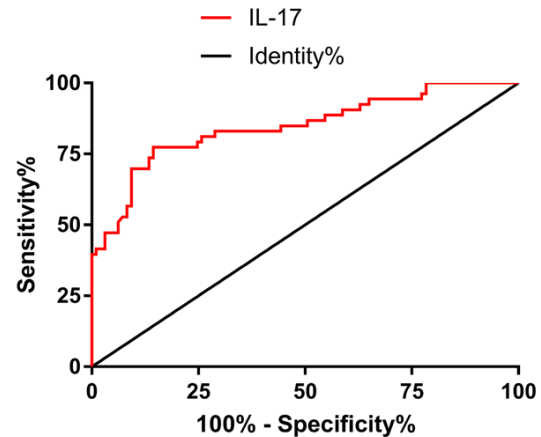


Figure 2. Curative effect predictive ROC curve of IL-17 in patients with psoriasis vulgaris. AUC = 0.846, 95 CI: 0.777~0.915, sensitivity: 77.36%, specificity: 85.57%, Youden index: 62.93%, Cut-off value: > 55.02 .

recurrent chronic erythema scales, accompanied by significant skin inflammation [14], so the disease has a significant impact on the patients' life and work, especially in their social interactions [15].

Narrow-band ultraviolet is the most often used treatment [16]. The patients are irradiated with the ultraviolet light at 311 nm to eliminate cell proliferation and to interfere with the metabolic function of the dermis-epidermal cells [17]. Acitretin is an artificially synthesized aroma retinoid drug with a certain anti-inflammatory effect [18]. In this study, the effect of narrow-band ultraviolet combined with acitretin on the conditions of patients with psoriasis vulgaris was analyzed. The results showed that the conditions of the two groups of patients were significantly improved after the treatment. However, the clinical curative effect in the observation group was significantly better than it was in the control group, indicating that the combined therapy can improve the clinical curative effect. The main reason is that acitretin can not only regulate the skin hyperplasia and hyperkeratosis, but it also regulates the differentiation of monocytes and lymphocytes and inhibits neutrophils. Thus, the immune response is adjusted and the condition is significantly improved [19].

In recent years, more and more studies have shown that Th17 (T helper cell 17) is closely related to psoriasis. As the main product

Table 5. Single-factor recurrence analysis

Factor		Recurrence group (n = 80)	Non-recurrence group (n = 70)	t/ χ^2 Value	P Value
Gender	Male	45 (56.25)	41 (58.57)	0.082	0.774
	Female	35 (43.75)	29 (41.43)		
Age		32.1 \pm 5.1	32.7 \pm 4.8	0.739	0.461
BMI (kg/m ²)		23.49 \pm 1.79	23.81 \pm 1.88	1.067	0.288
Course of disease (year)		4.51 \pm 2.15	4.56 \pm 2.19	0.141	0.888
Past medical history	Hypertension	19 (23.75)	15 (21.43)	0.115	0.735
	Diabetes mellitus	12 (15.00)	6 (8.57)	1.461	0.227
	COPD	4 (5.00)	4 (5.71)	0.038	0.846
Smoking history	Yes	47 (58.75)	44 (62.86)	0.264	0.607
	No	33 (41.25)	26 (37.14)		
Alcoholism history	Yes	19 (23.75)	6 (8.57)	6.193	0.013
	No	61 (76.25)	64 (91.43)		
Place of residence	City	54 (67.50)	42 (60.00)	0.912	0.34
	Village	26 (32.50)	28 (40.00)		
Family history	Yes	70 (87.50)	50 (71.43)	6.027	0.014
	No	10 (12.50)	20 (28.57)		
Infection	Yes	64 (80.00)	45 (64.29)	4.642	0.031
	No	16 (20.00)	25 (35.71)		
Irregular medication of acitretin	Yes	60 (75.00)	40 (57.14)	5.357	0.021
	No	20 (25.00)	30 (42.86)		

Table 6. Assignment table

Factor	Assignment
Recurrence (Y)	Recurrence = 1, non-recurrence = 0
Alcoholism	Yes = 1, No = 0
Frequency of attack	First time = 1, ≥ 2 times = 0
Family history	Yes = 1, No = 0
Infection	Yes = 1, No = 0
Irregular medication	Yes = 1, No = 0

secreted by Th17, IL-17 is of great significance in autoimmune diseases and the body's defense response [20, 21]. After quantifying them, we found that the expressions of IL-17 in the two groups of patients were significantly improved after the treatment. The expressions of IL-17 in the observation group were significantly lower than they were in the control group. Moreover, Wu et al. [22] found that acitretin combined with glycyrrhizin can also improve the expression of IL-17 and the clinical curative effect in patients with psoriasis. Their results were similar to ours. However, there is no relevant study on whether IL-17 can be used as a predictor of the curative effect. Therefore, the patients were divided into the good curative

effect group and the poor curative effect group according to their clinical curative effect. After the comparison, the results showed that the expressions of IL-17 in the good curative effect group before the treatment were significantly lower than they were in the poor curative effect group, indicating that IL-17 can be considered a predictor of the potential curative effect in patients with psoriasis vulgaris. Afterwards, we further plotted the ROC curve according to the expressions of IL-17. The results showed that the area under the IL-17 curve was 0.846, the sensitivity was 77.36%, and the specificity was 85.57%, indicating that IL-17 is a potential predictor of the clinical curative effect.

At the end of study, we analyzed the patient recurrence for 1 year after the treatment. Psoriasis frequently recurs. Therefore, it is very important to ensure the reduction of recurrence after treatment by analyzing the recurrence risk factors. The clinical data were collected for a single-factor analysis. The factors with differences were given a binary logistic multiple-factor analysis. The results showed that alcoholism, family history, infections, and irregular medication use were the independent

Table 7. Multi-factor logistic regression

Factor	β	S.E	X^2	P Value	Exp (B)	95% CI. of LEXP (β)	
						Lower Limit	Upper Limit
Alcoholism	1.077	0.524	4.223	0.040	2.936	1.051	8.201
Family history	1.094	0.465	5.537	0.019	2.986	1.201	7.428
Infections	1.000	0.391	6.529	0.011	2.719	1.262	5.856
Irregular medication	0.972	0.387	6.319	0.012	2.644	1.239	5.643

risk factors for recurrence. After one drinks alcohol, it enters the human body and expands the blood vessels. Thus, the permeability of the blood vessels is increased, and the infiltration of neutrophils into the vascular endothelial cells is accelerated. As a result, arachidonic acid is released, and the activity of cMAP is reduced. Finally, an abnormal hyperplasia of the epidermal cells occurs [23]. As a familial inherited disease, psoriasis can continuously affect patients' condition and promote recurrence when the patients are subject to external influences and autoimmunity genetic mutations [24]. Infections are an important factor in inducing psoriasis. The Meta found that fungi, bacteria, and viruses can be considered risk factors for recurrence [25]. Due to the longer course of the disease and a lack of relevant medical knowledge, blind searches for short-term radical treatments and drug abuse can easily cause a recurrence in patients and even a further worsening of the disease [26]. Therefore, we need to strengthen the patients' health education and treatment compliance, tell the patients to clean their skin, reduce their skin injuries, and kick their bad habits. In this way, the recurrence of the disease is lessened.

In this study, we found that: 1) Acitretin combined with narrow-band ultraviolet can effectively reduce the expression of IL-17 in the serum and improve the patients' conditions; 2) Alcoholism, family history, infections, and irregular medication use are the independent risk factors for recurrence. However, there are still some limitations to this study. First, there was a small cohort in this single-center study, and the recurrence risk factors were not compared with data from other sites. Second, the relevant mechanisms between IL-17 and psoriasis have not been further studied. Therefore, we hope that our sample size will be increased in a future study, and the relationship between IL-17 and psoriasis is further analyzed in basic experiments.

In summary, 1) Acitretin combined with narrow-band ultraviolet can effectively reduce the expression of IL-17 in serum and improve patients' conditions; 2) Alcoholism, family history, infections and the irregular use of acitretin are independent risk factors for recurrence.

Disclosure of conflict of interest

None.

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