

HPV and Genital Warts

Combating the most common STD with vaccines and promising new treatments.

BY THEODORE ROSEN, MD

Human papillomavirus (HPV) is the most common sexually transmitted disease (STD) worldwide. According to the Centers for Disease Control and Prevention (CDC), more than 90 percent of sexually active men and 80 percent of sexually active women will have at least one type of HPV infection in their lifetime.¹ There are approximately 100 types of HPV, about 40 of which affect the anogenital area, causing conditions such as genital warts.²

Although HPV is common, most infections are asymptomatic.³ The fluidity of HPV's natural history ranges from successful elimination by the body's own immune system, to invisible and asymptomatic infection, to infection that becomes symptomatic weeks or even years after initial infection.

The HPV vaccine is helping. In the first six years of HPV vaccine use (2006 to 2012), infection decreased 64 percent in females aged 14 to 19 and 34 percent in the 20 to 24 age group.⁴ However, we still see about 350,000 new cases of anogenital warts in the US in a single year.⁵ As dermatologists, we can promote compliance with HPV vaccine recommendations and help develop new treatments for genital warts.

HPV VACCINE EFFECTS AND LIMITATIONS

Originally conceived as protection against cervical cancer, the HPV vaccine has three types: one that protects girls against cancer-causing HPV types 16 and 18 (Cervarix, GlaxoSmithKline); another that includes HPV types 16 and 18, as well as types 6 and 11, which cause about 90 percent of anogenital warts (Gardasil, Merck);⁶ and a third that adds five cancer-causing types (31, 33, 45, 52, and 58) to those four (Gardasil 9, Merck). The two Gardasil vaccines are approved for both females and males to prevent genital warts and raise immunity to HPV. Following the introduction of the nonavalent HPV vaccine, it is likely that the quadrivalent HPV vaccine will no longer be available in the near future.

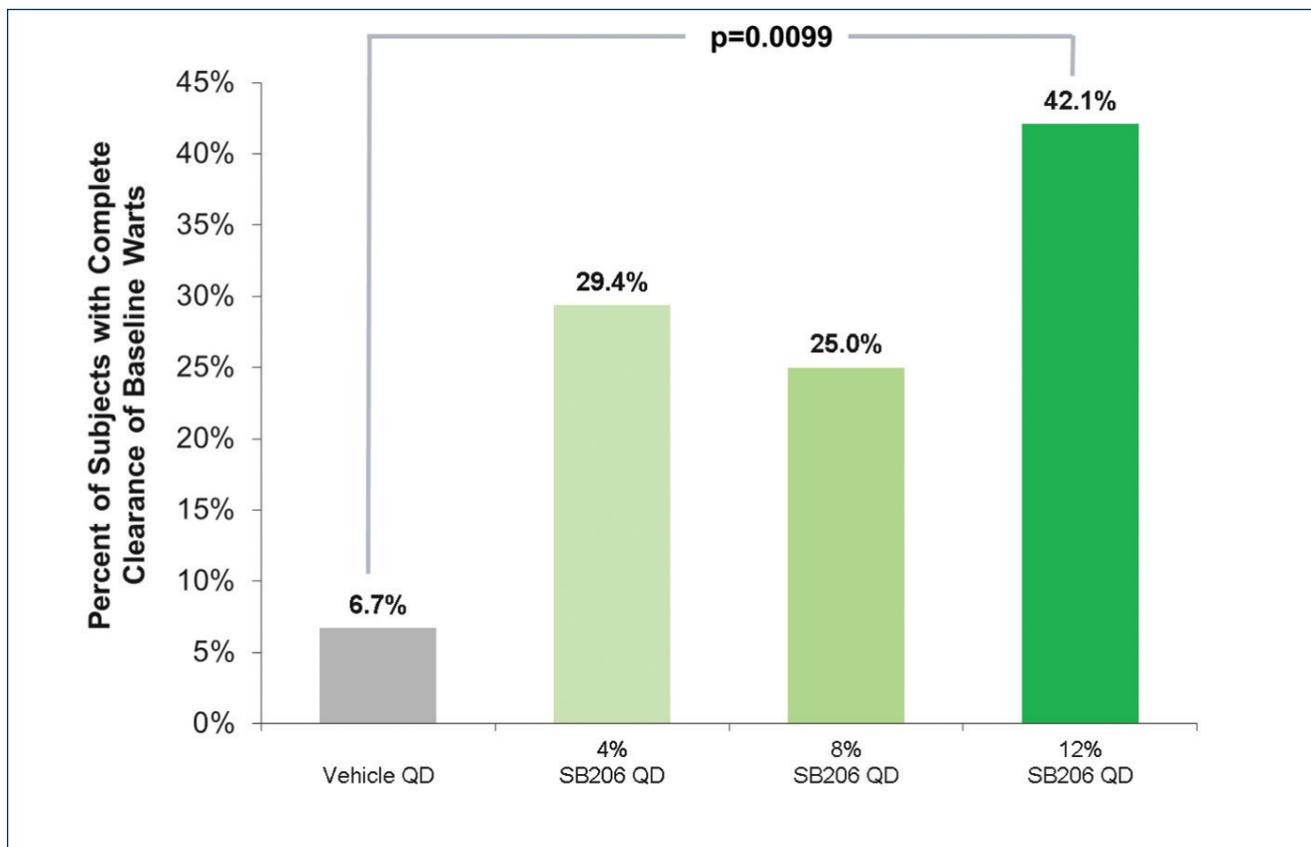
Given as indicated, the HPV vaccine is over 90 percent effective

“And even if 100 percent of children, adolescents and young adults for whom it is indicated received the vaccine, that would not protect against the types of HPV that cause 10 percent of genital warts (and about 20 percent of genital HPV-related malignancies). Thus, we still need to treat genital warts and attempt to develop new therapies for this infection.”

in preventing infection of due to the types of HPV included in the vaccine.⁴ It may provide a modest amount of cross protection against genetically similar HPV types that are not included in the vaccine,⁷ but this is somewhat controversial.⁸

Despite the proven efficacy of HPV vaccines, many children in the United States do not complete the series of three injections or do not get the vaccine at all. On average, 60 percent of girls 13 to 17 years of age initiate the HPV vaccination series, but only 39.7 percent receive all three doses; only 41.7 percent of boys initiate HPV vaccination, and a paltry 21.6 percent complete the series.⁹ It is best to get the vaccine before sexual activity begins because the vaccine cannot protect against an existing infection. Dermatologists are in a perfect position to talk to parents of children as well as adolescents in the vaccine's age range about getting the HPV vaccine.

Although the medical profession and public health authorities work to increase the rate of vaccination against HPV, we know that it is impossible to eliminate genital warts completely.



Awareness of the vaccine, concern about its known minimal side effects such as syncope, and general vaccine fears limit its success. And even if 100 percent of children, adolescents and young adults for whom it is indicated received the vaccine, that would not protect against the types of HPV that cause 10 percent of genital warts (and about 20 percent of genital HPV-related malignancies). Thus, we still need to treat genital warts and attempt to develop new therapies for this infection.

TRADITIONAL TREATMENTS

Patients with genital warts see their primary care physician, gynecologist, urologist or dermatologist for treatment. Despite clear recommendations from the CDC, this diversity of perspectives results in a lack of consensus about managing the disease. For example, gynecologists frequently treat genital warts using caustic agents, but dermatologists rarely take that approach.

The CDC's recommendations divide genital wart treatment into two types: healthcare provider-administered therapies and patients' self-administered treatments. Healthcare provider-administered therapies are generally destructive in nature. These include liquid nitrogen, loop electrode excision, CO₂ laser ablation, and in-office drugs such as bichloroacetic (also called dichloroacetic) or trichloroacetic acid. Liquid nitrogen and laser treatment are variably uncomfort-

“The promise of emerging treatments for HPV genital warts is exciting. When you treat patients who are suffering physically with the infection’s symptoms and mentally with its broader health and social implications, you want to offer these patients simple, effective, safe and comfortable treatment.”

able and can cause dyspigmentation and scarring.

I prefer patient-applied treatments because they are generally less painful and can be done in the privacy of the patient's own home. Podophyllotoxin is one option, but its schedule of administration with days on and off is difficult to remember. Imiquimod has several concentrations and schedules. Patients who use the 5% concentration three times per week for 16 weeks have a clearance rate of 37 percent to 50 percent.¹⁰



Genital Warts' Emotional Toll

Unlike the herpes virus, there is no direct evidence that stress prompts HPV virus to cause genital wart outbreaks. However, genital warts are most assuredly a major source of stress for patients with the disease.

Genital warts are associated with both embarrassment and psychosocial distress. Those who are infected frequently have to apply ointment to their genital areas, as well as advise any potential sexual partners about their infection. It is easy to understand how this affects an individual's mental state.

In addition, patients with HPV worry about fertility and cancer. Although different types of HPV virus cause genital warts and cancer, the presence of genital warts makes patients worry that they also may carry cancer-causing types of the virus.

As we manage the physical symptoms of genital warts, it is important to consider the emotional toll of the disease and the anxiety introduced into patients' lives. Based on our discussions with patients, we can recommend online forums, literature and even talk therapy to help patients cope with this disease.

NEWER ADVANCES

Traditional treatments for genital warts have their drawbacks, so we are always working to develop better therapies. One newer therapy is 15% sinecatechins ointment, a product derived from green tea. The mechanism of action is not entirely understood, but it may relate to induction of infected cellular apoptosis, immune upregulation and/or a direct antiviral effect.¹¹ Recurrence rates for this treatment are exceptionally low—about six to nine at 12 weeks

post-therapy.¹² Patients apply sinecatechins ointment three times per day for up to 16 weeks. Doctors have to motivate patients to stick to the schedule, but patients do appreciate that this is a natural botanical product.

In the pipeline is Novan's SB206, which recently completed Phase 2 trial with positive results (See figure). SB206 is an investigational topical gel that uses a nitric oxide mechanism of action inside a carrier molecule, releasing the gas and destroying the wart, presumably by damaging or killing the causative virus. The trial evaluated three concentrations against a control. The highest concentration, 12% used once daily, showed the greatest benefit, with 42.1 percent of patients completely clear of baseline warts within 12 weeks.¹³ Tolerability was good for once-daily dosing. Phase 3 trials are anticipated in 2017.

The promise of emerging treatments for HPV genital warts is exciting. When you treat patients who are suffering physically with the infection's symptoms and mentally with its broader health and social implications, you want to offer these patients simple, effective, safe and comfortable treatment. If our efforts can make this a reality, we will have many grateful patients. ■

Theodore Rosen, MD, is Chief of the Dermatology Service at Michael E. DeBakey Veterans Affairs Medical Center and Professor of Dermatology at Baylor College of Medicine in Houston.



Watch Dr. Rosen's interview on DermTube.com: HPV Infections in the Dermatology Clinic

1. Chesson HW, Dunne EF, Hariri S, Markowitz LE. The estimated lifetime probability of acquiring human papillomavirus in the United States. *Sexually Transmitted Diseases*. 2014; 41(11):660-664. DOI: 10.1097/OLQ.0000000000000193
2. de Villiers EM, Fauquet C, Broker TR, et al. Classification of papillomaviruses. *Virology*. 2004;324:17-27. DOI: 10.1016/j.virol.2004.03.033
3. Myers ER, McCrory DC, Nanda K, et al. Mathematical model for the natural history of human papillomavirus infection and cervical carcinogenesis. *Am J Epidemiol*. 2000;151:1158-71. PMID: 10905528
4. Chesson HW, Ekwueme DU, Saraiya M, et al. Estimates of the annual direct medical costs of the prevention and treatment of disease associated with human papillomavirus in the United States. *Vaccine* 2012;30:6016-9. DOI: 10.1016/j.vaccine.2012.07.056
5. Markowitz LE, Liu G, Hariri S, Steinau M, Dunne EF, Unger ER. Prevalence of HPV After Introduction of the Vaccination Program in the United States. *Pediatrics*. 2016 Mar;137(3):e20151968. DOI: 10.1542/peds.2015-1968
6. Garland SM, Steben M, Singis HL, et al. Natural history of genital warts: analysis of the placebo arm of 2 randomized phase III trials of a quadrivalent human papillomavirus (types 6, 11, 16, and 18) vaccine. *J Infect Dis* 2009;199:805-14. DOI: 10.1086/597071
7. Tabrizi SN, Brotherton JM, Kaldor JM, et al. Assessment of herd immunity and cross-protection after a human papillomavirus vaccination programme in Australia: a repeat cross-sectional study. *Lancet Infect Dis*. 2014 Oct;14(10):958-66. DOI: 10.1016/S1473-3099(14)70841-2
8. Tarnay C, Pagan M, Klaric J, et al. HPV Vaccination Does Not Provide Herd Immunity for Unvaccinated Women or Cross-Protection for Nonvaccine HPV Types [12]. *Obstet Gynecol*. 2016 May;127 Suppl 1:4S. DOI: 10.1097/01.AOG.0000483628.84944.92
9. Walling EB, Benzoni N, Dornfeld J, et al. Interventions to Improve HPV Vaccine Uptake: A Systematic Review. *Pediatrics*. 2016 Jul;138(1). pii: e20153863. DOI: 10.1542/peds.2015-3863
10. Perry CM, Lamb HM. Topical imiquimod: a review of its use in genital warts. *Drugs*. 1999 Aug;58(2):375-90. PMID: 10473026
11. Rosen T. Green tea catechins: biologic properties, proposed mechanisms of action, and clinical implications. *J Drugs Dermatol*. 2012 Nov;11(11):e55-60. PMID: 23135094
12. Sutherland BA, Rahman RM, Appleton I. Mechanisms of action of green tea catechins, with a focus on ischemia-induced neurodegeneration. *J Nutr Biochem*. 2006 May;17(5):291-306. DOI: 10.1016/j.jnutbio.2005.10.005
13. Novan Announces Statistically Significant Phase 2 Clinical Trial Results for SB206; 2016. Available at: <http://investors.novan.com/phoenix.zhtml?c=254342&p=irol-newsArticle&iD=2226044>. Accessed January 16, 2017.