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INVITED COMMENTARY

Current Developments in Viral Skin Diseases

Rana Majd Mays · Rachel A. Gordon · Whitney J. LaPolla · Stephen K. Tyring

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Abstract Viral skin diseases comprise an important category of frequently encountered conditions in the dermatology practice. Here we will discuss current recommendations in therapy and new modalities in diagnosis and prevention of some of the most common viral skin conditions.

Keywords Viral · Skin · Infection · Dermatology · Therapy

Introduction

Viral skin diseases are encountered by dermatologists on a routine basis. A few of the most common skin conditions resulting from viral infection include oral and/or genital herpes (herpes simplex virus), shingles (varicella zoster virus), common and genital warts (human papilloma virus) and molluscum (molluscum contagiosum virus). We discuss the new advancements in diagnosis and prevention plus current recommended guidelines in therapy for each specific condition.

R. M. Mays (✉) · R. A. Gordon · W. J. LaPolla
Center for Clinical Studies,
451 N Texas Ave,
Webster, TX, USA
e-mail: rmays@ccstexas.com

R. A. Gordon
e-mail: rgordon@ccstexas.com

W. J. LaPolla
e-mail: wlapolla@ccstexas.com

S. K. Tyring
Center for Clinical Studies, University of Texas Medical School at Houston, Department of Dermatology,
Houston, TX, USA
e-mail: styring@ccstexas.com

Herpes Simplex Virus 1 and 2

Herpes simplex virus 1 and 2 (HSV1 and HSV2) are members of the herpes family of viruses. Transmission of these viruses occurs via direct contact with mucous membranes and/or infected vesicles. The overall incidence of HSV1 is significantly higher than that of HSV2, which occurs more frequently in women and in subpopulations with high-risk sexual behavior. The oral mucosa is the most common site for HSV1 infection, clinically presenting as oropharyngeal or orolabial herpes (cold sores); however HSV1 can also affect the genital region. More than 57% of the US population between the ages of 14 and 49 are seropositive for HSV1. HSV2 is traditionally the culprit when patients develop genital herpes lesions; however, HSV1 infection is contributing to a larger proportion of genital infections, nearly 50% in certain populations.

Herpetic lesions are characterized by painful crops of clear vesicles on an erythematous base that later ulcerate and crust. Superinfection with *Staphylococcus* or *Streptococcus* can be seen with further impetiginization of lesions. The recommended method of diagnosis is clinical, with polymerase chain reaction (PCR) or viral culture of the vesicles as confirmation in unclear cases; however PCR is quickly becoming the gold standard of diagnosis.

The recommended antiviral therapy for acute HSV1 or HSV2 infection (orolabial or genital) is acyclovir, valacyclovir (prodrug of acyclovir), or famciclovir (prodrug of penciclovir). All three agents inhibit viral DNA synthesis and replication. In children with moderate to severe primary disease, acyclovir 15 mg/kg five times per day for 7 days has been shown to decrease the duration of acute lesions. In adults, treatment modalities with all three agents are

considered equally efficacious. Standard regimens include acyclovir 400 mg thrice daily (TID) for 7 to 10 days, valacyclovir 1 g twice daily (BID) for 7 to 10 days, or famciclovir 500 mg BID for 7 to 10 days.

Topical therapy for acute orolabial herpes also exists, although these options are notably less efficacious than systemic antivirals. Treatment with docosanol 10% cream (Abreva®, GlaxoSmithKline) has demonstrated more rapid healing of new onset lesions compared with placebo. Penciclovir 1% cream (Denavir®, Novartis) and acyclovir 5% cream (Zovirax®, BTA Pharmaceuticals) have also shown therapeutic efficacy in early and late stage lesions.

In recurrent herpes labialis, administration of antiviral therapy (patient-initiated therapy) at the onset of symptoms further reduces healing time. First-line agents consist of famciclovir 1,500 mg once, valacyclovir 2 g BID for 1 day, or acyclovir 800 mg TID for 2 days. For patients with multiple episodes of herpes labialis, chronic suppression with valacyclovir 500 mg daily is an effective option.

In recurrent genital herpes, valacyclovir, acyclovir, or famciclovir can be administered either episodically to ameliorate or shorten the duration of lesions or continuously as suppressive therapy to reduce the frequency of recurrences. Daily 500 mg valacyclovir decreases the frequency of genital herpes recurrence by 70%–80% in patients who have frequent recurrences (≥6 episodes per year). Alternative regimens include acyclovir 400 mg BID or famciclovir 250 mg BID. Valacyclovir was also recently shown to reduce sexual transmission of genital herpes. In 2003, the US Food and Drug Administration (FDA) approved daily treatment with 500 mg valacyclovir for reduction of HSV2 transmission in discordant, heterosexual couples in which the source partner has a history of genital HSV2 infection.

Varicella Zoster Virus

Herpes zoster (shingles) is caused by reactivation of the varicella zoster virus (VZV, a herpes virus) in the dorsal root ganglia. Individuals with a history of primary varicella infection (chickenpox) have a 10% to 20% lifetime chance of developing zoster. Currently, the standard of care for treatment of zoster includes valacyclovir 1 g orally TID or famciclovir 500 mg TID within the first 7 days of vesicle appearance. Both agents have demonstrated superior efficacy compared to acyclovir. Initiation of antiviral therapy after 7 days of vesicle onset has not shown to be beneficial in clinical studies.

Complications of herpes zoster include but are not limited to significant pain, bacterial superinfection, hypopigmentation, hyperpigmentation, and post-herpetic neuralgia (PHN). PHN has significant morbidity and associated healthcare costs, and in rare instances can continue lifelong. In a recent study, the administration of gabapentin in conjunction with valacyclovir significantly reduced the rate of PHN, making this regimen the recommended standard of care for patients with acute painful zoster.

In 2006, the herpes zoster vaccine Zostavax® (Merck) was approved for the prevention of zoster in adults ≥60 years of age. Recently, the FDA extended the indication to include individuals ≥50 years of age. In clinical trials, the vaccine has demonstrated approximately 60% (adults ≥60 years) and 70% (adults ≥50 years) reduction in zoster as compared to placebo, respectively. The vaccine is a one-time live-attenuated injection and provides life-long immunity. It is contraindicated in pregnancy, immunosuppressed patients such as those with HIV/AIDS, organ transplant, on biologic therapy, and/or patients with history of active malignancy. Although uncommon, a small percentage of vaccinated individuals may still go on to develop zoster; in these patients, Zostavax® has shown to decrease the risk of PHN by approximately 60% in comparison to placebo. Rare adverse reactions include erythema, pain, and swelling at the site of injection, and mild headache. Despite the demonstrated efficacy and safety of the vaccine, immunization rates are still well below desired levels, especially in the newly approved younger age group. Possible reasons for the low immunization rate include lack of health insurance coverage, low patient awareness, and belief of not being at risk for herpes zoster infection.

Human Papilloma Virus

Human papilloma virus HPV is responsible for verruca vulgaris (common warts) and verruca acuminata (genital warts). Certain subtypes of the virus incorporate into the host epithelial DNA and cause malignant transformation leading to cervical, vaginal, and/or anal cancer.

Current therapy for common warts includes topical acidic preparations (such as salicylic acid), cantharidin, podophylin resin, and destructive procedures such as cryotherapy and electrodessication. Pulse dye and CO_2 lasers have been used for the treatment of common warts with more beneficial results, although major studies are lacking. Laser therapies carry a higher risk of scarring and the treatment can be painful and costly.

Successful eradication of genital warts is achieved most commonly with destructive measures such as cryotherapy. In 1997, the FDA approved imiquimod 5% (Aldara®, 3 M Pharmaceuticals) and in 2011, 3.75% (Zyclara®, Graceway Pharmaceuticals) for treatment of genital and perianal warts in patients age 12 years and older. Imiquimod has also been used off label for common warts with moderate success in patients >12 years old. In 2006, Veregen® (MediGene AG) became the second FDA-approved agent for the treatment of

genital warts. The main active ingredient in this agent is 15% sinecatechins derived from a concentrate of green tea extract. Resolution or improvement of lesions with Veregen® therapy may take an average of 2 to 4 weeks longer than other modalities.

In 2009, the HPV vaccine Cervarix® (GlaxoSmithKline) was approved for prevention of HPV subtypes 16 and 18, the subtypes most commonly associated with development of cervical cancer. Vaccination is recommended in females age 9 to 26 years. The quadrivalent vaccine Gardasil® (Merck) was approved in 2006. It protects against subtypes 6 and 11 in addition to 16 and 18, and it is recommended for the prevention of cervical cancer, vaginal cancer, vulvar cancer, and genital warts. It is currently approved for use in both males and females. Both Cervarix® and Gardasil® have demonstrated an average of 96% to 100% efficacy, depending on the particular neoplasm involved. Although rare, it is important to note that despite HPV vaccination, a small percentage of patients may still develop HPV-related cancers. Most common adverse reactions occur in 20% of patients and include erythema and swelling at injection site, headache, myalgia, nausea, and arthralgia.

Molluscum Contagiosum Virus

Molluscum is a common disorder seen usually in children and immunocompromised adults. Current treatment modalities for molluscum include cantharidin, podophylin, trichloroacetic acid, curettage, and cryotherapy. Australian lemon myrtle (*Backhousia citriodora*) dissolved in olive oil used daily for 3 weeks showed more than 90% resolution of lesions in one uncontrolled study. In 2004, a small randomized controlled trial illustrated 10% benzoyl peroxide cream for 4 weeks to be more effective than tretinoin 0.05% cream for 6 weeks in treatment of molluscum. Local irritation and intolerability were the main adverse effects reported for both benzoyl peroxide and lemon myrthle therapy. Recently, the 585-nm pulsed dye laser has demonstrated excellent results in cooperative patients and is especially useful for treatment of multiple lesions. Although not FDA approved, off-label use of 3.75% or 5% imiquimod for treatment of molluscum has shown success, allowing tolerability of side effects. The main adverse effects reported with imiquimod were local irritation and erosion of surrounding healthy skin.

Conclusions

Viral skin diseases have had numerous advances in therapy and prevention, specifically in the areas of herpes labialis, genital herpes, common and genital warts, zoster, and molluscum. Treatments should be tailored to each individual patient, with proper disclosure of adverse reactions and alternative therapy.

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