MAJOR ARTICLE

Phase II Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Cidofovir Topical Gel for the Treatment of Patients with Human Papillomavirus Infection

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Genital condylomata acuminata are nonmalignant human papillomavirus (HPV)–induced tumors in which HPV types 6 and 11 are most commonly found. Usual treatments for condylomata acuminata are nonspecific and are based on the destruction or removal of infected tissue. These procedures are often painful and are characterized by a high relapse rate. We report here what is to our knowledge the first double-blind, placebo-controlled study of the use of cidofovir, a nucleotide analogue, for the treatment of genital papillomavirus infections. Thirty patients were enrolled in the study; 19 received cidofovir, and 11 received placebo. The median number of warts and the median baseline wart area were comparable for both groups. Nine (47%) of 19 patients in the cidofovir group had a complete response (total healing), compared with 0 of the patients in the placebo group ($P = .006$). None of the patients in the cidofovir group experienced progression of the disease, compared with 5 (45%) of 11 patients in the placebo group. The side effects recorded for both groups were comparable.

Anogenital warts are benign epithelial tumors commonly found on cutaneous surfaces and are caused by one of the many human papillomavirus (HPV) types. More than 100 viral genotypes of HPV have now been described; they can be categorized on the basis of site of occurrence (cutaneous or mucosal), but they can also be categorized as high risk or low risk on the basis of their potential to induce the development of malignant proliferation. HPV types 16 and 18 are most often associated with intraepithelial neoplasia (cervical, vaginal, vulvar, or penile), whereas types 6 and 11 are recovered from benign anogenital warts [1–3].

HPV-induced lesions occur most frequently in immunocompromised patients, particularly HIV-infected women, in whom the disease tends to be more aggressive. The presence and the severity of cervical neoplasia in HIV-positive women depend on T cell dysfunctions, measured quantitatively and qualitatively [4–6].

There is currently no virus-specific drug therapy available for the treatment of HPV infections. Present practice for the therapy of HPV infections relies on nonspecific destruction or removal of infected tissue by often painful ablative procedures. The surgical procedures for HPV

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Written informed consent was obtained from all patients before enrollment in the study.

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diseases include cryotherapy (dry ice or liquid nitrogen), carbon dioxide laser therapy, electrocautery, and local excision. Various localized topical or intralesional treatments have been used, including acids (such as salicylic acid and bi- and trichloroacetic acids) and chemotherapeutic agents (such as podophyllin, colchicine, bleomycin, cantharidin, and 5-fluorouracil) [2, 3, 7–10].

(S)-1-(3-hydroxy-2-phosphonylmethoxypropyl)cytosine (cidofovir) is an acyclic nucleoside phosphonate with broad-spectrum antiviral activity against DNA viruses [11–14]. Cidofovir has been demonstrated to be active in vitro and in vivo in limiting HPV-induced epithelial cell proliferation [15–25].

In view of the promising in vitro and animal data regarding the potential utility of cidofovir as an anti-HPV agent, we performed a randomized, double-blind, placebo-controlled study evaluating the use of 1% cidofovir gel as a topical treatment for genital warts (condylomata acuminata).

MATERIALS AND METHODS

Objectives. The present study was designed to explore the effects of cidofovir topical gel, compared with those of placebo gel, on regression rate, duration of suppression, and recurrence rate of anogenital warts.

Inclusion criteria. Men and women with external biopsy-proven genital warts, perianal warts, or both were included in the study. Patients enrolled in the study were patients consulting at the Dermatology Department (Erasme and Saint-Luc hospitals, Brussels, and St. Rafael Hospital, Leuven) or the Gynaecology Department (Etterbeek-Ixelles Hospital Center, Brussels) of the participating centers. The use of an adequate means of birth control during the study was required, and partners were asked to use barrier contraception.

Exclusion criteria. Patients were excluded from the randomization if they had any wart >10 mm in height or >20 warts; if they had any other dermatologic condition in the anogenital area; if they had a history within the previous 12 months of significant renal, hepatic, or hematologic abnormalities or of substance abuse; if they had a serum creatinine level >2 mg/dL; if they were women with current evidence of vulvar or cervical intraepithelial neoplasia (CIN) grade II or III; if they had internal warts requiring immediate treatment; if they were known to be seropositive for HIV or had a history of underlying immunodeficiency; if they had been treated within the previous 4 weeks with any drug of known or potential anti-HPV activity; if they had been treated within the previous 8 weeks with IFN; and if they were women who were pregnant, lactating, or planning to become pregnant.

Study design. The study was a double-blind, placebo-controlled study of the safety and efficacy of cidofovir gel for the treatment of patients with HPV infections. Randomization was weighted 1:2 (placebo:cidofovir) and stratified by the total lesion surface area of screening: <50 mm^2 versus $\geqslant 50$ mm^2. Fifteen patients were planned per stratum. Randomization was performed by permuted blocks of size 3 within strata. Each investigator was assigned blocks. Only randomized patients who received at least 1 cycle of treatment and observation were considered for the efficacy analysis. Any patient who could not be evaluated for efficacy was replaced with a newly randomized patient. All eligible patients who received at least 1 dose of the study drug were included in the safety analysis.

Drug administration. Cidofovir gel or placebo was applied once daily for 5 consecutive days every other week for a maximum of 6 cycles (a cycle was defined as 1 week of gel application followed by 1 week of observation). The composition of the gel was as follows: 20% (w/w) propylene glycol, 2% (w/w) hydroxyethylcellulose, 0.18% methylparaben, 0.02% propylparaben, and 0.02% edetate disodium for the placebo, with the addition of 1% (w/w) cidofovir for the active formulation. Purified water was added to bring the volume to 100%, and the pH of the water was adjusted to 6.9, using sodium hydroxide and hydrochloride. Topical gel was applied at bedtime. All external warts, including new warts that developed after the baseline assessment, were treated. The first administration of the drug was made under the supervision of a doctor. Later applications were self-administered on an outpatient basis. The gel was applied with a cotton-tipped swab or a rubber glove in a thin layer sufficient to cover the wart area and to extend beyond the edge of each wart by a margin of 5 mm. Each tube of medication was for a single use only.

The patients were advised to keep the gel on the tested area for at least 4 h. Occlusive dressing or bandages were not used. The treated areas, particularly those occluded by skin folds or foreskin, were washed the next morning to remove residual gel, minimizing the potential for local skin reactions.

The treatment and observation period extended for a planned duration of $\leqslant$12 weeks, depending on lesion response. "Complete response" was defined as total healing; if a complete response was achieved any time during the 12 weeks of active treatment, the patient continued treatment through 1 additional 2-week cycle and then proceeded to follow-up. "Partial response" was defined as $\geqslant$50% decrease in total surface area. "No change" was defined as $<$50% decrease or $<$25% increase in total surface area; the patient continued the 12 weeks of treatment and observation before being removed from the study and proceeding to follow-up. "Progression" was defined as $\geqslant$25% increase in total surface area; the patient completed 3 cycles of treatment and observation, then terminated therapy if progression was documented and proceeded to follow-up.

Study end points. Tolerance to cidofovir topical gel was a primary safety end point and was assessed throughout the

Table 1. Baseline characteristics of patients enrolled in a study of treatment of human papillomavirus infection with 1% cidofovir gel.

Variable	Treatment group		Total (n = 30)
	1% Cidofovir gel (n = 19)	Placebo (n = 11)	
Age in years, median (range)	27 (20–51)	27 (21–41)	27 (20–51)
Race/ethnicity, %			
White	79	91	83
African	5	9	7
Asian	5	0	3
Other	11	0	7
Sex, no. of men/no. of women	8/11	5/6	13/17
Previous wart therapy, %	42	45	43
Baseline wart area in mm^2, median (range)	56.4 (8.4–1259.2)	55.7 (15.3–1756.1)	56.1 (8.4–1756.1)
No. of warts, median (range)	9 (1–18)	7 (2–20)	8.5 (1–20)

treatment period by clinical examination. Laboratory tests were performed on a regular basis throughout the treatment and observation period. The primary efficacy end point was the proportion of patients with lesion regression, which was determined on the basis of change in overall surface area of the treated lesions compared with baseline for the final evaluation in the first 12 weeks. New lesions appearing after the baseline assessment were treated and quantified but were not included as part of the primary efficacy end point.

Secondary end points included time to best response, duration of response for those achieving a complete regression, and recurrence rate in those who had achieved a complete response.

One month after completion of the treatment period or after removal from the study, patients underwent a complete follow-up evaluation, including a physical examination and blood and urine analyses. For patients who responded completely to treatment, a 6-month follow-up was performed to assess the duration of response.

HPV typing. HPV DNA detection was performed on biopsy tissue by PCR. Consensus oligonucleotide primers HY11 and HY09 amplified a 450-bp fragment in the conserved L1 capsid region [26]. A control primer set (PCC04 and GH20) that amplified a 286-bp β-globin fragment was included in the reaction mixture to confirm the presence of an adequate amount of amplifiable DNA. Approximately 10 μL of the reaction product was digested with *Rsa*I, and the resulting fragments were resolved on a horizontal 3% agarose gel, yielding HPV genotype–specific restriction fragment patterns. PCR products were sequenced by cycle sequencing for confirmation.

Statistical analysis. The proportion of patients achieving the primary efficacy end point was compared by the stratified Wilcoxon rank sum test. The Kaplan-Meier method and log-rank tests were used for time-to-event analyses.

RESULTS

Patients. A total of 31 adult patients were included in the study. One patient was determined to be ineligible for the study after 1 week of treatment because of a lack of biopsy confirmation of condylomata. Data from this patient have been excluded from further analysis, and the patient was replaced by a newly randomized patient. Of the remaining 30 patients, 19 were randomly assigned to receive 1% cidofovir gel, and 11 were randomly assigned to receive placebo. The median age in each group was similar. The percentage of patients who had previously undergone wart therapy, the median baseline wart area, and the median number of warts in each group were also similar (table 1).

Safety. Three patients experienced adverse events that were graded as severe; 2 of these patients were in the placebo group and 1 was in the active medication group. Only ulcerations seen on the labia majora and labia minora of patients receiving cidofovir therapy were considered to be associated with use of the study drug. Four patients in the cidofovir group prematurely left the study for reasons other than completion of treatment or progression of disease: 2 were lost to follow-up, and 2 requested discontinuation of therapy. The most frequently reported adverse events were pain, pruritus, and rash at the application site. Such reactions were recorded in 13 patients (68%) in the cidofovir group, compared with 7 patients (64%) in the placebo group ($P = 1.0$), and were reversible on termination of study drug application. Erosion or ulceration occurred in 11 (55%) of the 20 patients with application-site reactions (6 patients who were receiving cidofovir and 5 who

were receiving placebo). Among the patients in the cidofovir group who had an ulceration, herpes simplex virus (HSV) was demonstrated in 1 by PCR. With regard to laboratory toxicities, 1 patient in the placebo group experienced a grade 3 or higher neutropenia.

Efficacy. Nine (47%) of the 19 patients in the cidofovir group had a complete response, compared with 0 in the placebo group ($P = .006$). For the 9 patients with complete response, the median duration of therapy was 43 days. Disease progressed in 5 patients in the placebo group, compared with 0 in the cidofovir group ($P = .003$). In the cidofovir group, 16 (84%) of the patients had a complete or partial response, compared with only 2 (18%) in the placebo group ($P = .001$). There was no difference between cidofovir and placebo in the responses, whether the results were considered globally or stratum by stratum (<50 mm^2 or $\geqslant 50$ mm^2). Of the 9 patients who experienced complete response, only 1 had a recurrence during a median follow-up period of 168 days (range, 77–217 days). This patient had a single recurrence at the same site 120 days after cessation of study drug therapy (table 2).

Typing. All biopsy samples were typed for HPV and revealed low-risk HPV (types 6–11).

Table 2. Response to cidofovir and placebo among 30 patients infected with human papillomavirus.

Response	No. (%) of patients, by treatment group: 1% Cidofovir gel ($n = 19$)	Placebo ($n = 11$)	P
Complete	9 (47.4)	0	.006
Partial	7 (36.8)	2 (18.2)	.001
No change	3 (15.8)	4 (36.4)	
Progression	0	5 (45.4)	.003

NOTE. Responses are defined in the subsection on drug administration in the Materials and Methods section.

DISCUSSION

HPV viruses have a strict epithelial tropism and infect differentiated keratinocytes of the stratified cutaneous or mucosal epidermis [1]. The mucosa-associated viruses can be divided into 2 groups: the low-risk HPV types, which are associated with genital warts, or condylomata acuminata, and the high-risk HPV types, which are associated with intraepithelial neoplasia that may progress to carcinoma.

The low-risk HPV types 6 and 11 have been found in >90% of benign genital lesions. They may regress spontaneously or persist for years. The high-risk HPV types 16, 18, 31, 33, and 35 have been found in moderate and severe dysplasias and in invasive carcinomas of the genital mucosa [2, 3]. HPV-induced lesions show an increasing incidence among immunocompromised patients, particularly among women infected with HIV, in whom the disease tends to be more aggressive [3, 4, 6], and among transplant recipients [27].

In the present study, we demonstrated that cidofovir, a broad-spectrum anti-DNA virus drug [11–14, 28], when used as topical gel, has significant activity compared with placebo in the treatment of genital HPV–induced lesions in nonimmunocompromised patients. In addition, the follow-up period for the patients with complete response (median, 168 days) revealed the sustained character of the response; only 1 patient had a recurrence at the site of treatment, which occurred 120 days after drug cessation. A similar study was performed in patients with HIV infection with refractory and genital condyloma acuminatum. Seventy-one patients were assigned to receive open-label cidofovir topical gel in 1 of 6 sequential regimens: 0.3%, 1%, or 3% strength, applied once daily for either a 5- or a 10-day treatment period, followed by 2 weeks of observation. Patients could receive as many as 3 cycles. The treatment was well tolerated, and application of cidofovir resulted in a complete or partial response in 66% of the patients [29] (H.S.J., personal communication). Treatment of genital HPV with cidofovir (applied topically as a 1% cream) was first reported for 3 patients with AIDS [20]. The patients had a complete response, and, during a follow-up at 6 months, no relapses were observed. Recently, in a preliminary study, 15 women with biopsy-proven CIN grade III were treated with 3 applications every other day of cidofovir gel 1%, followed by conization within 3 weeks. Seven of the 15 patients experienced a complete response histologically; 5 patients had a partial response characterized by the persistence of CIN grade II or III lesions. One patient had a dysplasia of a lower grade, and 2 patients did not show changes in histology [22].

Cidofovir was also effective for the treatment of squamous papilloma of the esophagus, an unusual presentation of HPV infection [19], as well as for the treatment of severe laryngeal papillomatosis, a recurrent and sometimes life-threatening presentation of HPV infections [23, 25]. We have demonstrated that cidofovir and other acyclic nucleoside phosphonates preferentially block the proliferation of HPV-positive cell lines over HPV-negative cell lines [16, 18]. These results were confirmed for cidofovir in vivo in a model of human cervical carcinoma xenografts in athymic nude mice [17].

The 1% topical gel formulation of cidofovir has also been used for the treatment of refractory HSV infections (i.e., thymidine kinase–deficient, acyclovir-resistant HSV strains) [30, 31] and for the treatment of recalcitrant mollusca contagiosa in a patient with AIDS [32].

There is currently no virus-specific drug therapy available for HPV infections. The surgical procedures for HPV diseases include cryotherapy, carbon dioxide laser therapy, and electrocautery or local excision. The loop electrosurgical excisional

procedure is a new approach for the treatment of intraepithelial neoplasia and condylomata acuminata, with outcome comparable to that achieved by laser therapy [8].

Among the systemic treatment procedures, ribavirin has been evaluated for the treatment of laryngeal papillomatosis, without success [33, 34]. Retinoids have also been used for the treatment of verruca plana or recurrent papillomatosis, without significant success. Similarly, results from phase III folic acid and β-carotene prevention trials for cervical cancer have been negative [35]. IFN has been widely used for the treatment of HPV infections, and, of the IFNs, IFN-α, whether natural or recombinant, has been proved to be the most efficacious. IFN has been used intralesionally, topically, and systemically and has been shown to be more effective in combination with either local surgery or podophyllotoxin, but not in combination with cryotherapy [8, 36]. Recently, a series of new approaches has been investigated, such as the use of topical photosensitizers associated with nonlaser light [37], new formulations of podophyllotoxin [38] or purified podophyllotoxin [39], and lithium succinate cream (8% lithium succinate, 0.05% zinc sulfate) [40]. A recent observation suggests that 5-fluorouracil (5% cream) could be used in the treatment of cervical HPV with minimal side effects when a cervical cap is utilized [41].

Indole-3-carbinol, which is found in high concentrations in cruciferous vegetables (e.g., cabbage, brussels sprouts, broccoli, and cauliflower), is a potent inducer of cytochrome P450 metabolism of estrogen. Immortalization by HPV-16 has been shown to alter estrogen metabolism by increasing the amount of carcinogenic estrogen metabolites, namely, 16-α hydroxyestrone. Treatment of HPV-16–positive cells with indole-3-carbinol resulted in reduction of carcinogenic estrogens [42]. Clinical trials with indole-3-carbinol are not yet available. A preliminary study of 18 patients with recurrent respiratory papillomatosis receiving indole-3-carbinol twice daily showed that one-third had a reduction in the growth of the lesion, one-third had a cessation of papilloma growth, and one-third showed no clinical response [43].

Imiquimod (Aldara), which is known to stimulate the production of IFN and ILs and to enhance cell-mediated cytolytic activity against viral targets, has been approved for the treatment of genital HPV-induced lesions [44]. Several studies have shown that 5% imiquimod cream applied to the condylomata is statistically more active than the vehicle [44, 45]. It has also been demonstrated that wart clearance is associated with tissue production of IFN-α, -β, and -γ and TNF-α. Regression of warts was strongly associated with a decrease in HPV DNA and in mRNA expression for both early and late viral proteins [46]. The most frequently reported local skin reactions were erythema, excoriation, and erosion [46, 47].

Many observations have associated the use of cidofovir with regression of a variety of HPV lesions (i.e., laryngeal or pharyngeal papillomata [19, 23], genital condylomata acuminata [20, present study], and CIN grade III [22]) in patients. These clinical findings have been amply supported by experimental in vitro and in vivo data [16, 17] on the growth-inhibitory effects of cidofovir on HPV-positive cells. Together, these observations indicate that treatment with cidofovir is a novel, potent strategy for management of a wide variety of HPV-associated diseases.

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