

# Therapeutic effect of photodynamic therapy combined with imiquimod in the treatment of anal condyloma acuminatum and its effect on immune function

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**Abstract.** Therapeutic effect of photodynamic therapy combined with imiquimod in the treatment of anal condyloma acuminatum (CA) was investigated to explore its effect on immune function. A total of 104 patients with anal CA were randomly divided into two groups: Patients in the study group were treated with photodynamic therapy combined with imiquimod, and ii) patients in the control group were treated with recombinant human interferon  $\alpha$ -2b cream. Clinical efficacy and immune function related indicators were compared between the two groups. After treatment for 6 weeks, the cure rate and total effective rate of study group was 53.85 and 92.31%, respectively, which were significantly higher than those of the control group (30.77 and 75.00%,  $P < 0.05$ ). Recurrence rate of study group was 3.85% within 6 months after treatment, which was significantly lower than that of the control group (19.23%,  $P < 0.05$ ). After treatment, levels of CD4<sup>+</sup>, CD4<sup>+</sup>/CD8<sup>+</sup> and IFN- $\gamma$  in the study group were significantly higher than those in the control group, and levels of CD8<sup>+</sup>, IL-4 and IL-10 in the study group were significantly lower than those in the control group ( $P < 0.05$ ). Photodynamic therapy combined with imiquimod in the treatment of anus CA can regulate T lymphocyte subsets and cytokine levels, enhance immune function, improve clinical efficacy, reduce recurrence rate, and have almost no side effects. Therefore, this treatment should be popularized in clinical practice.

## Introduction

Condyloma acuminatum (CA) is a common sexually transmitted disease that is mainly caused by the infection of anus,

perineum, genital and other parts of the human body by human papillomavirus (HPV). The strong transmission and recurrence rate of CA is high and its effects on patient's physical and psychological activities are strong (1). Anal CA is very common in clinical practice and is usually treated by electrocautery, laser, microwave or surgical excision to damage the local skin lesions. However, these are all temporary solutions and the recurrence rate is high. In recent years, clinical studies have found that the body's immune function plays an important role in the occurrence, development and recurrence of this disease. Therefore, in recent years, more emphasis has been focused on the application of immunotherapy in the treatment of CA, however, the exact effect is unknown (2). In the present study, effects of photodynamic therapy combined with imiquimod and recombinant human interferon  $\alpha$ -2b on T lymphocyte subsets and cytokines in the treatment of anal CA were compared to provide references for the treatment of this disease.

## Patients and methods

**General information.** A total of 104 anal CA patients who were treated in Liaocheng People's Hospital (Liaocheng, China) from January 2013 to January 2015 were included and randomly divided into the study group (n=52) and the control group (n=52). Study group consisted of 17 males and 35 females aged from 20 to 60 years with an average of  $29.15 \pm 2.34$  years; course of disease ranged from 7 days to 3 years, with a mean course of  $3.65 \pm 1.26$  months, and the number of skin lesions ranged from 1-7, with a mean number of  $3.62 \pm 1.05$ . The control group included 19 males and 33 females aged 22 to 65 years with a mean age of  $30.24 \pm 2.55$  years; course of disease ranged from 2 days to 2.5 years, with a mean course of  $3.91 \pm 1.32$  months; the number of skin lesions ranged from 1-6, with a mean number of  $3.45 \pm 1.13$ . No significant differences in general data were found between the two groups ( $P > 0.05$ ).

**Diagnostic criteria.** Anal CA was diagnosed in line with 'the principle of diagnosis and treatment of condyloma acuminata' (3), that is, a history of CA exposure, typical clinical manifestations, positive acetic acid test results or confirmed by histopathological examination.

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### Inclusion and exclusion criteria

**Inclusion criteria of the patients.** Diagnostic criteria: Lesions are located in the anus. Aged 18-65 years. Patients did not receive laser treatment or oral or external use of antiviral drugs in the past 2 weeks. Patients received no oral or topical treatment with immune regulator/inhibitor within 1 month. Diameter of wart body <1.0 cm, the number of lesions is unlimited. The study was approved by the Ethics Committee of Liaocheng People's Hospital. Patient voluntarily joined the trial and signed informed consent.

**Exclusion criteria.** Patients combined with severe heart, liver, brain, lung, kidney, hematopoietic system and neuropsychiatric disorders. Patients with autoimmune diseases, cancer, diabetes and other diseases. Patients combined with CA at other parts and other sexually transmitted diseases. Patients with long-term use of immune suppressor/regulators or glucocorticoid hormone. Patients received CA-related treatment within the past 2 weeks. Women during pregnancy and lactation. Patients unable to complete treatment and referral. Patients who were allergic to the drugs used in this study.

### Treatment

**Basic treatment.** Patients in both groups received bland diet. Efforts were made to maintain anal and perineal clean. Spicy food and food difficult to digest were avoided. Smoking and alcohol were forbidden. No other oral or topical drugs were used during treatment.

**Treatment in two groups.** Control group patients were subjected to topical application of recombinant human interferon  $\alpha$ -2b cream, 2 times/day for 6 weeks. Patients in the observation group were given photodynamic therapy combined with imiquimod. Photodynamic therapy: Amino ketones ersan was prepared at a concentration of 20% to drop on the thin film, and the film was used to cover the lesions. Size greater than the verrucous body by 1 cm is best. Then the lesions were wrapped with plastic wrap. Amino ketones ersan solution as used every 30 min for 3 h, followed by photodynamic therapy with power at 100 mw, 30 min/time, 1 time/week. Imiquimod: Imiquimod (5%) was used to cover the lesions before rest at night with a massage to fully absorb the drug, once a day for 6 weeks.

### Observation indicators

**Changes in disease conditions.** The fading and formation of skin lesions were recorded. Cumulative recurrence rate within 6 months after treatment was recorded.

**T lymphocyte subsets.** Peripheral blood T lymphocyte subsets including CD4<sup>+</sup> and CD8<sup>+</sup> were measured and CD4<sup>+</sup>/CD8<sup>+</sup> was calculated before and 3 months after treatment.

**T lymphocyte factor.** Levels of cytokines, including interleukin-4 (IL-4), IL-10 and IFN- $\gamma$  in peripheral blood T lymphocytes of patients were measured before and 3 months after treatment.

**Safety assessment.** Occurrence of adverse drug reactions was recorded during follow-up. Routine blood and urine tests,

Table I. Comparison of clinical efficacy of two groups after treatment (n, %).

Groups	Cases	Recovery	Effective	Ineffective	Total effective
Study	52	28 (53.85) <sup>a</sup>	20 (38.46)	4 (7.69)	48 (92.31) <sup>a</sup>
Control	52	16 (30.77)	23 (44.23)	13 (25.00)	39 (75.00)

<sup>a</sup>P<0.05, compared with the control group.

electrocardiogram and liver and kidney function tests were also performed to evaluate drug safety.

**Efficacy determination criteria.** Lesion reduction index was calculated by using the following formula: Lesion reduction index = (pretreatment lesion area - lesion area after treatment)/lesion area before treatment  $\times$  100%. Recovery: Skin lesions completely disappeared, and no new lesions appeared during 1 month of follow-up and acetic acid white test was negative. Effective: Skin lesion reduction index  $\geq$ 30%, and recurrence rate of lesions were reduced compared with pretreatment level, or no new lesions were found but acetic acid white test was positive. Ineffective: Lesions reduction index <29%.

**Statistical analysis.** SPSS 18.0 statistical software package (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. Measurement data were expressed as mean  $\pm$  SD, and compared by t-test. Enumeration data are expressed as a percentage. P<0.05 was considered to indicate a statistically significant difference.

### Results

**Comparison of clinical efficacy.** The cure rate and total effective rate of the study group were significantly higher than those of the control group (Table I, P<0.05).

**Comparison of recurrence rate.** Within 6 months after treatment, recurrence rate of the study group was significantly lower than that of the control group (Table II, P<0.05).

**Comparison of peripheral blood T lymphocyte subsets.** After treatment, CD8<sup>+</sup> in both groups were significantly decreased. CD4<sup>+</sup> and CD4<sup>+</sup>/CD8<sup>+</sup> were significantly increased (P<0.05), while the improvement in the study group was more obvious than that in the control group (Table III, P<0.05).

**Comparison of cytokine levels.** After treatment, levels of IFN- $\gamma$  in both groups were significantly increased, while levels of IL-4 and IL-10 were significantly decreased (P<0.05). Improvement in the study group was more obvious than that in the control group (Table IV, P<0.05).

**Adverse reactions.** During treatment, no obvious local drug allergic reaction or systemic adverse reaction occurred in either group, and the medication was safe.

Table II. Comparison of recurrence rate between two groups (n, %).

Groups	Cases	Within 6 weeks after treatment	Within 3 months after treatment	Within 6 months after treatment	Cumulative recurrence rate
Study	52	2 (3.85)	2 (3.85)	1 (3.85)	2 (3.85) <sup>a</sup>
Control	52	4 (7.69)	4 (7.69)	2 (3.85)	10 (19.23)

<sup>a</sup>P<0.05, compared with the control group.

Table III. Comparison of peripheral blood T lymphocyte subsets before and after treatment (mean ± SD, %).

Groups	Time-points	CD4 <sup>+</sup>	CD8 <sup>+</sup>	CD4 <sup>+</sup> /CD8 <sup>+</sup>
Study	Before treatment	35.42±2.23	34.17±4.25	1.04±0.17
	After treatment	41.39±6.78 <sup>a,b</sup>	26.13±3.57 <sup>a,b</sup>	1.58±0.22 <sup>a,b</sup>
Control	Before treatment	34.79±2.46	34.22±4.16	1.02±0.18
	After treatment	38.31±5.71 <sup>a</sup>	30.09±3.68 <sup>a</sup>	1.27±0.20 <sup>a</sup>

<sup>a</sup>P<0.05, compared with pretreatment level; <sup>b</sup>P<0.05, compared with control group.

Table IV. Comparison of cytokine levels before and after treatment (mean ± SD, pg/ml).

Groups	Time-points	IFN-γ	IL-4	IL-10
Study	Before treatment	13.02±4.13	11.02±3.41	30.21±9.56
	After treatment	21.55±7.21 <sup>a,b</sup>	6.67±2.06 <sup>a,b</sup>	18.17±8.05 <sup>a,b</sup>
Control	Before treatment	12.89±3.89	11.26±3.19	29.78±9.14
	After treatment	18.05±6.64 <sup>a</sup>	8.34±2.25 <sup>a</sup>	24.45±8.12 <sup>a</sup>

<sup>a</sup>P<0.05, compared with pretreatment level; <sup>b</sup>P<0.05, compared with control group.

## Discussion

CA is a sexually transmitted disease caused by factors such as HPV infection. There are no obvious symptoms in the early stage of infection, and obvious signs of skin lesions are usually observed 3-6 months after the onset (4). Physical therapy (laser, microwave, ionization) and cytotoxic drugs such are effective in the treatment of CA, but the recurrence rate is high, and 6 months recurrence rate can be as high as 69% (5). Without timely treatment, HPV treatment can cause the occurrence of cancer. It has been reported that approximately 4-5% of patients with vulvar cancer has a history of CA (6). Therefore, early treatment CA is the key to reduce the recurrence rate.

There is no standard treatment program for the clinical treatment of CA, and different treatments can all lead to recurrence (7). HPV infection can be detected in skin 1 cm around the lesions, which is a major cause of the recurrence of CA (8). Photodynamic therapy combined with topical drugs can improve immune system to achieve satisfactory therapeutic effects (9). Imiquimod is a synthetic non-nucleoside ring imidazole drug with strong antiviral activity. Imiquimod is mainly used to regulate the body's immune mechanism and induce immune response to achieve antiviral effects. In the treatment of anal CA, application of photodynamic combined with imiquimod not only can inhibit inflammation and protect lesion surface, but also can regulate immunity and prevent cancer. In this study, patients in the study group were treated with photodynamic therapy combined with imiquimod, while patients in the control group were only treated with topical application of recombinant human interferon  $\alpha$ -2b cream. The results showed

that the cure rate and total effective rate of the study group was 53.85 and 92.31%, respectively, which was significantly higher than that of the control group (30.77 and 75.00%, P<0.05). It is concluded that the photodynamic therapy combined with imiquimod is better than topical administration of recombinant human interferon  $\alpha$ -2b for treatment of anal CA.

Clinical studies have shown that the cause for the poor treatment outcomes and high recurrence rate of CA are: i) HPV can be stored in the urethra or scrotum and other sites to increase the potential risk of recurrence; ii) re-exposure causes HPV re-infection; and iii) low immune function increases the risk of opportunistic infections. Among those factors, immune function is the key, and T lymphocytes can directly reflect body's immune function status. Wang and Wu (10) found that CD4<sup>+</sup> and CD4<sup>+</sup>/CD8<sup>+</sup> were significantly reduced, while CD8<sup>+</sup> was significantly increased in CA patients than in healthy people, indicating the T lymphocyte subsets disorder in CA patients. With traditional Chinese medicine bath treatment, CD8<sup>+</sup> was significantly reduced, while CD4<sup>+</sup> and CD4<sup>+</sup>/CD8<sup>+</sup> were significantly increased, indicating traditional Chinese medicine bath treatment of CA can regulate immune function, playing an antiviral role, and thus improve clinical prognosis. T lymphocyte subsets disorder can lead to imbalance of Th1/Th2 ratio, that is, the secretion of IL-2 and IFN-γ and other cytokines by Th1 cell decrease, while the secretion of IL-4 and IL-10 and other cells factors by Th2 cells increase. Reduced Th1/Th2 ratio is closely correlated with the development of CA (11,12). Erman-Vlahovic *et al* (13) found that peripheral blood levels of IL-2 and IFN-γ were significantly lower, while levels of IL-4 and IL-12 were significantly higher in CA patients than in healthy

controls. Thus, regulation of immune function and regulation of T lymphocyte subsets and their cytokine levels are conducive for the prevention and treatment of CA and the reduction of recurrence. In addition, it has been reported that the combination of photodynamic therapy and imiquimod can increase TLR1 and TLR3-positive rates, suggesting that photodynamic therapy combined with imiquimod may inhibit the expression of TLR1 and TLR3, to inhibit HPV infection and improve clinical efficacy (14,15). In this study, after treatment, levels of CD8<sup>+</sup>, IL-4 and IL-10 in the two groups were significantly decreased, and the levels of CD4<sup>+</sup>, CD4<sup>+</sup>/CD8<sup>+</sup> and IFN- $\gamma$  were significantly increased compared with pretreatment level. It is considered that T lymphocyte subsets and their cytokines are effectively controlled in both groups after treatment, and the effect of immune function of photodynamic therapy combined with imiquimod is stronger than that of the control group. With the improvement of immune function, recurrence of CA will be effectively prevented. Cumulative recurrence rate of study group within 6 months after treatment was only 3.85%, which was significantly lower than that of the control group (19.23%,  $P < 0.05$ ). It was further confirmed that photodynamic therapy combined with imiquimod in the treatment of anus CA could effectively regulate the immune function and reduce the recurrence rate. No significant adverse reactions were observed during treatment, indicating the high safety and reliability of the medication.

In conclusion, photodynamic therapy combined with imiquimod in the treatment of anal CA can effectively regulate T lymphocyte subsets and cytokines, enhance immune function, improve clinical efficacy and reduce the recurrence rate of CA, but causes no obvious side effects. Photodynamic therapy combined with imiquimod is reliable and safe for the treatment of anal CA. Therefore, it is worthy to be popularized in clinical practice.

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### Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

### Authors' contributions

XM was responsible for patient treatment and contributed to writing the manuscript. YL recorded the change of T lymphocyte subsets. HL analyzed T lymphocyte factor. XS contributed to interpretation of changes in disease conditions. All authors read and approved the final manuscript.

### Ethics approval and consent to participate

The study was approved by the Ethics Committee of Liaocheng People's Hospital (Liaocheng, China). Patients who participated

in this research had complete clinical data. Signed informed consents were obtained from the patients or guardians.

### Patient consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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