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Clinical Efficacy and Immune Response of Recombinant Human Interferon α2b Vaginal Effervescent Tablets in the Treatment of High-risk HPV-induced Cervical Intraepithelial Neoplasia Grade 1

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ABSTRACT

High risk human papillomavirus (HR-HPV) induced cervical intraepithelial neoplasia grade 1 (CIN1) is a low-grade lesion closely associated with persistent viral infection, and clinical management remains challenging. This study aimed to investigate clinical efficacy and immune response of recombinant human interferon α2b vaginal effervescent tablets in CIN1 caused by HR-HPV.

In a retrospective study, 60 patients with HR-HPV and diagnosed with CIN1 from Shandong Provincial Hospital between December 2023 and December 2024 were divided into CT (n=30) and CR (n=30) groups, both groups were treated with conventional therapy, and recombinant human interferon α2b vaginal effervescent tablets were added to the CR group. The main assessment of both groups were inflammatory factor indicators, immune indicators, vaginal microenvironmental factors [hydrogen peroxide (H2O2) positivity, sialidase (SNA) positivity, leukocyte esterase (LE) positivity, N-acetylaminogalactosidase (NAG) positivity], HR-HPV conversion rate and clinical efficacy. Secondary outcomes included life quality scores, complication and adverse effect rates.

After treatment, the indicators of both groups were significantly different from the pre-treatment. The changes in inflammatory indicators, immune indicators, SNA positivity rate, LE positivity rate, HR-HPV conversion rate, clinical efficacy, life quality, complications, and adverse reactions in the CR group were better than those in the CT group. No marked discrepancy was found in the comparison of H2O2 positivity rate and NAG positivity rate between both groups.

Recombinant human interferon α2b vaginal effervescent tablets have significant therapeutic effects, as they alleviate inflammatory reactions, regulate immune indicators, and are worthy of clinical application and promotion.

Keywords: Cervical intraepithelial neoplasia; Human papillomavirus; Immune response; Inflammatory markers; Recombinant human interferon α2b

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INTRODUCTION

Human papillomaviruses (HPVs) are a class of enveloped viruses with double-stranded circular DNA genomes, whose viral particles consist of a protein capsid and a core single-copy viral genomic DNA.More than 200 types have been identified, which are classified into low-risk and high-risk types on the basis of their oncogenic potential.[1] Persistent infection with high-risk HPV (HR-HPV) is the main cause of cervical malignancy, and the E6 and E7 oncogenes in its genome can promote aberrant cell proliferation by combining with the oncogenes of the host cell, p53 and Rb, leading to cell cycle deregulation and inhibition of apoptosis. HPV infections are usually highly histophilic and predominantly invade human skin and mucosal epithelial cells.[2] Most HPV infections are subclinical or occult, with patients having no obvious clinical symptoms; the presence of the virus is only detected by molecular biology testing. Some patients may develop benign lesions such as genital warts, while HR-HPV infection may progress to cervical intraepithelial neoplasia (CIN) or even cervical cancer when it persists.[3] There are individual differences in clinical symptoms after infection, and some patients may develop mood disorders such as anxiety and depression due to psychological stress, especially after learning of HR-HPV infection, and concerns about their health and fertility can remarkably affect their life quality.[4]

Cervical intraepithelial neoplasia (CIN) is a group of precancerous lesions closely related to invasive carcinoma of the uterine cervix, reflecting successive pathological stages in the development of uterine cervical cancer, and can be classified into three levels, CIN1, CIN2 and CIN3, according to the degree and extent of abnormal epithelial proliferation.[5] Its etiology is mainly associated with persistent HR-HPV infection, in which viral infection of the basal cells of the squamous epithelium of the uterine cervix contributes to the heterogeneous alteration of the epithelial cells by interfering with cell-cycle regulation, inducing genomic instability, and other mechanisms.[6] Among them, HR-HPV-induced CIN1, as a low-grade intraepithelial neoplasia, shows pathological features such as the appearance of heterogeneous cells in the lower 1/3 layer of the epithelium, with enlarged and deeply stained nuclei, and visible scooped cells, but the differentiation of cells in the upper 2/3 layer of the epithelium is relatively normal. Clinical symptoms are often atypical, and some patients may present with increased leukorrhea and contact bleeding, however, these symptoms lack specificity and are often overlooked. Although CIN1 lesions may regress spontaneously within 2 years and show benign regression, some cases may progress to high-grade CIN (2/3) or even invasive carcinoma of the uterine cervix.[7]

Currently, clinical treatment strategies for CIN1 face a dilemma of choice. For cases with a high likelihood of natural regression, overly aggressive interventions, such as leeping and cold knife conization, may lead to structural destruction of the cervix and increase the risk of pregnancy complications (e.g., preterm labour, miscarriage), as well as physiological and psychological trauma to the patient; whereas simply watching and waiting may miss the opportunity for early intervention in cases at high risk of progression.[8] Existing treatments include regular follow-up, physiotherapy, surgery, and pharmacological interventions, but there is no standardized treatment protocol, and there are significant challenges in identifying those at high risk of progression and optimizing the timing and modalities of treatment.

Recombinant human interferon α2b vaginal effervescent tablets are a protein-based biological preparation prepared by cloning the human leukocyte interferon α2b gene into host cells for expression by genetic engineering technology, and then purified and lyophilized. Its drug dosage form is designed as an effervescent tablet, which rapidly disintegrates in body fluids after entering the vagina and releases carbon dioxide gas to form a foamy dispersion system, which can be uniformly attached to the surface of the vaginal and cervical mucosa, remarkably increasing the contact area between the drug and the lesion and prolonging the local retention time, thus optimizing bioavailability.[9] Compared with LEEP and cold knife conization, recombinant human interferon α2b vaginal effervescent tablets have significant advantages in fertility protection: the latter requires cutting cervical tissue, which can easily damage cervical structure, shorten cervical length, increase the risk of miscarriage, premature birth, and may also hinder sperm penetration. This therapy is a local medication, non-invasive, and can fully preserve cervical function, avoiding related complications, etc.[10] The pH value of the preparation is usually controlled between 3.5–5.5, which is compatible with the physiological environment of the vagina, and can not only maintain the biological activity of

interferon, but also inhibit the propagation of pathogenic bacteria, and create a suitable microenvironment for local immune regulation. Its main component, recombinant human interferon α2b, exerts a broad-spectrum antiviral effect by binding to specific receptors on the surface of target cells, activating intracellular signaling pathways, and inducing the expression of a variety of antiviral proteins. At the same time, the drug can also regulate the body's immune function, enhance the activity of natural killer cells and macrophages, and promote the proliferation and differentiation of T lymphocytes to enhance the local immune response capacity.[11] In clinical application, recombinant human interferon α2b vaginal effervescent tablets are mainly used for the treatment of gynecological diseases caused by viral infections, such as condyloma acuminatum, herpes simplex virus infection, etc., and have been gradually attracting attention, especially in the treatment of diseases related to HR-HPV infection. Its mechanism of action not only targets the replication process of HPV virus, but also enhances host recognition and clearance of virus-infected cells by modulating the local immune microenvironment.[12] Given its dual efficacy of both antiviral and immunomodulatory effects, it provides a theoretical basis for exploring its application in the treatment of HR-HPV-induced CIN1, i.e., by inhibiting viral replication and enhancing the local immune response, it promotes the regression of CIN1 lesions and reduces the risk of disease progression.

The aim of this study was to systematically evaluate the clinical efficacy of recombinant human interferon α2b vaginal effervescent tablets in the treatment of HR-HPV-induced CIN1 and to delve into the immune mechanism of its action. The study hypothesized that the drug could promote the reversal of CIN1 lesions by inhibiting HPV viral replication and modulating the local immune microenvironment of the cervix, and that its efficacy might be related to the degree of activation of the body's immune response. In this study, the effectiveness and safety of recombinant human interferon α2b vaginal effervescent tablets in treatment of CIN1 were clarified through clinical observation, providing a non-surgical choice of pharmacological intervention in the clinic, and in particular, providing a basis for avoiding over-treatment and reducing the risk of medically induced injury. By evaluating the changes in local immune indicators (e.g. cytokine levels) of patients before and after treatment, it will reveal the immune molecular mechanism of the drug's action, providing a theoretical basis for optimizing the treatment regimen and screening for the advantageous population. In addition, the results of this study are expected to provide new ideas for immunomodulatory treatment of diseases related to HR-HPV infection and promote the development of individualized and precise treatment strategies for CIN1, thereby improving the prognosis and life quality, with significant social and economic benefits.

MATERIALS AND METHODS

Study Design

This study was a single-center retrospective cohort study following the norms of observational study design in clinical epidemiology, aiming to establish an individualized treatment strategy based on evidence-based medicine by systematically analyzing the clinical data of recombinant human interferon α2b vaginal effervescent tablets in treatment of HR-HPV-associated CIN1. The study period was set from December 2023 to December 2024, covering two complete natural years to reduce seasonal bias, and the study subjects were patients with persistent HR-HPV infection and pathologically confirmed diagnosis of CIN1 by colposcopic biopsy in the gynecology outpatient clinic of Shandong Provincial Hospital. At the beginning of the study, 70 patients who met the criteria were included, and after exclusion, 66 patients were included. During the follow-up period, 6 patients were lost to follow-up, and a total of 60 patients were analyzed. The specific reasons for exclusion are as follows: 3 cases were excluded if they did not meet the exclusion criteria. One patient withdrew due to personal reasons. During the follow-up process, 6 patients lost contact due to changes in contact information, seeking medical treatment in another location, or personal reasons, and were unable to complete follow-up treatment and indicators. They were treated as lost to follow-up. The grouping strategy followed the actual clinical treatment protocol. According to the treatment modality, they were categorized into CT group (n=30) and CR group (n=30), both groups underwent conventional treatment, and the CR group was additionally treated with recombinant human interferon α2b vaginal effervescent tablets. The results were analyzed using a combination of data collection and retrospective analysis. In this study, the therapeutic effect of recombinant human interferon α2b vaginal effervescent tablets in treatment of CIN1 caused

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by HR-HPV was analyzed by comparison, which provides a scientific basis for the clinically relevant drug treatment plan. The flow chart of this study is illustrated in Figure 1.

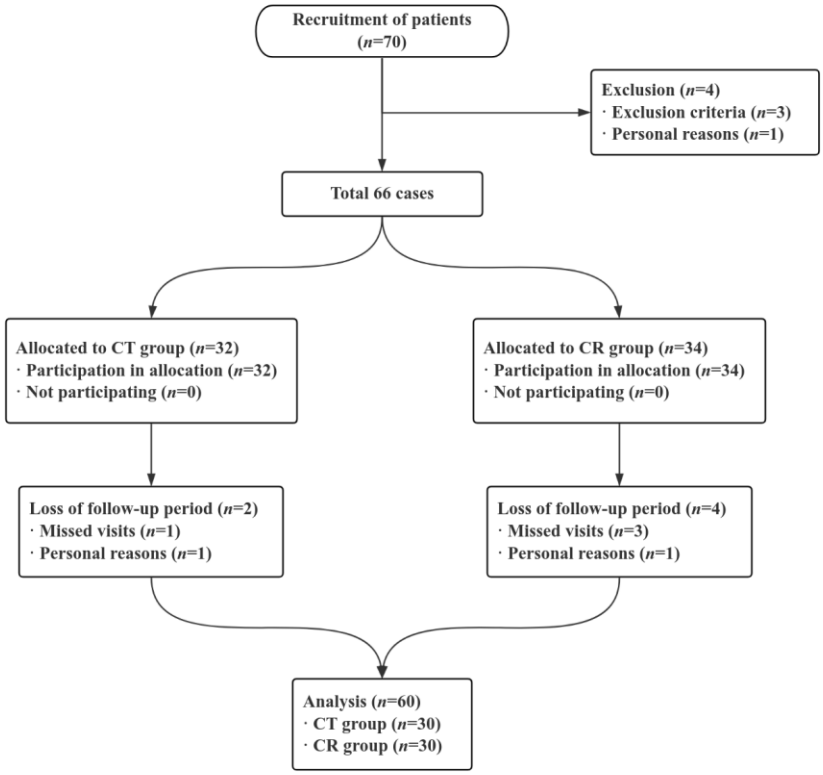

Figure 1. Flowchart of a single center retrospective cohort study in this study.

Inclusion and Exclusion Criteria

Inclusion criteria: (1): Patients who met the diagnostic criteria for HR-HPV infection,[13] and belonged to CIN grade 1 by histological examination. Diagnosis method for CIN level 1: Cervical tissue is taken through vaginal colposcopy guided biopsy. 2–4 pieces of visible lesions are taken, and if not, samples are taken at four points. If necessary, the cervical canal is scraped. The specimen was fixed, embedded, and sliced into 4 μm sections, which were then stained with HE. Two physicians with over 5 years of experience conducted double-blind review of the slides, and any discrepancies were reviewed by the chief physician according to the 2021 standard; (2) Age 18 to 50 years old; (3) Not receiving other anti-HPV therapy or immunotherapy; (4) Patients with good compliance and willingness to cooperate with the treatment plan developed by the study; (5) The patients have good overall mental status, are basically healthy, and can truthfully express their complaints about their symptoms and answer relevant questions from healthcare professionals; (6) Those who can tolerate the drugs involved in this study; (7) Patients and their family members are informed and agreeable and have signed an informed consent form.

Exclusion criteria: (1) Pregnant or lactating females; (2) Patients with comorbid severe systemic diseases or immune system diseases; (3) Malignant tumor of any site or type; (4) Patients with combined hemorrhagic and coagulation disorders, or with severe liver or renal function defects, severe cardiovascular disease or other more serious diseases; (5) Combined chronic infectious diseases, combined with other sexually transmitted diseases (such as syphilis, gonorrhea, etc.); (6) Combined brain, heart, liver and kidney function abnormalities; (7) Those who are allergic to interferon or the components of the study drug; (8) Patients who have participated in clinical drug trials or clinical studies; (9) Requests to stop treatment or automatic discharge for personal reasons; (10) Patients with

gynecological complications that require active intervention, including but not limited to acute or subacute pelvic inflammatory disease, cervicitis, and vaginitis. Including endometriosis and adenomyosis with active or obvious symptoms, recent (within 3 months) history of gynecological surgery and incomplete wound healing; (11) Other circumstances that, in the opinion of the study physician, should not be included; (12) Other circumstances affecting the indicators of follow-up observation.

Ethical Statement

The study was performed in compliance with the Declaration of Helsinki and hospital ethical guidelines and was approved by the hospital ethics committee.

Interventions

Both groups received basic treatment: maintaining vulvar hygiene, instructing patients on the precautions to be taken during the use of medication; maintaining personal hygiene; changing underwear and disinfecting the clothes worn; dietary instructions to consume a mild diet, avoiding spicy or irritating foods eating more high-protein, high-vitamin foods; and patients were advised to avoid public baths.

CR group received recombinant human interferon α2b vaginal effervescent tablets treatment (manufacturer: Beijing Kain Science and Technology Co, Ltd, China; Approval No. State Pharmaceutical Permit S20120019, specification: 500 000 IU/capsule). Patients were instructed to clean the vulva and insert one capsule into the vaginal vault at bedtime. This was administered once daily, every other day, for 12 continuous weeks. During the use of the drug, need to pay attention to the use of the drug after any adverse reactions, if the use of the drug during the discomfort, such as lumbar and abdominal pain, vaginal discomfort, fever, etc., to inform the patient in advance that there is no need to worry about is a normal phenomenon, after stopping the drug will be recovered on its own.

Observation Indicators

Main Indicators

Inflammation indicators

Fasting peripheral venous blood of 3 mL was drawn from patients pre- and post-treatment, centrifuged and kept refrigerated for testing, and enzyme-linked immunosorbent assay (ELISA) was used to determine and calculate the levels of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and ultrasensitive C-reactive protein (hs-CRP) in the patient's serum samples.[14] The kits used were Human TNF-α ELISA kit (Item No. ml077385, Shanghai Enzyme-linked Biotechnology Co, Ltd., China), Human IL-6 ELISA kit (Item No.: ml027379, Shanghai Enzyme-linked Biotechnology Co, Ltd., China) and Human hs-CRP ELISA kit (Item No. ml106583, Shanghai Enzyme-linked Biotechnology Co, Ltd., China).

Immune indicators

Immunological indexes were observed in both groups, and the levels of immunological indexes in peripheral blood samples were measured using ELISA.[15] The $CD4^+$ and $CD8^+$ T cells percentage were detected by Human $CD4^+$ T cells ELISA kit (JKbio 14552, Shanghai Jingkang Bioengineering Co, Ltd, China), Human $CD8^+$ T cells ELISA kit (JKbio 14553, Shanghai Jingkang Bioengineering Co, Ltd, China), respectively.

Vaginal microenvironmental factors

The vaginal microenvironmental factors of the patients were examined using disposable swabs to collect vaginal secretions before and after treatment respectively, mainly including hydrogen peroxide (H_2O_2) positivity, sialidase (SNA) positivity, leukocyte esterase (LE) positivity, and N-acetylaminogalactosidase (NAG) positivity. The kit was the Vaginitis Pentameter Test Kit (100 tests/box, Zhengzhou Antu Bioengineering Co, Ltd, China).[16]

HR-HPV conversion rate

The HR-HPV conversion rate was assessed by real-time fluorescence quantitative PCR.[17] DNA was extracted after collection of cervical exfoliated cells, amplified against the conserved region of the HPV genome, and the conversion rate was analyzed according to the fluorescence signal interpretation. Conversion rate=(number of converted cases/total number of cases tested)×100%.

Clinical efficacy

Compare the clinical efficacy of both groups. Efficacy evaluation criteria: obvious effect: the rate of HR-HPV conversion increased by more than 30% from the baseline, serum inflammatory indexes decreased by≥50% compared with the pre-treatment period; the rate of vaginal microenvironmental H_2O_2 positivity was≥70%, and the rate of SNA/LE/NAG positivity

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was≤30%; the patients' subjective symptoms (e.g., abnormal secretion, contact bleeding) completely disappeared, and the immune indexes increased by≥20%. Effective: HR-HPV conversion rate increased by 15% to 30%; inflammatory indicators decreased by 20% to 50%; vaginal microenvironment H_2O_2 positivity rate of 50% to 70%, SNA/LE/NAG positivity rate of 30% to 50%; reduction of subjective symptoms, and immune indicators increased by 10% to 20%. Ineffective: HR-HPV conversion rate increased by<15% or not converted, inflammatory indicators did not change remarkably or even increased; vaginal microenvironmental indicators did not improve; subjective symptoms and clinical signs did not improve. Total effective rate=(obvious effect + effective)/total × 100%.

Secondary Indicators

Life quality

The life quality in both groups was compared using the Short Form of the Health Status Survey (SF-36 score) in the dimensions of physiological functioning, physical functioning, somatic pain, general health status, social functioning, emotional functioning, and mental health, with a total score of 100 scores, with higher scores indicating a better life quality.[18]

Complications

The occurrence of complications in both groups was recorded, including shock, hypoxemia, cervical injury or infection, venous thrombosis, pelvic inflammatory disease, fever, heart failure, localized vaginal dysbiosis and phlebitis.

Adverse reactions

Record the occurrence of adverse reactions during treatment in both groups, including vaginal itching, vaginal wall burning, frequent urination, painful urination, oral leukoplakia, angioedema, menstrual disorders.

Follow-up Visits

This study was primarily scheduled for a 3-month post-treatment follow-up to assess the durability of effects and to address any potential adverse reactions or problems.

Sample Size Calculation

Perform power analysis using G*Power 3.1.9.7 computer software to calculate the sample size required for detecting statistically significant differences. This study used HPV seroconversion rate as the main outcome measure, and the effect size assumption was based on the common value criteria of previous HPV related intervention studies, set at Cohen's d=0.8 (moderate to strong effect size). Under the condition of setting the alpha level to 0.05 (two-sided test) and the test efficacy (1−β) to 80%, the minimum sample size of 26 patients required for each group was calculated using software. Considering potential uncertainties such as loss to follow-up and missing data during the follow-up period, the final sample size selected for this study is 30 cases per group and a total sample size of 60 cases, ensuring that the study has sufficient statistical testing power to detect inter group differences. We believe that the sample size of this study can draw reliable conclusions.

Statistical Methods

SPSS28.0 statistical software was used for data analysis. Lucidchart was used to draw flow charts. The data in this study were tested for normal distribution. Baseline characteristics were described as numbers and variables (expressed as mean ± SD). Inflammatory markers, immune markers, vaginal microenvironmental factors and life quality outcomes were expressed as mean ± SD. Comparison between both groups was tested using independent samples t-test. The rates of HR-HPV conversion, clinical efficacy, complications and adverse effects in the results were expressed as proportions (%). Comparison between both groups was analyzed by χ^2 test. All statistical tests were two-sided and $p<0.05$ indicated statistically significant differences.

RESULTS

Basic Information

The 60 patients diagnosed with HR-HPV infection with CIN1 at Shandong Provincial Hospital between December 2023 and December 2024 were included in this study and were categorized into CT (n=30) and CR (n=30) groups according to treatment modalities. Baseline data of patients in both groups were collected in detail before the study, including age and other demographic characteristics. For statistical analysis, independent samples t-test was used for continuous variables, chi-square test was applied for categorical variables, and rank sum test was performed for

hierarchical data. After rigorous statistical processing, the results (Table 1) clearly showed that the differences in baseline characteristics between the two groups were not statistically significant(p>0.05). It showed that both groups were well comparable. This balance effectively controls the interference of confounding variables such as demographic factors and other clinical factors and lays a scientific foundation for the subsequent precise and reliable evaluation of the clinical efficacy of recombinant human interferon α2b vaginal effervescent tablets in the treatment of this condition, ensuring the reliability of the conclusions of the study on the clinical efficacy and immune mechanism.

Inflammation Indicators

The results of the comparison of inflammatory indicators in both groups are demonstrated in Table 2. Before treatment, the levels of TNF-α, IL-6 and hs-CRP in both groups were analyzed using the independent samples t-test, and the results showed p>0.05, which indicated that no remarkable discrepancy in the levels of inflammatory indicators were found between both groups. After treatment, the levels of inflammatory indicators were (34.23 ± 2.50) ng/L, (39.29 ± 3.71) ng/L and (14.70 ± 1.90) mg/L in the CT group and (29.41 ± 1.95) ng/L, (30.29 ± 4.22) ng/L and (10.25 ± 2.26) mg/L in the CR group, respectively. The within-group paired t-test was performed on the data of both groups after treatment, and the results showed p<0.05, indicating that the levels of inflammatory indexes in both groups were remarkably reduced after treatment than pre-treatment. Further testing of the level of inflammatory indicators in both groups after treatment revealed that the CR group was remarkably below the CT group (p<0.05). It indicated that the levels of inflammatory indicators in both groups were remarkably reduced after treatment, and the patients in the CR group revealed better improvement. This implies that recombinant human interferon α2b vaginal effervescent tablets have a unique advantage in controlling the inflammatory response of HR-HPV-induced CIN1 patients, which may be related to its multiple mechanisms of action such as regulating body immunity, inhibiting viral replication, and alleviating local inflammatory damage.

Immune Indicators

We conducted an in-depth analysis of the immune function indicators of patients in both groups, and the results are presented in Table 3. Pre-treatment, the various immune function indicators of both groups were analyzed and revealed no remarkable discrepancy (p>0.05), which indicated that the basic immune status of both groups of patients was at a similar level at the beginning of the treatment. After treatment, the immune function of both groups revealed remarkable improvement. Specifically, the $CD4^+$ T cells percentage and the $CD4^+/CD8^+$ ratio were remarkably elevated. The $CD4^+$ T cell percentage of patients in the CT group was elevated to (42.92 ± 3.82)%, and the $CD4^+/CD8^+$ ratio reached (1.45 ± 0.37). In contrast, patients in the CR group had a higher percentage of $CD4^+$ T cells at (48.85 ± 4.36)% and a more favorable $CD4^+/CD8^+$ ratio of (1.82 ± 0.43). There was a remarkable discrepancy between both groups (p<0.05), showing that the CR group had a more prominent improvement in these two indicators. Meanwhile, the $CD8^+$ T cells percentage was remarkably reduced in both groups. Patients in the CT group decreased to (25.86 ± 4.51)%, while patients in the CR group further decreased to (23.38 ± 2.25)%, with a remarkable discrepancy (p<0.05), indicating that the CR group was more effective in decreasing the $CD8^+$ T cells percentage. Comprehensive analysis of the above shows that the immune function of both groups has been remarkably improved after treatment, but the comparison of the specific data clearly shows that the immune function of the patients in the CR group has been enhanced more remarkably, and it has obvious advantages in enhancing the body's immune response and optimizing the proportion of immune cells.

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Table 1. Patient demographics and baseline disease characteristics (mean ± SD, n).

Parameter	CT group (n=30)	CR group (n=30)	95% CI Lower	95% CI Upper	t/χ^2	*p*
Age, y	38.13 ± 7.02	38.04 ± 6.26	-3.25	3.07	-0.052	0.958
Height, cm	161.97 ± 4.50	161.70 ± 5.02	-2.53	1.99	-0.219	0.827
Weight, kg	62.42 ± 7.37	62.27 ± 7.65	-3.78	3.48	-0.077	0.939
Body mass index, kg/m^2	23.85 ± 3.12	23.84 ± 2.98	-1.33	1.31	-0.013	0.990
Ethnicity (Han Chinese/Minority)	30/0	30/0	-	-	-	-
Education (Below high school/High school and above)	0/30	0/30	-	-	-	-
Marital status (Married/Unmarried)	28/2	28/2	-	-	0.000	1.000
Disease history						
Diabetes (yes/no)	3/27	2/28	-	-	0.579	0.447
Hypertension (yes/no)	0/30	1/29	-	-	3.046	0.081
Polycystic ovary syndrome (yes/no)	1/29	0/30	-	-	3.046	0.081
Past infection history within 1 year (yes/no)	8/22	7/23	-	-	0.000	1.000
HPV vaccination (yes/no)	6/24	5/25	-	-	0.000	1.000
Other vaccination history within 1 year (yes/no)	21/9	22/8	-	-	0.000	1.000
Surgical history						
Breast nodules (yes/no)	1/29	0/30	-	-	3.046	0.081
Caesarean section (yes/no)	4/26	3/27	-	-	0.442	0.506
Oophorectomy (yes/no)	4/26	3/27	-	-	0.442	0.506
Induced abortion (yes/no)	1/29	0/30	-	-	3.046	0.081
Smoking (yes/no)	0/30	0/30	-	-	-	-
Drinking alcohol (yes/no)	0/30	0/30	-	-	-	-
Signs are normal (yes/no)	30/0	30/0	-	-	-	-
Normal system (yes/no)	30/0	30/0	-	-	-	-
Temperature, °C	36.48 ± 0.27	36.43 ± 0.34	-0.17	0.07	-0.631	0.531
Respiration, breaths/min	17.88 ± 1.92	17.48 ± 2.36	-1.46	0.66	-0.720	0.474
Heart rate, beat/min	74.74 ± 5.64	74.47 ± 4.94	-2.74	2.20	-0.197	0.844
Systolic blood pressure, mm Hg	118.62 ± 5.08	118.83 ± 5.53	-2.26	2.68	0.153	0.879
Diastolic blood pressure, mm Hg	74.80 ± 3.75	74.64 ± 2.56	-1.74	1.42	-0.193	0.848

CI: confidence interval; CR: conventional therapy plus recombinant human interferon α2b; CT: conventional therapy; HPV: human papillomavirus.

Table 2. Comparison of inflammatory indicators between two groups before and after treatment (mean ± SD).

Norm	Time	CT group	CR group	95% CI Lower	95% CI Upper	t	*p*
TNF-α, ng/L	Pre-treatment	53.48 ± 5.06	53.56 ± 5.97	-2.32	2.48	0.056	0.956
	Post-treatment	34.23 ± 2.50[a]	29.41 ± 1.95[a]	-5.98	-3.66	-8.327	<0.001
IL-6, ng/L	Pre-treatment	83.30 ± 6.65	83.76 ± 4.95	-2.37	3.29	0.304	0.762
	Post-treatment	39.29 ± 3.71[a]	30.29 ± 4.22[a]	-10.89	-7.11	-8.773	<0.001
hs-CRP, mg/L	Pre-treatment	23.46 ± 1.61	23.08 ± 2.20	-1.27	0.51	-0.763	0.448
	Post-treatment	14.70 ± 1.90[a]	10.25 ± 2.26[a]	-5.63	-3.27	-8.255	<0.001

Represents marked discrepancy compared with pre-treatment, $p<0.05$. CI: confidence interval; CR: conventional therapy plus recombinant human interferon α2b; CT: conventional therapy; hs-CRP: high-sensitivity C-reactive protein; IL: interleukin; TNF: tumor necrosis factor.

Table 3. Comparison of immunological indicators between two groups before and after treatment (mean ± SD).

Norm	Time	CT group	CR group	95% CI Lower	95% CI Upper	t	*p*
$CD4^+$ T cells, %	Pre-treatment	36.62 ± 3.16	36.89 ± 2.29	-1.05	1.59	0.379	0.706
	Post-treatment	42.92 ± 3.82[a]	48.85 ± 4.36[a]	3.87	7.99	5.603	<0.001
$CD8^+$ T cells, %	Pre-treatment	29.49 ± 3.58	29.89 ± 3.69	-1.28	2.08	0.426	0.672
	Post-treatment	25.86 ± 4.51[a]	23.38 ± 2.25[a]	-4.42	-0.54	-2.695	<0.05
$CD4^+/CD8^+$	Pre-treatment	1.24 ± 0.27	1.21 ± 0.27	-0.14	0.08	-0.430	0.669
	Post-treatment	1.45 ± 0.37[a]	1.82 ± 0.43[a]	0.19	0.55	3.572	<0.001

Represents marked discrepancy compared with pre-treatment, $p<0.05$. CD: cluster of differentiation; CI: confidence interval; CR: conventional therapy plus recombinant human interferon α2b; CT: conventional therapy.

Vaginal Microenvironmental Factors

The positive rates of vaginal microenvironmental factors in both groups are presented in Table 4. Before treatment, the two groups of patients did not present statistically significant differences in terms of H_2O_2 positivity ($p>0.05$), SNA positivity, NAG positivity, and LE positivity, due to the complexity of individual differences and the randomness of the samples, which indicates that both groups are at a similar level of these indexes in the initial state. In contrast, after receiving different treatment regimens, the SNA positivity and LE positivity rates were significantly lower in the CR group than in the CT group($p<0.05$). SNA positivity often suggests the presence of infections such as bacterial vaginosis, and its lower positivity rate implies that the CR group had a better improvement in the status of associated bacterial infections in the vaginal microecology after treatment. LE positivity reflects leukocytosis, which is usually associated with inflammatory response, and the lower positivity rate of this indicator in the CR group suggests that the control of inflammatory response after treatment was more prominent in this group. However, there was still no statistically significant difference in the comparison of H_2O_2 positivity and NAG positivity between both groups ($p>0.05$), and H_2O_2 positivity was related to the number and activity of lactobacilli, the normal dominant bacteria in the vagina, and NAG positivity might be related to fungal or trichomonas infections and so on. This means that in these two indicators reflecting specific aspects of vaginal microecology, the two treatment regimens produced similar effects, failing to show a clear advantage of one treatment regimen over the other.

HR-HPV Conversion Rate

The HR-HPV conversion rate of patients in both

groups are demonstrated in Figure 2. The post-treatment data revealed that the HR-HPV conversion rate was 56.67% in the CT group and 73.33% in the CR group, and the discrepancy between the groups was statistically significant (p<0.05). This result indicated that recombinant human interferon α2b vaginal effervescent tablets (CR group) were remarkably better than the control treatment regimen (CT group) in clearing HR-HPV infection. Compared with the CT group, the 73.33% conversion rate in the CR group not only reflects the higher viral clearance efficiency but also suggests that the drug may reduce the risk of CIN1 progression to high-grade lesions through the synergistic effect of antiviral-immunomodulatory-anti-inflammatory. This result provides a key basis for choosing an effective and safe treatment for HPV-related cervical lesions, especially for patients who need to preserve fertility or avoid invasive treatments.

Table 4. Comparison of vaginal microenvironment related indicators between two groups before and after treatment [n(%)].

Norm	Time	CT group	CR group	χ^2	p
H_2O_2	Pre-treatment	18 (60.00)	19 (63.33)	0.190	0.663
	Post-treatment	11 (36.67)	10 (33.33)	0.352	0.553
SNA	Pre-treatment	21 (70.00)	22 (73.33)	0.221	0.638
	Post-treatment	11 (36.67)	2 (6.67)	26.224	<0.001
LE	Pre-treatment	21 (70.00)	20 (66.67)	0.209	0.648
	Post-treatment	14 (46.67)	4 (13.33)	27.524	<0.001
NAG	Pre-treatment	14 (46.67)	13 (43.33)	0.323	0.570
	Post-treatment	6 (20.00)	5 (16.67)	0.298	0.585

CR: conventional therapy plus recombinant human interferon α2b; CT: conventional therapy; H_2O_2: hydrogen peroxide; LE: leukocyte esterase; NAG: N-acetylaminogalactosidase; SNA: sialidase.

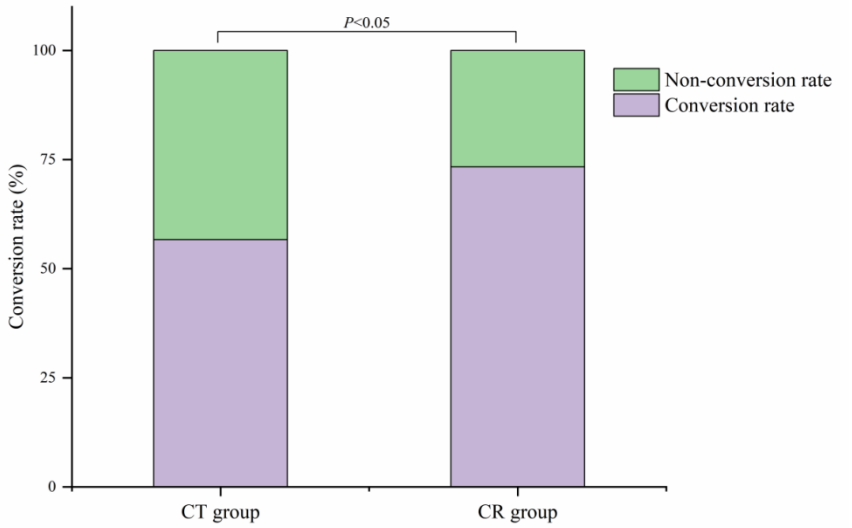

Figure 2. Comparison of HR-HPV conversion rates between two groups after treatment [n(%)].

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Clinical Efficacy

The clinical efficacy of patients in both groups is presented in Table 5. The results after treatment revealed that the total effective rate of the CR group was 93.33% (28/30), significantly higher than the 73.33% (22/30) of the CT group, and the difference between the groups was statistically significant (p<0.05). This result was highly consistent with the trend of improvement in HPV conversion rate, inflammatory indicators and immune function, further confirming the clinical advantages of recombinant human interferon α2b vaginal effervescent tablets in the treatment of CIN1. The results suggest that recombinant human interferon α2b vaginal effervescent tablets may be a preferred conservative treatment option for patients with HPV infection combined with CIN1, especially for those who wish to preserve cervical function or avoid the trauma of surgery, and that its high efficacy rate and multiple mechanisms of action are expected to be important in reducing the risk of lesion progression and improving long-term prognosis.

Life Quality

The results of the comparison of the life quality scores in both groups are presented in Table 6. Before treatment, there was no marked discrepancy between the SF-36 life quality scores of both groups (p>0.05), indicating that the physiological and psychological functions and social adaptability of both groups were at a similar level in the baseline state. After treatment, the SF-36 score of the CR group was elevated to (95.44 ± 2.13), which was remarkably above the (90.23 ± 3.52) score of the CT group (p<0.05), and this result further supports the clinical advantages of recombinant human interferon α2b vaginal effervescent tablets at the level of the patients' subjective experience. The results provide an important reference for clinical decision-making. For patients who pay attention to the maintenance of life quality, especially women of childbearing age, recombinant human interferon α2b vaginal effervescent tablets can better maintain their quality of life while effectively controlling the disease.

Complications

In this study, the complications that occurred during the treatment of patients in both groups were analyzed, including shock and hypoxemia, etc., and the specific results are demonstrated in Table 7. After statistical testing, the comparison between the two groups did not show remarkable differences in the incidence of serious complications such as shock and hypoxemia (p>0.05), indicating that the basic treatment plan was similar between the two groups in terms of the risk of triggering these types of complications. As for the comparison of the total complication rate, the total complication rate of patients in the CR group was 10.00% (3/30), which was remarkably below that of 20.00% (6/30) in the CT group, with a statistically significance discrepancy between the groups (p<0.05). This series of data shows that compared with a single treatment modality, the CR group program can effectively reduce the probability of various complications in the treatment process through the mechanism of multiple pathways and multiple targets, which helps to improve the comfort and compliance during treatment and provides a more reliable guarantee for the smooth progress of treatment.

Table 5. Comparison of clinical efficacy between two groups after treatment [n(%)].

Group	Obvious effect (n)	Effective (n)	Ineffective (n)	Total effective rate (n, %)
CT group	10	12	8	22 (73.33)
CR group	13	15	2	28 (93.33)
χ^2				14.174
p				<0.001

CR: conventional therapy plus recombinant human interferon α2b; CT: conventional therapy.

Table 6. Comparison of SF-36 scores between two groups before and after treatment (mean ± SD, score).

	CT group	CR group	95% CI Lower	95% CI Upper	t	*p*
Pre-treatment	83.38 ± 2.94	83.71 ± 2.97	-1.19	1.85	0.433	0.667
Post-treatment	90.23 ± 3.52	95.44 ± 2.13	3.78	6.64	6.936	<0.001
95% CI Lower	5.23	10.35				
95% CI Upper	8.47	13.11				
t	8.181	17.579				
p	<0.001	<0.001				

CI: confidence interval; CR: conventional therapy plus recombinant human interferon α2b; CT: conventional therapy; SF-36: Short Form of the Health Status Survey.

Table 7. Comparison of incidence of complications between two groups after treatment [n(%)].

	CT group	CR group	χ^2	*p*
Shock	1 (3.33)	0 (0.00)	3.046	0.081
Hypoxemia	0 (0.00)	0 (0.00)	-	-
Cervical injury or infection	1 (3.33)	1 (3.33)	0.000	1.000
Venous thrombosis	0 (0.00)	0 (0.00)	-	-
Pelvic inflammatory disease	1 (3.33)	1 (3.33)	0.000	1.000
Fever	1 (3.33)	0 (0.00)	3.046	0.081
Heart failure	1 (3.33)	1 (3.33)	0.000	1.000
Localized vaginal dysbiosis	0 (0.00)	0 (0.00)	-	-
Phlebitis	1 (3.33)	0 (0.00)	3.046	0.081
Total incidence	6 (20.00)	3 (10.00)	3.922	<0.05

CR: conventional therapy plus recombinant human interferon α2b; CT: conventional therapy.

Adverse Effects

In this study, we carried out a follow-up of the patients to closely observe the adverse reactions during the treatment. In both groups, different degrees of adverse reactions such as vaginal itching occurred in the course of treatment, as demonstrated in Table 8. Statistically analyzed, the discrepancy between both groups in the manifestation of adverse reactions such as vaginal itching was not remarkable (p>0.05). However, in terms of the total incidence of adverse reactions, the incidence in the CT group was 16.67% (5/30), which was remarkably above that of patients in the CR group, which was 6.67% (2/30), with a statistically significance discrepancy (p<0.05). In terms of clinical significance, the lower incidence of adverse reactions implies that the patients were able to better tolerate the treatment regimen during the course of treatment. The treatment used by the CR group patients not only demonstrated advantages in terms of therapeutic efficacy but also excelled in terms of safety. This may be attributed to the fact that the treatment is less disruptive to the patient's bodily functions and reduces the incidence of adverse effects.

Table 8. Comparison of adverse reactions between two groups after treatment [n(%)].

	CT group	CR group	χ^2	*p*
Vaginal itching	1 (3.33)	0 (0.00)	3.046	0.081
Burning of the vaginal walls	1 (3.33)	1 (3.33)	0.000	1.000
Frequent urination	0 (0.00)	0 (0.00)	-	-
Painful urination	1 (3.33)	1 (3.33)	0.000	1.000
Oral leukoplakia	0 (0.00)	0 (0.00)	-	-
Angioedema	1 (3.33)	0 (0.00)	3.046	0.081
Menstrual disorders	1 (3.33)	0 (0.00)	3.046	0.081
Palpitations	0 (0.00)	0 (0.00)	-	-
Total incidence	5 (16.67)	2 (6.67)	4.735	<0.05

CR: conventional therapy plus recombinant human interferon α2b; CT: conventional therapy.

DISCUSSION

HPV is a key driver of cervical cancer and high-grade cervical lesions. Persistent HR-HPV infection leads to viral gene integration into the human genome, inducing genetic mutations in cervical epithelial cells and abnormal proliferation.[19] CIN1-mildly abnormal cervical epithelial proliferation arising from this process-represents an early stage of cervical precancerous lesions. Most CIN1 patients are asymptomatic and diagnosed incidentally during gynecological examinations, but untreated lesions may progress to severe cervical pathology or even cervical cancer.[20] Clinical management of HR-HPV-induced CIN1 is heterogeneous. Options include regular follow-up with close lesion monitoring, lifestyle modifications to enhance immunity (aiding HPV clearance and lesion regression),[21] physical therapies (e.g., cryotherapy, laser) to ablate diseased tissue, or surgical interventions (e.g., cervical conization) for severe or high-risk cases. However, these approaches have limitations: regular follow-up may delay optimal treatment, immunity-based regression is inconsistent and time-consuming, physical therapy may not eliminate the virus (carrying recurrence risks), and surgery can damage the reproductive system and impact fertility.[22] Thus, safer and more effective treatments are urgently needed. Recombinant human interferon α2b vaginal effervescent tablets, a novel therapeutic agent, offer new potential for CIN1 management.

Recombinant human interferon α2b vaginal effervescent tablets have unique therapeutic advantages. Its main ingredient, recombinant human interferon α2b, has broad-spectrum antiviral properties, which can combine with specific membrane receptors on the cell surface, activate the cellular antiviral protein gene, generate antiviral protein, and then effectively inhibit viral replication. At the same time, it can also regulate the body's immune function, enhance the phagocytosis of macrophages as well as the cytotoxicity of lymphocytes to target cells, and improve the body's antiviral ability.[23] When used in the treatment of HR-HPV-induced CIN1, it can be absorbed through the epithelium of the vaginal mucosa, directly exerting antiviral efficacy locally in the cervix and vagina, with a high local concentration of the drug and a rapid onset of action. Moreover, the drug can also regulate the level of estrogen and progesterone in the body, reduce cervical secretions, alleviate tissue oedema and exudation, and promote the repair and healing of cervical trauma.[24]

Together, these mechanisms support the rationale for investigating recombinant human interferon α2b vaginal effervescent tablets as a therapeutic option for HR-HPV-induced CIN1. In the present work, we focused on determining its clinical effectiveness and corresponding immune alterations, with the aim of establishing evidence for its ability to promote HR-HPV clearance, ameliorate local inflammation, restore immune balance, and improve clinical outcomes in affected patients.

The results of this study showed significant differences in all indicators. In terms of inflammatory indicators, no significant discrepancy in the levels of inflammatory indicators such as TNF-α, IL-6 and hs-CRP between both groups pre-treatment, but the levels of these inflammatory indicators in the CR group were remarkably below in the CT group post-treatment (p<0.05). This suggests that recombinant human

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interferon α2b vaginal effervescent tablets have a positive effect in reducing the inflammatory response. Inflammatory response plays an important role in the development of HR-HPV infection and CIN1, and a persistent inflammatory state may promote disease progression. TNF-α and IL-6, as key pro-inflammatory cytokines, can induce immune cell activation, and when overexpressed, they can cause local tissue damage and microenvironmental alterations, affecting the body's immune defense against viral infection and cellular repair mechanisms.[25] Recombinant human interferon α2b may reduce the release of these pro-inflammatory factors by regulating the function of immune cells, thus effectively controlling the level of inflammation, creating a favorable environment for the body's immune cells to play an antiviral role, and facilitating the repair of the local tissues of the cervix and restoring the normal state.

At the level of immune cells, the percentage of $CD4^+$ T cells and $CD4^+/CD8^+$ ratio of patients in the CR group were remarkably above in the CT group, and the percentage of $CD8^+$ T cells was below in the CT group ($p<0.05$). As helper T cells, $CD4^+$ T cells play a central regulatory role in the immune system, which can assist B cells to produce antibodies, activate cytotoxic T cells ($CD8^+$ T cells) and macrophages, etc., and enhance the body's immune response to fight viral infection. The $CD4^+/CD8^+$ ratio is an important indicator of the body's immune balance, and a higher ratio means that the immune system is in a more active anti-viral state. While $CD8^+$ T cells have the function of killing virus-infected cells, overactivation or imbalance of the ratio may lead to immune injury in some chronic viral infection situations.[26] Recombinant human interferon α2b vaginal effervescent tablets can regulate the proportion of T cell subsets, enhance $CD4^+$ T cell function and immune cell synergy, enhance the body's ability to recognize and clear HR-HPV infected cells, and thereby inhibit the progression of CIN1. At the same time, it should be noted that after local administration, some drug components can be absorbed through the mucosa to trigger systemic immune regulation. Through the linkage of "peripheral immunity local immunity", it can supplement and activate immune cells locally in the cervix, enhance virus clearance efficiency, and indirectly assist in the restoration of vaginal microbiota balance. It should be clarified that the core target of vaginal local administration still focuses on the cervix and vaginal area, and systemic regulation is only a supplementary enhancement of local effects rather than dominant. In the future, its contribution can be further quantified by detecting blood drug concentrations and analyzing differences in immune cell phenotypes.

In analyzing the modulating effect of recombinant human interferon α2b vaginal effervescent tablets on vaginal microecology, changes in microbiological indicators before and after treatment revealed its unique characteristics of action. There were no statistical differences in H_2O_2 positivity, SNA positivity, NAG positivity, and LE positivity between the two groups before treatment, suggesting that the vaginal microecological backgrounds of the two groups were consistent at baseline. After treatment, the SNA-positive rate and LE-positive rate were remarkably lower in the CR group than in the CT group ($p<0.05$). This result suggests that the decreased SNA positivity rate indicates that the drug may reduce the microecological imbalance associated with bacterial vaginosis by inhibiting the adhesion and metabolism of pathogenic bacteria. The decrease in LE positivity directly reflected the reduction of local inflammatory cell infiltration in the cervix, which echoed the decrease in inflammatory indicators (TNF-α, IL-6), suggesting that the drug improved the local microenvironment through the dual mechanism of 'anti-inflammatory and anti-bacterial'.[27] It is worth noting that the H_2O_2 positivity rate and NAG positivity rate did not differ remarkably between both groups, probably because H_2O_2 positivity is mainly dependent on the colonization and metabolism of Lactobacillus, whereas recombinant interferon α2b is more oriented to immunomodulation and antiviral, and has little effect on the direct proliferation of Lactobacillus, so that it did not cause any discrepancy in the level of H_2O_2 between the groups. NAG positivity is associated with specific pathogens such as fungi/trichomonads, and it is possible that the lack of comorbidity of such infections in the included cases in the present study resulted in a non-significant effect of the drug on this indicator. This selective microecological regulation characteristic reflects the mechanism difference between interferon drugs and traditional antibiotics: they do not broad-spectrum inhibit all microorganisms, but directly inhibit HPV replication, reduce the damage of mucosal inflammation to the epithelial barrier, regulate immune inflammatory response, and specifically inhibit pathogenic links related to HPV infection (such as bacterial vaginosis synergistically promoting persistent HPV infection, etc.), thus creating conditions for lactobacilli proliferation (CIN1 reversal). This

mechanism further explains why the clinical efficacy and immune indicators of the CR group are better: the restoration of vaginal microbiota balance can reduce the release of local inflammatory factors (such as IL-6 and TNF-α), reduce the inhibition of inflammation on T cell immune function, promote $CD4^+$ T cell proliferation and $CD4^+/CD8^+$ratio balance, and enhance HPV clearance efficiency. The synergistic effect of "antiviral microbiota regulation immune enhancement" is precisely the core advantage of recombinant human interferon α2b vaginal effervescent tablets in treating CIN1. Li et al. also reported in their study on the relationship between vaginal microecological enzyme changes and HPV infection that positive expression of acetylaminoglucosidase in vaginal microecology may be remarkably associated with the outcome of vaginal inflammation and HPV infection,[28] which is similar to the findings of the present study. This finding also suggests that in the future, macrogenomic analysis of vaginal flora could be combined to further clarify the modulation pattern of drugs on core genera.

After treatment, the HR-HPV conversion rate and clinical efficacy of the CR group were remarkably higher than that of the CT group ($p<0.05$). Meanwhile, in terms of life quality, there was no statistically significant discrepancy in the SF-36 life quality scores of patients in both groups before treatment ($p>0.05$), and the SF-36 scores of the CR group were remarkably above the CT group after treatment ($p<0.05$). The CR group was remarkably below the CT group in terms of the total incidence of complications and the total incidence of adverse reactions ($p<0.05$). This series of results comprehensively indicated that recombinant human interferon α2b vaginal effervescent tablets had significant advantages in the treatment of CIN1 caused by HR-HPV. It can not only effectively increase the rate of viral conversion, improve the clinical symptoms of patients, and enhance the therapeutic effect of the disease, but also remarkably improve the life quality of patients and reduce treatment-related complications and adverse reactions. Zhao et al reported similar findings in a study on the efficacy of recombinant human interferon α2b combined with cervical loop electrosurgical excision procedure in the treatment of cervical precancerous lesions.[29] This provides a safe and effective therapeutic option for the clinical treatment of HR-HPV-induced CIN1, which has an important promotional value and is expected to bring a better therapeutic outlook for more patients, helping them to restore their health while effectively controlling their disease and minimizing the pain and adverse effects of the treatment process. It is worth noting that virus clearance and lesion regression are two independent and asynchronous key indicators in the treatment of HPV related lesions. Virus clearance refers to the negative result of HPV nucleic acid testing in the body, reflecting the inhibitory effect of antiviral therapy on pathogens. The regression of lesions requires pathological or imaging examination to confirm the repair, reduction, or disappearance of cervical lesion tissue, and its process is also influenced by multiple factors such as mucosal repair ability and local inflammation degree. The observed increase in HPV seroconversion rate in this study does not necessarily equate to synchronous regression of lesions. It is recommended that clinical evaluation of treatment efficacy should be based on a comprehensive assessment of both indicators.

This study has several limitations. First, the small sample size (30 cases per group) and single-center retrospective design may introduce selection and information biases, limiting the statistical power for analyzing rare complications and the generalizability of conclusions to broader populations. Second, the short follow-up period only captured short-term efficacy, with no long-term tracking of prognosis (e.g., cervical cancer incidence) or recurrence risk and lacked analysis of CIN1 spontaneous regression—potentially affecting the comprehensiveness of efficacy assessment. Third, no stratified analysis by HPV subtype (e.g., HPV16/18 vs. other high-risk types) was performed, which may obscure subtype-specific drug effects. Finally, the study only evaluated peripheral blood immune indicators, without investigating cervical mucosal local immunity (e.g., immune cell infiltration, cytokine secretion), leading to insufficient insight into the drug's mechanism of action. Future research should address these limitations by expanding the sample size, conducting HPV subtype-stratified analysis, and adding a natural observation control group. Extending follow-up to 2–3 years will enable monitoring of long-term prognosis and recurrence. Combining cervical mucosal biopsy with single-cell sequencing, transcriptomics, and in vitro functional assays will help elucidate local immune microenvironment changes and molecular mechanisms, establishing a complete evidence chain to optimize clinical treatment strategies.

In this study, the efficacy of recombinant human interferon α2b vaginal effervescent tablets in treating

HR-HPV-induced CIN1 was compared between the CT group and the CR group, which provides a scientific reference for optimizing clinical treatment plans. The results revealed that the CR group has significant advantages in reducing inflammatory indexes, regulating immune function, improving vaginal microecology, increasing HPV clearance rate and clinical efficacy. It also improves patients' quality of life and reduces the incidence of complications and adverse reactions. However, this study has limitations, including small sample size, short follow-up period, lack of stratified analysis by HPV type, and insufficient investigation into local cervical immune mechanisms. Multi-center, large-sample, long-term follow-up clinical studies are required to further stratify efficacy across different populations and analyze the drug's mechanism of action using molecular biology techniques. This will fully validate its clinical value and optimize treatment strategies.

STATEMENT OF ETHICS

This study was approved by the Ethics Committee of Shandong Provincial Hospital (YZ-20230608).

FUNDING

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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None.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author, upon reasonable request.

AI ASSISTANCE DISCLOSURE

The authors declare that no artificial intelligence (AI) tools or AI-assisted writing services were used in the preparation, writing, editing, or data analysis of this manuscript. All work was completed by the listed authors independently.

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