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The Role of Human Papillomavirus in Common Skin Conditions: Current Viewpoints and Therapeutic Options

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FACULTY AND DISCLOSURE INFORMATION

The Role of Human Papillomavirus in Common Skin Conditions: Current Viewpoints and Therapeutic Options

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TARGET AUDIENCE

This activity has been designed to meet the educational needs of practicing dermatologists, primary care physicians, physician assistants, nurse practitioners, and other healthcare professionals who are involved in the diagnosis, treatment, and management of patients with external genital and perianal warts (EGWs), nonmelanoma skin cancer, and actinic keratosis (AK).

STATEMENT OF NEED/ACTIVITY OVERVIEW

This activity explores issues relating to the role of cutaneous human papillomavirus (HPV) and the correlation of the virus and its pathogenesis with EGWs, nonmelanoma skin cancer, and AK.

EDUCATIONAL OBJECTIVES

After completing this activity, the participant should be better able to:

- Analyze the epidemiology of HPV infection and its pathogenic correlation with common skin disorders.
- Summarize the putative role of HPV in the development of EGWs, nonmelanoma skin cancer, and AK.
- Discuss the molecular modulating effects of approved topical therapies for EGWs and AK.

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MEDIA FORMAT

A printed report was selected as the instructional format to accommodate the learning preferences of a significant portion of the target audience.

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This activity is based on information presented at a satellite symposium held on August 5, 2010, in Chicago, Illinois, prior to the American Academy of Dermatology Summer Meeting. Industry-supported symposia are independently organized and are not an official part of the Summer Academy Meeting. DAW Group assisted with fact-checking, editing, and preparing the manuscript for submission.

A direct causal relationship between human papillomavirus (HPV) infection and cervical neoplasia is well-accepted, but the specific role of HPV in the pathogenesis of other cutaneous disorders is less clear. This article explores the role of HPV in 2 common disorders associated with considerable morbidity: external genital and perianal warts (EGWs) and actinic keratosis (AK). Because the potential role of HPV in the pathogenesis of EGW and AK may have implications that influence management, the available topical pharmacotherapy for each disorder also is reviewed.

External genital and perianal warts represent a possible phenotypic expression of HPV infection and results from hyperkeratosis and hyperplasia of keratinocytes. The cell cycle disruption caused by low-risk anogenital HPV subtypes (eg, HPV-6, HPV-11) is similar to high-risk HPV subtypes, except low-risk HPV E6 and E7 proteins likely bind regulatory proteins with less affinity. Although UV light clearly has a primary causal role in the development of AK, new data suggest that HPV infection, particularly with β-HPV subtypes, may serve as a cocarcinogen. By impairing normal DNA repair and apoptotic mechanisms, HPV may set the stage for later UV-induced transformation. It also has been suggested that HPV may increase the severity of AK lesions and contribute to their recurrence following therapy.

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Papillomaviruses are a diverse group of small (55–60 nm), nonenveloped, icosahedral-shaped viruses containing double-stranded DNA genome.[1] More than 120 human papillomavirus (HPV) subtypes have been identified. Capable of infecting epithelial cells, HPV has been associated with a number of diseases affecting the skin and mucosal surfaces. For some disorders, such as cervical neoplasia, a well-accepted, direct, causal relationship between HPV infection and the clinical entity exists. For other diseases, the role of HPV is less clear. We explore the role of HPV in 2 common dermatologic disorders: external genital and perianal warts (EGWs) and actinic keratosis (AK). Because the potential role of HPV in the pathogenesis of these disorders may have implications that influence management, we also review available pharmacotherapy for each disorder.

Although not associated with clinically significant mortality, both EGW and AK are associated with considerable morbidity. Each disorder is explored separately in this article, but both result from an imbalance of cell proliferation and apoptosis (ie, programmed cell death). Furthermore, the natural progression of each disorder is dependent largely on the innate immunity of a patient. Both disorders generally can be diagnosed by clinical presentation, though biopsy and subsequent histologic examination can be used when the diagnosis is uncertain. Preventative measures such as the use of condoms and routine use of photoprotection appear capable of reducing the risk for EGW and AK, respectively. A number of treatments, including both procedural and topical therapies, are available for the safe and effective management of these disorders.

HPV Basics

The genome of HPV is small, consisting of approximately 8000 bases.[1] Early genes E1 and E2 are responsible for viral transcription and replication, while E5, E6, and E7 are considered oncogenes and believed to be responsible for many of the molecular alterations leading to abnormal cell activity. The late genes L1 and L2 code for structural proteins that make up the viral capsid. Human papillomaviruses are categorized using a system of taxonomy determined by homology of the L1 gene. Five genera of HPV have been identified: α, β, γ, μ, and ν.[1] Human papillomavirus

subtypes also can be categorized as mucosal, wart associated, or cutaneous based on genome analysis and clinical manifestation.

External Genital and Perianal Warts

Approximately 1% of the sexually active population in the United States is estimated to have EGW.[2] The incidence of EGW is greatest among adults aged 20 to 30 years, but the disorder affects sexually active individuals of all ages, accounting for approximately 600,000 healthcare visits annually.[3,4] On physical examination, EGW can present as acuminate, papular, or macular lesions, and approximately half of patients will present with lesions at multiple sites.[4] Lesions generally are asymptomatic but can be associated with inflammation; pruritus; bleeding; dyspareunia; and, in rare cases, obstructive symptoms. External genital and perianal warts often can be diagnosed based on history and physical examination, but a biopsy should be considered in cases in which the diagnosis is questionable; the patient is immunocompromised; or the lesions are large, atypical, or refractory to treatment.[4] Biopsy is not recommended for the sole purpose of identifying the causative HPV subtype. Patients with EGWs report substantial impairment of quality of life, self-perception, and social lives.[5,6]

Role of HPV—External genital and perianal warts represent a possible phenotypic expression of anogenital HPV infection. Most individuals infected with HPV have subclinical infections, and the immune system often can completely clear HPV infection.[7] Human papillomavirus subtype, skin integrity (eg, existence of local trauma), and immune response all impact the clinical presentation, or lack thereof, of HPV infection. The natural tendency for some EGWs to spontaneously regress likely contributes to the relatively high placebo response observed in controlled trials of pharmacotherapy.

Human papillomavirus subtypes capable of infecting anogenital epithelium can be broadly classified as low risk or high risk based on their association with benign or malignant cervical lesions.[8] Risk factors for genital HPV infection are summarized in Table 1.[9,10] Most EGWs are caused by HPV-6 and/or HPV-11 infections.[4,7] Prophylactic vaccination against HPV-6 and HPV-11, in addition to HPV-16 and HPV-18, using a quadrivalent vaccine is anticipated to reduce prevalence of EGW.[11] Four-year efficacy data, however, have demonstrated that although the overall rate of EGW is reduced following vaccination, the reduction is not as great as observed for EGWs secondary to vaccine-specific HPV subtypes,[12] suggesting that the proportion of EGWs associated with nonvaccine HPV subtypes may be changing.

Table 1.

Risk Factors for Genital Human Papillomavirus Infection[9,10]

Young adult age (<25 years)
Age at first sexual activity
Number of sex partners
Short interval between meeting a new sex partner and first intercourse
Being uncircumcised (males only)
Coinfection with another sexually transmitted infection
Immunosuppression (eg, human immunodeficiency virus, posttransplant)
Potential Risk Factors
Oral contraception
Smoking

Overall, EGWs are caused by both hyperkeratosis and hyperplasia of keratinocytes that result from up-regulation of proliferation signals and down-regulation of differentiation and growth-suppressive signals (eg, transforming growth factor β1, IFN-β, p53).[13,14] Although the molecular mechanisms underlying the development of cervical carcinoma following high-risk HPV infection are well-described, the cellular interactions of low-risk HPVs and keratinocytes remain unclear.[13] Unlike high-risk HPVs (eg, HPV-16, HPV-18), low-risk HPVs do not integrate their DNA into the host cell genome but instead remain episomal.[4,7] In high-risk HPV infection, binding of the viral oncoproteins E6 and E7 to the tumor protein p53 and retinoblastoma protein leads to their inactivation.[15] The E6 protein from a number of HPV subtypes also can suppress the inflammatory cytokine IL-8.[16] It generally is believed that the cell cycle disruption caused by low-risk HPV is similar to high-risk HPV, except low-risk HPV E6 and E7 proteins bind regulatory proteins with lower affinity than their high-risk counterparts.[13] For instance, low-risk E6 binds only weakly to p53.

Table 2.

Properties of Catechins[26-34]

Type of Effect	Properties
Anticarcinogenic effects	Induce apoptosis, arrest cell cycle, regulate gene expression
Antioxidative effects	Free radical scavengers, chelate redox-active transition metal ions, inhibit redox-sensitive transcription factors, inhibit pro-oxidant enzymes, induce antioxidant enzymes
Antiangiogenic effects	Inhibit vascular endothelial growth factor
Antiatherogenic effects	Inhibit angiotensin II
Antimicrobial effects	Act against *Helicobacter pylori,* herpes simplex, adenovirus, influenza, and *Candida albicans*
Immunostimulatory effects	May lead to the release of inflammatory mediators and recruit immune cells

Treatment—Reasons to treat EGWs include addressing cosmetic considerations, relieving symptoms, restoring function, improving quality of life, and reducing psychosocial stigma. The impact of treatment on transmission of the virus remains unknown.[7] Treatments can be classified broadly as either provider or patient administered. Provider-administered therapies can be further divided into chemical therapies (ie, podophyllin resin, trichloroacetic and bichloroacetic acids, interferon) or ablative therapies (ie, cryotherapy, laser therapy, surgical removal). Three topical, patient-applied modalities (ie, podofilox, imiquimod, sinecatechins) offer the ability to treat EGWs in the privacy of one's home but require that therapy be continued for weeks to months.

Podofilox, which is available as a 0.5% solution or gel, is applied twice daily for 3 consecutive days and then is discontinued for 4 consecutive days. This 1-week cycle of treatment should be repeated until all lesions are cleared or for a maximum of 4 weeks.[17,18] The active ingredient is podophyllin, and the formulation lacks the mutagens found in podophyllin resin (ie, quercetin, kaempferol).[14] Podofilox inhibits mitosis by blocking polymerization of tubulin into microtubules, thus inducing necrosis of warts.[19] Clearance rates of podofilox treatment have ranged from 45% to 75%, but recurrence rates have ranged from 30% to 70%.[14]

Imiquimod cream 5% should be applied to the affected area at bedtime 3 nights per week and washed off 6 to 10 hours after application. Therapy should be continued until total clearance is achieved or for a maximum of 16 weeks.[20] It has been proposed that the clearance of warts following therapy with imiquimod results from increased transcription of IFN-α, IFN-β, IFN-γ, tumor necrosis factor α, IL-2, and 2',5'-oligoadenylate synthetase RNA.[21] In randomized double-blind trials, complete clearance rates following imiquimod therapy have ranged from 50% to 75%. Recurrence rates have ranged from 0% to approximately 20%.[22]

Sinecatechins ointment 15%, the most recently approved agent in the United States for the treatment of EGW in adults, should be applied to the affected area 3 times daily until total clearance is achieved up to 16 weeks.[23] Sinecatechins represents the first botanical drug approved by the US Food and Drug Administration.[24] It includes a partially purified fraction of the water extract of green tea leaves from *Camellia sinensis (L) O Kuntze*, and 85% to 95% (by weight) of the drug substance is composed of catechins, predominantly epigallocatechin gallate.[23-25] The precise mechanisms of action of sinecatechins in the treatment of EGW remain unclear, but a number of actions of catechins have been observed in preclinical studies (Table 2). In a pooled analysis of pivotal trials of patients treated with sinecatechins ointment 15%, complete clearance was achieved by 54.9% of the efficacy-analyzable population (n=388), while recurrence occurred in 6.8% of patients.[25] It is expected that sinecatechins will be included in upcoming

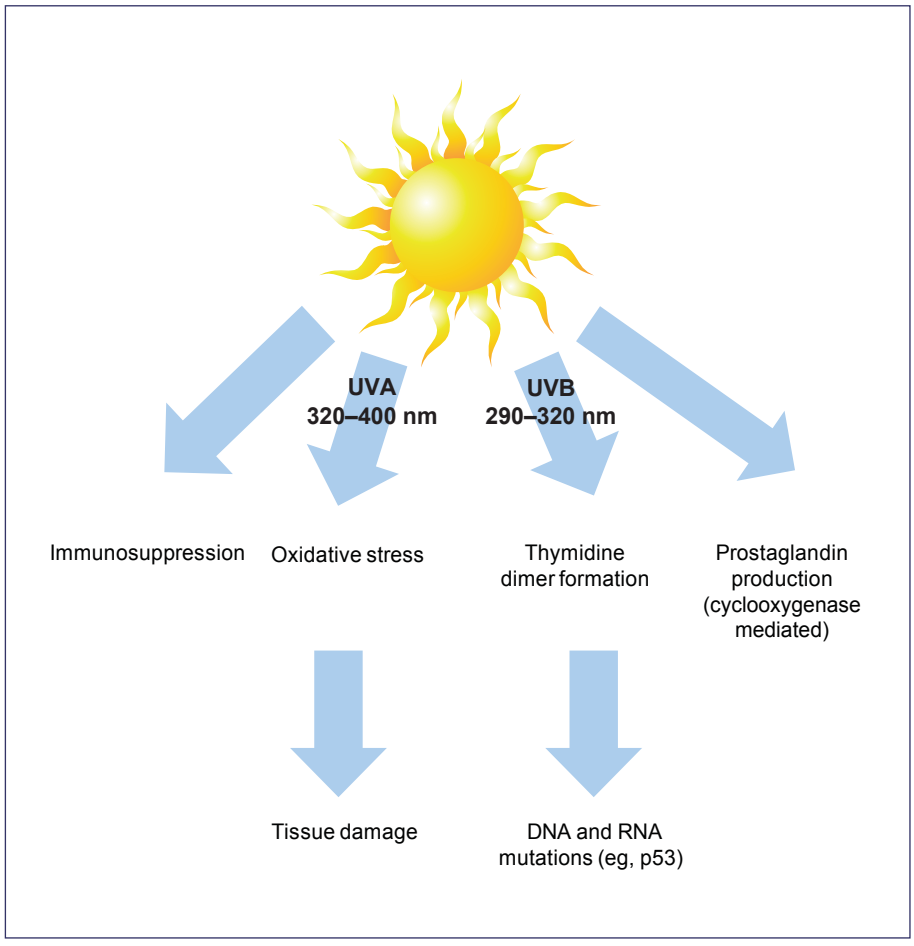

Figure 1. Mechanisms by which UV radiation contributes to actinic keratosis pathogenesis.[41,42]

Centers for Disease Control treatment guidelines for EGW.[35]

Actinic Keratosis

Actinic keratosis is estimated to affect more than 58 million individuals in the United States[36]; it accounted for more than 5.2 million visits to dermatologists in 2003.[37] Clinically, AK presents as skin-colored or red-brown, ill-defined, keratotic macules, papules, or plaques with superficial scale. The lesions typically are asymptomatic but can be accompanied by a burning sensation or pruritus. On palpation, AKs often are described as having a texture similar to sandpaper.

Histologically, AKs represent focal proliferations of atypical keratinocytes with microscopic changes confined to the epidermis. Although AKs can present as solitary lesions, patients often present with multiple lesions, suggesting that molecular alterations are induced in many cells in sun-exposed skin, a concept called field cancerization.[38] Consistent with the concept of field cancerization is the presence of subclinical AK lesions and local recurrences. Although cosmetic concerns may prompt patients to seek treatment, the risk for progression to invasive squamous cell carcinoma (SCC) compels appropriate management of AKs. Although the precise rate at which individual AK lesions progress to SCC is unclear, current estimates suggest that the 10-year progression rate is between 6% and 20%.[39]

Role of UV Light—UV light plays a primary role in the pathogenesis of AK. Actinic keratoses present on sun-exposed areas such as the face, ears, scalp, neck, and dorsal surface of the hands. Increased UV exposure, as influenced by proximity to the equator and outdoor occupational or recreational activities, is a risk factor for the development of AK.[40] Fair skin and disorders resulting in impaired photoprotection (eg, xeroderma pigmentosum) also are associated with AK. UV light causes disturbances in cellular apoptotic mechanisms and induces inflammation, both believed to contribute to tumorigenesis (Figure 1).[41,42]

Molecular Alterations—A recent study examining the gene expression profiles of

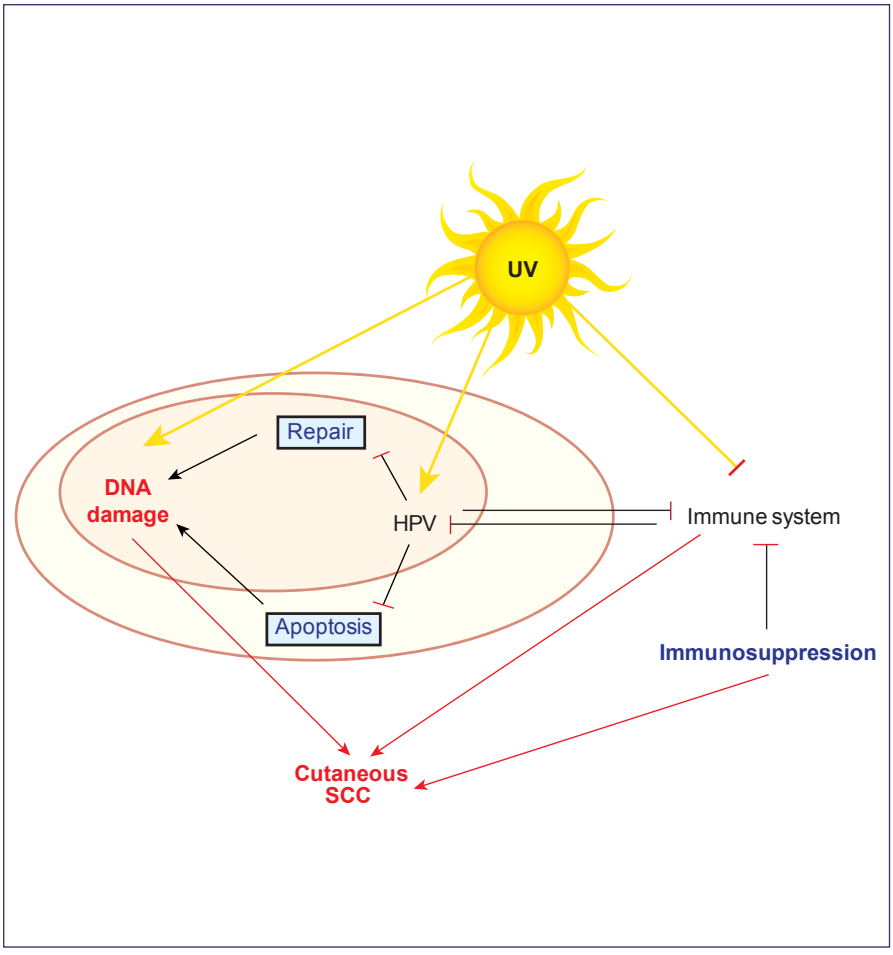

Figure 2. Putative role of human papillomavirus (HPV) infection as a cocarcinogen in the pathogenesis of actinic keratosis and squamous cell carcinoma (SCC). Reprinted from Nindl et al,[56] Copyright 2007, with permission from IOS Press.

healthy skin, sun-exposed skin, AK, and SCC confirmed the genetic similarity of AK and SCC.[43] Dysregulation of the tumor protein p53 is considered a key and early step in tumorigenesis.[44] Increased telomerase activity, leading to reduced apoptosis, also has been suggested as a step in AK formation.[44] Additionally, an increase in expression of the Bcl-2 protein (an antiapoptotic effector), is believed to contribute to the development of AK and SCC.[40] Cyclooxygenase 2 overexpression consistently is observed in AK and SCC.[41,45]

Role of HPV—The proposed role of HPV in the pathogenesis of AK and SCC stems from observations that patients with epidermodysplasia verruciformis (Lewandowsky-Lutz dysplasia), a rare autosomal-recessive disorder, develop wartlike lesions capable of progressing to SCC.[46] These lesions commonly contain HPV-5 and other subtypes (eg, HPV-8, HPV-12, HPV-14, HPV-17, HPV-20, HPV-47) collectively included in the β-HPV genus.[15,46] Notably, skin cancers that develop in patients with epidermodysplasia verruciformis are found on sun-exposed skin, highlighting the role of UV light, even in patients with an underlying genetic defect.

Observations that immunosuppressed patients (eg, posttransplant) carry an increased risk for AK lend support to hypothesized interactions among HPV infection, immune status, and AK/SCC. The incidence of SCC in organ transplant recipients is up to 250 times greater than the general population.[8] The co-localization of warts, AK, and SCC, as well as the detection of HPV in these lesions, further support the role of HPV.[8,46]

The association of HPV, AK, and SCC also has been examined in nontransplant patients. In a recent large, population-based, case-controlled study, a number of β-HPV subtypes were associated with an increased risk for SCC, including HPV-8, HPV-24, and HPV-76. Furthermore, there was a significant trend between the number of β-HPV subtypes for which a person was seroreactive and the risk for SCC ($P \leq .003$). No association between basal cell carcinoma and HPV seroreactivity was demonstrated.[47] Recent studies also have examined the presence of β-HPV in AK and other nonmelanoma skin cancers.[48-50]

Table 3.

Overview of Treatment Options for Actinic Keratosis

Lesion-Directed Treatments	Field-Directed Treatments
Cryotherapy	Fluorouracil cream 0.5%, 5%; solution 2%, 5%
Laser therapy	Imiquimod cream 3.75%, 5%
Curettage	Diclofenac sodium gel 3%
Excision	Photodynamic therapy
Dermabrasion	Chemical peels
	Retinoids[a]

[a]Not approved by the US Food and Drug Administration for the treatment of actinic keratosis.

The HPV subtypes implicated in AK and SCC development are distinct from those associated with EGW or cervical cancer, and the risk factors for infection by cutaneous HPV subtypes are largely unknown. Seroreactivity to at least one cutaneous HPV subtype is nearly ubiquitous.[51] Data suggest that colonization by specific cutaneous HPV subtypes occurs in infancy and are shared among family members; additionally, in contrast to cervical HPV, infections tend to persist over time.[52]

The precise mechanisms by which HPV infection contributes to AK development are not fully understood. The E6 protein of cutaneous HPV can contribute to reduced levels of Bak protein, which normally has proapoptotic effects, its activation being considered a major protective response of keratinocytes to UV exposure.[8,53] It has been suggested that rather than being responsible for maintaining oncogenic transformation, β-HPV is capable of impairing normal DNA repair and apoptotic mechanisms, leading to "a pool of genomically unstable cells at risk of transformation."[54] It also has been suggested that HPV may serve to increase the severity of AK lesions and contribute to their recurrence following therapy.[55]

Overall, researchers believe that although an association between AK and HPV appears to exist, in contrast to UV exposure, HPV infection is not required for the development of AK. As such, HPV infection should be considered a cocarcinogen in the development of AK and SCC (Figure 2).[56]

Treatment—Because of the risk for progression, treatment of all AK lesions generally is recommended.[40] Treatment modalities can be broadly categorized as lesion directed or field directed (Table 3). Field-directed therapies offer the potential to treat subclinical lesions and include 3 distinct topical agents approved for the treatment of AK: fluorouracil, imiquimod, and diclofenac. Each agent is associated with a distinctive mechanism of action and dosing regimen that can impact its particular clinical profile. Prescribed management regimens should be tailored to each patient's needs. Also, consider the patient's medical status, lesion characteristics (ie, size, location, duration), prior response to therapy, cost, and clinician familiarity.

Topical fluorouracil is available in a number of concentrations for the management of AK. A cream formulation with a 0.5% concentration is indicated for the treatment of AK lesions on the face and anterior scalp and should be applied once daily for up to 4 weeks.[57] Fluorouracil also is available in 2% (solution) and 5% (solution and cream) formulations that should be applied twice daily for 2 to 4 weeks until erosions appear.[58] The mechanism of action of fluorouracil is nonspecific; it binds to and inactivates thymidylate synthetase, resulting in depleted thymidine nucleotides, reduced synthesis of DNA, and inhibited cell growth.[59] Fluorouracil should not be used on mucous membranes and is teratogenic.[57,58]

Two formulations of imiquimod cream are approved in the United States for the treatment of AK: 3.75% and 5% formulations. As a cream formulation with a 5% concentration, imiquimod should be applied twice weekly and left on the skin for 8 hours; it should be used for 16 weeks on an area approximately 25 cm^2 on the face or scalp.[20] Imiquimod also is available in a cream formulation with a 3.75% concentration. It should be applied

to the skin of the affected area (either the entire face or balding scalp) once daily and washed off after 8 hours; two 2-week treatment cycles should be separated by a 2-week no-treatment period.[60] Application of imiquimod to the lips and nostrils should be avoided.[20,60] Imiquimod is an immune response modifier that is thought to exert its effect largely via agonist activity on toll-like receptors 7 and 8, which results in stimulation of the cellular immune system secondary to increased production and release of numerous cytokines (eg, IFN-α, tumor necrosis factor α, IL-2, IL-6, IL-8).[22,59] It also may have antiangiogenic and proapoptotic effects.[22]

Diclofenac sodium gel 3% is approved for the treatment of AK and is not limited by body site, but it should not be applied to ophthalmic or intravaginal membranes. It should be applied twice daily for 60 to 90 days.[61] Diclofenac preferentially inhibits cyclooxygenase 2 and therefore is thought to inhibit angiogenesis and keratinocyte hyperplasia.[41,59] In vitro studies in SCC cell lines indicate that diclofenac directly induces apoptosis.[62] Treatment of AKs with diclofenac sodium gel 3% resulted in significantly reduced expression of anti-p53 (P=.009) and anti–MiB-1 (P=.021) antibodies.[63]

Conclusion

New research continues to uncover additional subtypes of HPV and identify mechanisms by which the virus interferes with cellular homeostasis. Although the oncogenic potential of HPV as it relates to cervical carcinoma is widely accepted, its role in the pathogenesis of other disorders is less clear. Scientific evidence conclusively implicates HPV, specifically HPV-6 and HPV-11, as the causative factor for the development of most cases of EGW, but the molecular alterations underlying the development of warts have not been fully elucidated. Although evidence of an association between β-HPV, AK, and SCC is mounting, studies regarding causality are needed. Currently, research suggests that HPV may act as a cocarcinogen in the pathogenesis of AK. An increased understanding of the role of HPV and the cellular changes associated with EGW and AK may allow for the development of new therapeutic options and further differentiation among existing options.

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The Role of Human Papillomavirus in Common Skin Conditions: Current Viewpoints and Therapeutic Options

1. Which genera of human papillomavirus (HPV) are most commonly found in actinic keratosis (AK) and squamous cell carcinoma lesions and may function as cocarcinogens?

- ☐ a. α
- ☐ b. β
- ☐ c. γ
- ☐ d. ν

2. Of the US Food and Drug Administration–approved topical therapies for AK, which one is believed to function as an anti-inflammatory treatment by inhibiting cyclooxygenase 2 expression?

- ☐ a. diclofenac sodium gel
- ☐ b. 5-fluorouracil
- ☐ c. imiquimod cream
- ☐ d. podofilox gel

3. In which patient with a "wart" would you be most likely to perform a biopsy?

- ☐ a. 18-year-old woman with lesions on the vulva and perianal region that respond to topical therapy
- ☐ b. 21-year-old man with solitary lesion at the urethral meatus
- ☐ c. 25-year-old immunocomprimised man with multiple lesions on the penile shaft
- ☐ d. 35-year-old woman with multiple 3-mm lesions in the perianal area

4. Which of the following statements regarding cutaneous HPV is true?

- ☐ a. colonization by β-HPV subtypes is rare
- ☐ b. colonization persists over time
- ☐ c. colonization typically occurs at puberty
- ☐ d. HPV is found in all AK lesions

5. In pivotal trials of sinecatechins ointment 15%, what percentage of patients treated with active therapy who exhibited complete clearance of all warts had a recurrence of lesions on follow-up?

- ☐ a. 1.6%
- ☐ b. 6.8%
- ☐ c. 19.4%
- ☐ d. 36.2%

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EXTENT TO WHICH PROGRAM ACTIVITIES MET THE IDENTIFIED OBJECTIVES

After completing this activity, the participant should be better able to:

Analyze the epidemiology of HPV infection and its pathogenic correlation with common skin disorders.	5 4 3 2 1
Summarize the putative role of HPV in the development of EGWs, nonmelanoma skin cancer, and AK.	5 4 3 2 1
Discuss the molecular modulating effects of approved topical therapies for EGWs and AK.	5 4 3 2 1

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