



Condylomas inside and outside, to treat or not to treat

E. Prens

Human papilloma virus (HPV) is a DNA virus of which more than 200 types have been detected. HPV is transmitted through human to human contact, especially sexual contact. The mean incubation period varies between three weeks to eight months, but HPV infection may become latent without any signs or symptoms. [1] The overall estimated prevalence of anogenital HPV infection ranges from 10 to 20 percent among unvaccinated persons. [2] A positive observation is that HPV infection rates show a clear downward trend in countries with a HPV vaccination program. [3]

Anogenital HPV infection manifest as soft brown to grey-brown papules or plaques on the genitalia, perianal skin, perineum, or groin called condylomata accuminata (CA) whereby HPV types 6 and 11 are the most frequent. [4]

Risk factors for acquisition of HPV infection are immunosuppression, smoking and men that have sex with men (MSM). In these cases, HPV infection is associated with the development of larger and more treatment-resistant CA, higher rates of recurrence, and malignant transformation of CA. [5] The importance of an intact immune system in terms of preventing HPV infection, is clear in persons with immunodeficiency or in immunosuppressed patients. In organ transplant recipients, HPV-induced warts are the most common skin disorder. [6] An intact immune system, is crucial for elimination of viral infections. This occurs via cell-mediated immune mechanisms including NK, CD4+, CD8+ cells and Th1 cytokines. [7]

Genital HPV types and HPV-associated squamous proliferations may be divided into low-risk and high-risk types based upon the associated risk for cancer. The low-risk types HPV 6 and/or HPV 11 are detected in around 90% of CA. HPV types 16 and 18 are considered the high-risk types. Low-grade and high-grade squamous intraepithelial lesions (LSIL and HSIL respectively), may be further classified to intraepithelial neoplasia (IN) of the cervix, vulva, vagina, penis, and anus, grade 1, 2, or 3. [4] For example, AIN 1 corresponds to anal LSIL, and AIN 2 and 3 to anal HSIL. The biologic consequences of anal SIL are considered analogous to those of cervical SIL. Anal HSIL, corresponding to AIN 3 is considered premalignant and may progress to anal cancer, similar to the progression of cervical HSIL to cervical cancer. Clinical features and histopathologic classification of anogenital intraepithelial lesions is not the focus of this article. A comprehensive article on this theme has been published in this journal in 2017, and since then this classification has not been changed (Henquet et al. 2017). [4]

CURRENT TREATMENT OPTIONS

Current medical therapies can be broadly divided in two categories (table):

1. Destructive therapies, they directly destroy the wart tissue and
2. Immunomodulating therapies, that activate the patient's immune system to clear the wart. [8]

Destructive therapies

Podophyllotoxin contains the biologically active compound from *podophyllum resin*, because it is in a cream of gel base, it is used at home as self-care. Both are not safe during pregnancy.

Trichloroacetic acid (TCA) is a caustic acid that coagulates the wart tissue chemically. It is safe during pregnancy.

Fluorouracil (FU) is an antimetabolite blocking DNA synthesis leading to cell death.

Table. Current medical therapies for CA.

Destructive therapies	Immunomodulating therapies
Podophyllotoxin and Podophyllum resin	Imiquimod
Trichloroacetic acid (TCA)	Sinecatechins
Fluorouracil (5FU)	Interferons
	Bacillus Calmette-Guerin
	MMR vaccine
	HPV vaccines
	Anti-viral: Cidofovir*

*It must be stated that no treatment is significantly superior to the other.

Dermatologist-Immunologist, Department of Dermatology, Erasmus MC, Rotterdam



Figure A,B. Warts before HPV vaccinations (A) and clinical result 3 months after 2nd nonavalent HPV vaccination (B).

Immunomodulating therapies

Both *imiquimod* and *interferon* start an immune response at the site of the CA that may clear the lesions. Interferons have antiviral, antiproliferative, and immune-activating effects. Interferons are in use as systemic therapy (intramuscular injection), topically, and as intralesional injections. Imiquimod is a toll-like receptor 7 agonist, acting as an immune response enhancer, and stimulates local cytokine induction.

Sinecatechins like e.g. Veregen, represent a plant-derived product for self-administration on CA. They contain catechins and other components of green tea. The exact mechanism of action of catechins is unknown.

Bacillus Calmette-Guerin comprises topical /intralesional administration of bacillus Calmette-Guerin (BCG). *MMR vaccines* are used in recalcitrant warts and work via non-specific local immune activation.

HPV vaccines are effective in the primary prevention of HPV infection. Their use in CA or prevention of recurrent disease is experimental. [9]

A recent study investigated intramuscular versus intralesional bivalent HPV vaccine for treatment of recalcitrant common warts. They found that intralesional therapy worked the better. Twenty-two adult patients with multiple recalcitrant warts received intramuscular bivalent HPV vaccine at zero, one, and six months. Another 22 patients were given an intralesional injection of bivalent HPV into the largest wart at two-week intervals until clearance, or for a maximum of six

injections. Complete clearance was seen in 18 patients (82%) from the intralesional group and in 14 patients (63%) from the intramuscular group, which was not statistically significant. The clearance rate of the warts was significantly faster in the intralesional group. [10]

Surgical treatment options comprise laser- or electro-surgical ablative, cryotherapy and excisional procedures. In daily practice, ablative, excisional and medical modalities are frequently combined. It is recommended to take biopsies in cases of giant, recalcitrant or atypical CA or warts, to exclude malignancy. Laser ablation is the preferred modality for extensive lesions especially in vulvar and anal lesions, because vulvar or anal anatomy are better preserved. It is recommended that the dermatologist / surgeon and assisting personnel should wear protective masks when performing laser ablation of CA, because HPV DNA has been demonstrated in the laser smoke.

For high-risk cases of CA, with risk of further deterioration into malignancy, we modified the procedure reported by Daayana et al. combining CO₂ laser ablation, local/regional vaccination with the quadrivalent Gardasil vaccine, followed by 6 weeks of imiquimod treatment. With this combination treatment we obtained high cure rates, even in patients with long-standing recurrent AIN, PIN and VIN. [11] The availability of a nonavalent HPV vaccine has even enhanced the outcome in patients with recalcitrant warts, resulting in rapid clearance of distant warts after vaccination (figure A,B). [12] With the use of the nonavalent vaccine, we expect even better outcomes, resulting in faster clearance, reduction in pain and morbidity in patients undergoing this combination treatment.

REFERENCES

1. de Villiers EM, Fauquet C, Broker TR, et al. Classification of papillomaviruses. *Virology* 2004;324:17.
2. Patel H, Wagner M, Singhal P, Kothari S. Systematic review of the incidence and prevalence of genital warts. *BMC Infect Dis* 2013;13:39.
3. Marty R, Roze S, Bresse X, et al. Estimating the clinical benefits of vaccinating boys and girls against HPV-related diseases in Europe. *BMC Cancer* 2013;13:10.
4. Henquet CJM. Pareltjes van de S.V.P. (SOA-vulva-proctologie) poli. *Ned Tijdschr voor Dermatologie en Venereologie* 2017;27:543.
5. Kaderli R, Schnüriger B, Brügger LE. The impact of smoking on HPV infection and the development of anogenital warts. *Int J Colorectal Dis* 2014;29:899.
6. Gormley RH, Kovarik CL. Human papillomavirus-related genital disease in the immunocompromised host: Part I. *J Am Acad Dermatol* 2012;66:867.e1.
7. Martin MP, Carrington M. Immunogenetics of viral infections. *Curr Opin Immunol* 2005;17:510-6.
8. Scheinfeld N. Update on the treatment of genital warts. *Dermatol Online J* 2013;19:18559.
9. McCormack PL, Joura EA. Quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine (Gardasil®): a review of its use in the prevention of premalignant genital lesions, genital cancer and genital warts in women. *Drugs* 2010;70(18):2449-74.
10. Nofal A et al. Intralesional versus intramuscular bivalent human papillomavirus vaccine in the treatment of recalcitrant common warts. *J Am Acad Dermatol* 2020;82:94-100.
11. Daayana S, Elkord E, Winters U, et al. Phase II trial of imiquimod and HPV therapeutic vaccination in patients with vulval intraepithelial neoplasia. *Br J Cancer* 2010;102:1129-36.
12. Ferguson SB, Gallo ES. Nonavalent human papillomavirus vaccination as a treatment for warts in an immunosuppressed adult. *JAAD Case Reports* 2017;3:367-9.

SAMENVATTING

De titel doet vermoeden dat het niet-behandelen van condylomata een optie is. Gezien de langetermijnrisico's en consequenties van chronisch persisterende HPV-infecties, is niet-behandelen uiteraard geen reële optie. De kans op de ontwikkeling van (pre)maligniteiten zoals M. Bowen en plaveiselcelcarcinomen is bij oncogene HPV ca. 10%. Dat percentage kan bij immunosuppressie en bij MSM en hiv+ oplopen tot boven de 50%. De klassieke en meer experimentele therapeutische opties zullen besproken worden. Het is de verwachting dat de huidige experimentele therapieën in de toekomst de standaard zullen worden.

TREFWOORDEN

anogenitale wratten – LSIL – HSIL – CO₂-laser – elektrochirurgie – imiquimod – HPV-vaccinatie

SUMMARY

The title suggests that not treating condylomata is an option. In view of the long-term consequences of chronically persistent HPV infections, not to treat is of course not a realistic option. The chance of developing (pre) malignancies such as M. Bowen and squamous cell carcinomas is approximately 10% in oncogenic HPV infections. In immunosuppressed patients and in the MSM and HIV +populations, that percentage can even increase to over 50%. The classic and more experimental treatment options will be discussed. It is expected that current experimental therapies will become the standard treatment in the future.

KEYWORDS

anogenital warts – LSIL – HSIL – CO₂ laser – electro surgery – Imiquimod – HPV vaccination

Gemelde (financiële) belangenverstremgeling
Geen

CORRESPONDENCE

Errol Prens

E-mail: e.prens@erasmusmc.nl