Novel Effective Non-invasive Clinical Treatment for Persistent High-Risk Human Papillomavirus Infection

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Abstract

High-risk human papillomavirus (hrHPV) is the major cause of cervical cancer. The majority of hrHPV infections resolve spontaneously. However, when hrHPV escapes host's immune system and establishes persistent infection in basal keratinocytes, self-clearance of the infection becomes exactly difficult, and medical intervention is urgently needed to eradicate viral infection and prevent cervical cancer. This review aimed to summarize our findings and achievements on REBACIN®—an anti-viral biologic with low cost, no cold chain and no hospitalization, and demonstrated that REBACIN® exhibits potent efficacy in clearing persistent hrHPV infections, promotes regression of associated lesions via targeted inhibition of viral E6/E7 oncogenes.

Introduction

High-risk human papillomavirus (hrHPV) infection is responsible for approximately 5% of all human cancers, and nearly all cases of cervical cancer are initiated by persistent hrHPV infection. According to the 2020 Global Cancer Statistics,[1] there are approximately 600,000 new cases of cervical cancer and 340,000 deaths worldwide annually. A large-scale epidemiological study of 138,000 Chinese women in 2020 revealed that the HPV infection rate in gynecological clinics was approximately 23.5%, of which hrHPV infection accounted for 19.4%.[2] Despite the implementation of standardized cervical cancer screening, persistent hrHPV infections remain extremely common in the clinic.[2-3] During persistent hrHPV infection, if the viral DNA becomes integrated into the host genome, constitutive overexpression of viral E6 and E7 oncoproteins induces the degradation of tumor suppressor p53 and pRb1, leading to cervical intraepithelial lesions and carcinogenesis.[4]Therefore, urgent clinical intervention is needed to eliminate persistent hrHPV infection and promote regression of HPV-associated high-grade squamous intraepithelial lesions (HSIL).

In recent years, HPV preventive vaccines have been applied clinically to prevent HPV infection; however, these vaccines do not generate strong therapeutic effects against existing HPV infections and established lesions.[5] Studies have demonstrated that 99% of cervical cancers harbor the hrHPV E6 and E7 oncogenes, making the E6/E7 viral oncogene an attractive target for the development of anti-hrHPV drugs or therapeutic vaccines.[6-7] The major difference between a therapeutic vaccine and a preventive vaccine is that the former confers cell-mediated immunity to kill infected cells instead of introducing neutralizing antibodies into the system. Some HPV therapeutic vaccines, such as VGX 3100, GX-188E, pNGVL4a-CRT/E7 (detox), and PepCan + Candin ADXS11-OO1, have undergone clinical trials, and some therapeutic modalities, such as genome editing and immunity therapy for E6/E7, have also been explored.[8-11]

REBACIN® is an innovative anti-HPV biologic. In 2010, we reported for the first time that the viral E6/E7 oncogenes were the target of REBACIN® in clearing persistent hrHPV infection.[12] In vitro,

REBACIN®significantly inhibited the expression of HPV E6 and E7 oncogenes in TC-1 and HeLa cells. In vivo, REBACIN® can effectively inhibit viral E6/E7-induced tumor growth in severe combined immunodeficiency disease (SCID) mice, and the experimental data in both cells and animals are shown in a dose-dependent manner.[13] Our clinical studies demonstrated that REBACIN® significantly eliminates persistent hrHPV infection and promotes regression of the associated intraepithelial neoplasia.[13-14] This review summarizes the progress of REBACIN® in clearing persistent hrHPV infection and promoting the regression of HPV-associated cervical precancerous lesions, with the aim of providing a new non-invasive clinical intervention option to clear persistent hrHPV infection and associated cervical lesions.

Intervention targeting viral E6/E7 oncogenes

The development of cervical cancer from the initial establishment to subsequent progression is entirely dependent on two major hrHPV oncogenes, E6 and E7, whose overexpression leads to tumorigenesis.[15-16] Therefore, targeting E6 and E7 oncogenes is the most promising strategy for developing therapeutic drugs or vaccines to eliminate persistent hrHPV infection and promote regression of cervical intraepithelial neoplasia.[17]Generally, hrHPV persists in infected host cells as a circular episome, but can also linearize and integrate into the host genome. High-risk HPV genome integration can lead to disruption of the E2 open reading frame, causing loss of expression of the E2 gene that represses the viral oncogenes, E6 and E7,[18] resulting in overexpression of viral E6 and E7 oncoproteins, which disrupt the functions of the tumor suppressor p53 and retinoblastoma protein pRB, damage host cell DNAs, and inhibit the host's innate immune system. Therefore, E6 and E7 are the most effective therapeutic targets.[17]

REBACIN® inhibits expression of oncogenes E6/E7

In both TC-1 and HeLa cell lines stably expressing E6/E7 oncogenes, the mRNA transcription of HPV E6/E7 was markedly inhibited by the application of REBACIN®.[13] In TC-1 cells, a low concentration of 19 μg/mL REBACIN®significantly inhibited E6 expression, whereas 78 μg/mL REBACIN® had a clear effect on the inhibition of E7 expression (also see the overview in Figure 1A and 1B). Similarly, in HeLa cells, 78 μg/mL REBACIN® markedly prevented E6 expression, whereas 19 μg/mL REBACIN® decreased E7 expression. In a clinical observation, one course (three months) of REBACIN® treatment remarkably reduced E6/E7 mRNA in hrHPV-infected patients, most of which became negative (see overview Figure 1C).[14] Consistent with this clinical observation in a case report, another clinical observation study demonstrated that after one course of treatment, 68.57% of patients showed complete suppression of HPV E6/E7 mRNA expression in the REBACIN® group and 20% in the control group.[19] In protein level, REBACIN®was also found to significantly inhibit the expression of HPV16 oncoprotein E7 in a dose-dependent (see overview Figure 1D)[14] and time-dependent manner[19]. All in vitro, in vivo, and clinical studies have demonstrated and confirmed that REBACIN® effectively targets and inhibits the expression of viral E6/E7 oncogenes, thereby demonstrating that REBACIN® may play a key role in clearing persistent hrHPV infection and in the regression of associated cervical epithelial lesions.

REBACIN® impedes growth ofcervical cancer cells

REBACIN® specifically inhibited the growth of cervical cancer cells of Ca Ski via inhibiting viral oncoprotein E6/E7 expression, and anti-REBACIN® antibody counteracted this inhibitory effect, but had no significant effect on the growth of 293T cells lacking the E6 and E7 genes (Figure 2A and 2B).[19] These findings demonstrated that REBACIN® can specifically target and inhibit the expression of hrHPV E6/E7 oncogenes.

REBACIN® prevents E6/E7-induced tumor growth

In the SCID model, REBACIN® treatment significantly inhibited E6/E7-stimulated tumor growth after three injections (on Days 1, 14, and 28).[13] Consistent with the finding that REBACIN® inhibited HPV E6/E7 expression (Figure 1), TC-1 cells with inhibition of E6/E7 expression after REBACIN® treatment (as low as 19 μg/mL) were significantly poor in inducing tumor growth (Figure 2C). Similarly, after inhibition of E6/E7 expression, HeLa cells also show poor tumor growth.[13] These studies demonstrate that the serious level of either TC-1 or HeLa cell-induced malignant transformation depends on the expression level of E6/E7,

suggesting a potential role of REBACIN® in the prevention of E6/E7-stimulated cervical carcinogenesis.

Intervention in clearance of persistent hrHPV infections

While most hrHPV infections are transient, 10–20% of infections persist latently, leading to disease progression and various forms of invasive cancer.[20] Infection of the basal cells of the lower epithelium by hrHPV through a micro-abrasion or wound in the stratified epithelium causes the virus particles to attach to heparan sulfate proteoglycans (HSPG) on the basement membrane, inducing a series of conformational changes that promote viral entry. HPV particles enter the basal keratinocyte cells by endocytosis, which is mediated by an uncharacterized secondary receptor on the membrane of host cells. After the basal cells of the cervical epithelium are infected with hrHPV virus particles, a small amount of established extrachromosomal viral genomes will persist in self-renewing basal cells of the lower epithelium. This pool of infected basal cells forms the base of the infected lesion and acts as a reservoir for persistent hrHPV infection.[21]After initial HPV DNA amplification, the viral genome must be "established" as a stable, low-copy number extrachromosomal element in the host cell nucleus. These genomes must evade detection by innate immune defenses in order to avoid recognition and clearance by the immune system. Therefore, hrHPV can sustain long-term infection in squamous stratified epithelium by viral DNA, preserving a low copy number of extrachromosomal plasmids for maintenance replication in dividing basal cells, while progeny viral genomes are amplified abundantly in differentiated superficial cells.[22]Hence, persistent hrHPV infection can evade immunity, which is difficult to self-clean, and requires clinical intervention.

REBACIN®effectively eliminates persistent hrHPV infection

In two independent parallel clinical studies, three months of REBACIN® treatment led to 62.11% (59/95) of hrHPV-positive patients becoming hrHPV-negative compared to 15.38% (16/104) in the control group (Table 1).[13] These two independent parallel clinical studies demonstrated that REBACIN® has a significant effect on clearing persistent hrHPV infections and highlighted the development of a novel non-invasive therapeutic intervention with significant efficacy in clearing persistent HPV infections.

Retrospective analysis in clearing of persistent hrHPV infection

In a retrospective analysis and meta-analysis,[23] the overall rate of efficacy of REBACIN® was 74.73% (272/364), of which 241 patients had a history of ineffective interferon therapy. The efficacy of REBACIN® was correlated with HPV type (odds ratio [OR]: 0.549, 95% confidence interval [CI]: 0.367–0.822, P =0.004) and pretreatment cytology (OR: 0.358, 95% CI: 0.173–0.739, P =0.005). [23]

Real-world evidence on clearing hrHPV infection

Real-world studies can provide better understanding of how a treatment is used in routine clinical practice. Real-world data enable a greater appreciation of the true efficacy and safety profile of a treatment in the real world, by reflecting the actual diagnosis, treatment process and health status of patients under real conditions. In a recent real-world study of 506 patients at nine hospitals in seven Chinese provinces (Figure S1), 69.57% of hrHPV-positive patients became hrHPV-negative following treatment (Table 2).[24] These real-world data are in agreement with the results of our two previous independent parallel clinical studies.[13] This real-world study further revealed the diversity among different hrHPV subtypes. The clearance rates of hrHPV subtypes 16, 18, and 52 were 77.78%, 85.37%, and 61.11%, respectively (Table 2). The real-world study also revealed there was no significant side effect during the treatment and all follow-ups, beside mild vaginal itch occasionally observed during treatments[24], which is in line with our previous clinical studies[13-14]. This study further supports the safety and efficacy of REBACIN® as a non-invasive clinical regimen for the clearance of persistent hrHPV infections.[24]

Analysis of the mechanism of action of REBACIN®

Owing to the complexity of persistent hrHPV infection, the development of anti-hrHPV drugs and therapeutic vaccines is still in progress despite many attempts. The results of three different modes of clinical evaluation in clearing persistent hrHPV infection were highly consistent: the negative conversion rate of

REBACIN®intervention was 62–70%, whereas the self-negative conversion rate of the control was 13–20.0%. All clinical studies confirmed that REBACIN® is a safe and effective non-invasive clinical intervention for the clearance of persistent hrHPV infection. Recently, Murakami et al. performed a comparative analysis investigating the specific requirements for HPV16 and HPV11 genome replication in "infected" basal-like keratinocytes. They observed that the HPV16 genome, but not HPV11, is maintained in keratinocytes during tissue culture; however, in the presence of HPV16 E6 and/or E7, HPV11 genomes also replicated in cultured tissue cells.[25] This finding indicates that hrHPV E6/E7 oncogenes play a pivotal role in enabling maintenance of hrHPV genome replication in host cells. If the hrHPV E6/E7 oncogene is suppressed, the viral genome cannot continue to replicate and the virus is thereby eliminated. Thus, this finding provides further evidence that REBACIN®eliminates persistent high-risk HPV infection via targeting and inhibiting the expression of hrHPV E6/E7 oncogenes.

A pioneer clinical study in regression of hrHPV associated HSIL

It is well known that hrHPV infection and integration of the hrHPV genome into the host chromosome are key early events in tumor progression of cervical lesions. The viral oncoproteins hrHPV E6 and E7 are responsible for initial changes in epithelial cells. Progression from hrHPV infection of epithelial cells to invasive carcinoma is a prolonged process, taking at least 15–20 years for transition from precancerous lesions to invasive carcinoma. During this period epigenetic changes in oncogenes and tumor suppressor genes occur. After HPV infects the host's basal squamous cells, it evades the host's immune system and continues to replicate in the basal epithelial cells. Cervical intraepithelial neoplasia grade 1 (CIN 1) is the stage at which the virus continues to infect cervical cells. CIN 1 lesions may progress to CIN 2/3 within 2–3 years of infection.[26]Therefore, the regression of cervical lesions can be promoted by inhibiting the expression of hrHPV E6/E7 oncoproteins, restoring the activity of p53 and pRb tumor suppressors, restoring cellular innate immunity, and recovering the repair function of cellular DNA. Based on the previous finding that REBACIN® can effectively target and inhibit the expression of viral E6/E7 oncogenes, several clinical exploratory and pioneering studies have been conducted on the regression of high-grade cervical intraepithelial neoplasia with REBACIN® treatment.

REBACIN®-mediated regression of HSIL

In a recent clinical observation of regression of HSIL (CIN2), 88.89% (16/18) of patients with HSIL (CIN2) and persistent hrHPV infection regressed after one to three courses of REBACIN®treatment, and exhibited clearance of hrHPV infection (Table S1).[14]

Although variable rates of spontaneous regression have been reported in patients with CIN2/3,[27-29] it is difficult to verify because of differences in patient enrollment and duration of clinical observation. In the current study, 88.89% (16/18) of patients with HSIL (CIN2) displayed not only regression but also clearance of hrHPV infection, indicating that REBACIN® intervention is indeed a potential non-invasive therapy for HSIL (CIN2) regression. However, owing to the limitation of participants in this observation, more data from prospective studies are required to accurately evaluate the effect of REBACIN® on HSIL regression.

Combinative effect of REBACIN ® with LEEP

In a previous investigation of patients with HSIL (CIN 2/3) and hrHPV infection who underwent loop electrosurgical excision procedure (LEEP) following REBACIN® treatment, 51 of 53 patients were negative for both CIN and hrHPV infection during the 24-month follow-up assessment. This 96.23% (51/53) disease-free rate was significantly higher than that of 73.47% (36/49) in the LEEP control group. Two patients in the REBACIN® treatment group showed persistent HPV positivity and re-developed CIN during follow-ups, resulting in a disease recurrence rate of 3.77% in the REBACIN® group, while the recurrence rate in the control group was 26.53% (Table S2).[30] This study illustrated that REBACIN® treatment in combination with LEEP can effectively enhance the cure rate of high-grade cervical intraepithelial neoplasia and significantly reduce relapse compared to treatment with LEEP only.

Conclusions and future perspectives

The main reason that HPV infection can cause cervical cancer and other related diseases is due to the ability of the virus to establish long-term persistent infection. Persistent hrHPV infection can abrogate the host's innate immunity and the anti-viral defense system, block DNA damage signaling and repair pathways by viral oncoproteins E6/E7, maintain the viral DNA replication in the stratified epithelium, and induce cervical cancer. Research has demonstrated that it takes ˜15–20 years for HPV-infected cervical cells to develop into cancerous tumors in women with normal immune systems and 5–10 years in women with weakened immune systems. This provides an opportunity for early clinical intervention to clear hrHPV infection and to promote regression of cervical intraepithelial neoplasia. However, the development of therapeutic vaccines and drugs for persistent viral infections is still in progress owing to the complexity of persistent hrHPV infection and the specificity of viral integration mechanisms. Effective intervention and treatment are still not available to patients diagnosed with persistent hrHPV infection. Therefore, patients with persistent hrHPV infection are only clinically observed and followed up until the development of high-grade cervical intraepithelial neoplasia (HSIL), after which surgical treatment must be performed. However, because residual hrHPV cannot be completely removed by surgery, recurrence of viral infection and CIN is common, and moreover some patients may have fertility or other concerns and refuse surgery. Hence, there is an urgent need for effective, non-invasive clinical intervention.

This review summarizes recent studies on the underlying mechanism, clinical observations, and real-world evidence of REBACIN® as a non-invasive clinical intervention with high efficacy in clearing persistent hrHPV infection and promoting regression of hrHPV-associated cervical intraepithelial lesions via targeted inhibiting expression of hrHPV E6/E7 oncogenes. Patients do not need to be hospitalized and can administer the treatment on their own under the guidance of a physician. Moreover, REBACIN® is a lyophilized preparation that does not require cold chain transportation or storage. Its safety, reliability, stable effect, low cost, and ease of use make REBACIN® a viable option for clinical application.

Disclosures of interests

The authors report no conflicts of interest.

Contribution to authorship

All authors contributed to this review, including research, writing, review, and editing, and approved the final version of the manuscript.

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Data availability

Data sharing is not applicable to this article because no new data were created or analyzed in this study.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. REBACIN® effect on the regression of hrHPV-induced CIN2

Table S2. REBACIN® reduced patient's relapse after LEEP

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Tables

Table 1: Efficacy of REBACIN® on HPV-clearance[13]

Group	Before treatment HPV^+	Before treatment HPV^-	After treatment HPV^+	After treatment HPV^-	After treatment Clearance rate
REBACIN®	95	0	36	59	62.11%***
Control	104	0	88	16	15.38%

Note that "+"represents "HPV positive," "–" represents "HPV negative"; $^{***}P < 0.001$ versus the control analyzed by the chi-square test (x^2).

Table 2. Real world study of hrHPV infection clearance rate

Subtype	Before Treatment HPV^+	Before Treatment HPV^-	After Treatment HPV^+	After Treatment HPV^-	After Treatment Clearance rate
HPVs	506	0	154	352	69.57%
HPV16	117	0	26	91	77.78%
HPV18	41	0	6	35	85.37%
HPV52	54	0	33	21	61.11%

Note that "+"represents "HPV positive," "–" represents "HPV negative"; the data is from Zhang GN, et al.[24]

Figure legends

Figure 1.

Overview of REBACIN® effect on the inhibition of hrHPV E6/E7 expression. (A–B) REBACIN® treatment inhibits mRNA expression in HPV16 E6/E7 of TC-1 cells stably expressing HPV16 E6/E7.[13] (C) REBACIN® treatment inhibits the mRNA expression level of hrHPV E6/E7 in clinical observations.[14] (D) REBACIN®treatment inhibits oncoprotein expression of HPV16 E7 in the cervical cancer Ca Ski cell line.[14]

Figure 2.

Overview of REBACIN® effect on cell and tumor overgrowth. (A–B) REBACIN® treatment prevents growth of the Ca Ski cervical cancer cell line, but not the 293T cancer cell line without containing the E6 and E7 genes.[19] (C) REBACIN® inhibits HPV16 E6/E7-induced tumor growth in SCID mice.[13]