THE EFFICACY OF CERVARIX VACCINE IN WART TREATMENT:
UPDATED MANAGEMENT

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ABSTRACT

Viral warts are one of the most common skin diseases. Wart is a small growth with rough texture that can appear anywhere on the body. Warts can be defined as hyperkeratotic papillomas caused by infection of the epidermis with human papillomavirus (HPV). It can be spread from one individual to another by direct contact or via the environment through contact with towels or shoes.

Cutaneous warts vary in their shape and sites. They can occur anywhere, but they are most common on the knuckles, fingers, elbows, and knees. There are many types of cutaneous warts such as plane warts, planter warts, filiform warts and common warts. The treatment of warts is a therapeutic challenge for both patients and physicians. No single therapy has been proven effective at achieving complete remission in every patient. Human papillomavirus vaccines have been available since 2006. There are currently three HPV vaccines licensed in Europe: the bivalent vaccine (Cervarix) that contains virus-like-particles (VLPs) of HPV types 16 and 18, the quadrivalent HPV vaccine (Gardasil/Silgard) that includes VLPs of HPV types 6, 11, 16 and 18 and the nonavalent vaccine (Gardasil 9), that contains VLPs of HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58. The mechanism of action of HPV vaccines in the treatment of warts is not yet established. This might be mediated by the development of IgG neutralizing antibodies directed against the major and minor capsid proteins, L1 and L2 of human papillomavirus generated as a result of vaccination.

Key words: Wart Treatment, Cervarix Vaccine.

I. CUTANEOUS WARTS

Warts are the commonest viral infections which are encountered in the dermatological practice, which are caused by DNA tumor viruses that belong to the family, Papova viridae (1). Warts have been recognized since Greek and Roman times. It is estimated that 10–20 % of visits to the dermatologist are prompted by warts (2).

Cutaneous warts are a common dermatological condition, showing a prevalence of up to 33 % among children between the ages of six to twelve and of about 3.5 % among adults (3).

Warts are benign epidermal tumors caused by human papillomaviruses (HPVs). Human papillomaviruses comprise a group of nonenveloped, double-stranded DNA (dsDNA) viruses that belong to the papillomaviridae family. They infect keratinocytes and induce hyperplasia and hyperkeratosis. This increased growth forms a wart (4).

Clinical types:
1) Common warts (verruca vulgaris):

They appear flat or raised papules or nodules with irregular hyperkeratotic surfaces. They occur most frequently on the backs of the hands and fingers and on the knees but can occur anywhere on the skin (5).
They are caused mainly by HPV type 2 but also by HPV 1, 4, 7, 27 and 57. Common warts are usually asymptomatic but may be tender. About 95% clear spontaneously within 4 years. It seems that clearance is slower in adults. Malignant transformation is extremely rare but has been reported in immunosuppressed hosts (6).

2) Plane warts (Verruca plana):
They are also called flat warts. They are slightly raised well demarcated papules ranges from 2 to 5 mm in diameter or more with flat, smooth or slightly rough surface. They have the same color of skin or may be slightly yellowish brown (7).

They commonly appear on the face and the dorsum of hands. Spontaneous regression is common, usually preceded by inflammation of the lesions. They are mainly caused by HPV 3 and HPV 10 and less commonly by 28 and 29 (8).

3) Plantar warts:
They appear on the planter aspect of the foot. Plantar warts exhibit an annual incidence of 14%. The majority of cases occur in children and adolescents. However, other populations, such as immunocompromised patients are at increased risk for acquiring plantar warts, which can lead to pain, embarrassment, and, in rare cases, cancer (9).

Patients with plantar warts most commonly present with pain or the sensation of a stone or swelling under their foot. On gross inspection, plantar warts may appear as a singular rough, flesh-colored to yellow or grey-brown, hyperkeratotic papule, or a thickened “cobblestoned” plaque, termed a mosaic wart, which consists of multiple plantar warts that have coalesced (10). They are mainly caused by HPV 1 but other types such as HPV 2, 27, 57 may be involved (9).

4) Filiform warts:
These are pedunculated lesions growing in a perpendicular or oblique way in relation to the skin surface. They appear as isolated or multiple lesions affecting mainly the face and neck. It is a morphological variation of the common wart, and the HPV types appear to be the same found in lesions of common warts, especially HPV 2 (3).

5) Butcher’s warts:
They are exclusively in butchers and meat handlers, cauliflower like exophytic lesions found on both sides of the hand but rarely periungually and mainly caused by HPV 7(5).

II. TREATMENT:
The main goal when treating warts is to eradicate the lesions, while attempting to minimize pain, avoid scarring and prevent recurrence. There is no specific definition of recalcitrance but typically, recalcitrant warts were defined as warts of more than 2 years duration that failed to respond to two therapeutic modalities or more (3).

Treating warts is a therapeutic challenge for family physicians. No single therapy has been proven effective at achieving complete remission in every patient (3).

Recalcitrant warts represent a frustrating challenge for both patients and physicians. Many warts are cosmetically unacceptable and may be painful as in the case of palmoplantar warts or destructive as in the case of periungual warts. In addition, recalcitrant warts continue to multiply and enlarge, making treatment more difficult and spreading infection to the patient (11).

There are numerous treatments for warts, which are used singly or in combination. Choice of treatment will depend on the location, size, number and type of warts, as well as on the age and level of cooperation of the patient. The experience of the treating physician may also have an influence (3).

Unfortunately, no therapeutic modality, alone or in combination, has been established as definitively superior to others. Therefore, several alternative treatment modalities for warts have been investigated. In particular, immunomodulatory agents targeted at the underlying HPV infection have produced the most encouraging outcomes (12).
Table 1: Treatments for Cutaneous warts (3).

| A) Destructive | 1-Chemical e.g.: Salicylic acid.  
| B) Virucidal | 2-physical e.g.: Cryotherapy, surgery, laser  
| C) Antiproliferative | 1- Formaldehyde  
| D) Immunological therapy | 2- Glutaraldehyde  
| | 3- Podophyllin and podophyllotoxin  
| | 4- 5-Fluouracil  
| | 5- Bleomycin  
| | 6- Retinoids  
| | 7- Cidofovir  
| | 8- Occlusotherapy (Duct tape)  
| E) Complementary and alternative treatments | 1- Hypnosis  
| | 2- Herbal  

A) Destructive treatments:

a) Chemical:

1) Salicylic acid:

It is considered a keratolytic agent that slowly destroys the HPV-infected epidermis. It is the first-line therapy chosen by many clinicians (13).

Advantages of salicylic acid over other treatment options include low cost, and minimal adverse effects. Salicylic acid is well tolerated, but the most common adverse effect is minor skin irritation. The therapy should not be used on the face because it can cause hypo- or hyperpigmentation. Salicylic acid therapy is slow to take effect and requires frequent application (13).

2) Cantharidin:

Cantharidin (CA), a toxic terpene produced by blister beetles (Coleoptera Meloidae) (14). This is a blistering agent that triggers acantholysis. It also has the advantage of painless application, with discomfort developing only when blistering occurs in the 24 h following application (14).

3) Glycolic acid 5%:

It has the smallest molecular weight amongst all the alpha-hydroxy acids. It penetrates skin easily, making it a popular peel agent. Glycolic acid peels have antiinflammatory, keratolytic, and antioxidant effects (15).

4) Pyruvic acid:

Pyruvic acid is an enole isomer of alpha hydroxyl acids (AHAs), an alpha keto acid, and a strong keratolytic agent. Pyruvic acid is used as a peeling agent. Hypertrophic scarring was reported in a patient using pyruvic acid 98% with 5-FU 2% for warts on the chest and arms (16).

5) Citric acid 50%:
Citric acid was compared with tretinoin in a prospective randomized, double blinded study of 75 patients with plane warts on the body. The study design used a side-to-side comparison, and the results were given as number of warts cleared. After 6 weeks 64% of citric acid-treated lesions were cleared, vs. 54% of the tretinoin-treated lesions (17).

6) Formic acid:
Formic acid is another low-cost treatment. It seems to be safe, relatively effective and not painful. (18).

7) Trichloroacetic acid and monochloroacetic:
Trichloroacetic acid (TCA) and monochloroacetic acid are caustic agents that destroy warts by chemical coagulation of proteins (19).

B) Physical

1) Cryotherapy:
Another in-office first-line therapy performed by clinicians is cryotherapy, or the application of liquid nitrogen directly to the verruca. Liquid nitrogen can be applied using a cryogun or a cotton swab (8).

This therapy causes a cell-mediated response via local inflammation but does not kill the virus directly. Common adverse effects of cryotherapy include pain, blistering, hypo- or hyperpigmentation, particularly in dark skin (8).

2) Hyperthermia:
There have been reports that local hyperthermia was effective in the treatment of viral warts. Its effect was not influenced by patient age, duration of disease, or number or size of lesions (20).

3) Surgery:
Surgical treatment of warts involves the radical eradication of lesions by conventional surgery, electro-surgery, or curettage. One of the advantages of surgery is that it provides a rapid solution and can be beneficial in the case of recalcitrant or isolated warts. It is, however, associated with high rates of bleeding, scarring and bacterial infections, and estimated recurrence is around 20% (21).

It is now less commonly used because of the requirement for local anesthetic injection, the risk of scarring and high rates of recurrence (21).

4) Photodynamic therapy:
When activated by ultraviolet light, the photosensitizing agent aminolevulinic acid produces a phototoxic product. It is typically applied to the wart several hours before phototherapy (22).

5) Laser Therapy:
Different types of lasers have been evaluated for the treatment of warts including carbon dioxide (CO2) laser, pulsed dye laser (PDL), erbium-yttrium aluminum garnet (YAG) laser and neodymium (Nd): YAG laser. Long-pulsed Nd: YAG lasers were reported to be a safe and effective treatment for warts, with response rates higher than those obtained with conventional therapies (23).

Pulsed-dye laser therapy causes direct micro vascular damage within the warts. It is well tolerated by children. Adverse reactions described for pulsed-dye laser therapy include pain, scarring, crusting, petechiae, and purpura (24).

B) Virucidal agents:

1) Formaldehyde:
It causes damage to the upper layers of epidermal cells that contain the virus, and thus destroying viruses. The most common side effects of formalin include redness, irritation and dryness of skin. Severe allergic reactions are rare (25).
2) Glutaraldehyde:
Glutaraldehyde is an antiviral agent. A 10% or 20% solution is applied daily over a period of 3 months. (3).

C) Antiproliferative agents:
1) Vitamin D analogues:
Recent reports have suggested that vitamin D₃ analogues have anti-tumor effects and may be effective in treating seborrhoic keratosis and warts. (26).

2) Dithranol (Anthralin):
It is a hydroxyanthrone, anthracene derivative that has the anti-proliferative and anti-inflammatory action (3).

3) Bleomycin:
Bleomycin is a glycopeptide antibiotic that acts by forming free radicals from binding to guanosine-cytosine-rich portions of DNA that cause DNA single-strand breaks ultimately resulting in cytotoxicity. Side effects of this medication include tenderness, redness, blistering, hyperpigmentation or hyperkeratosis. Pain can be reduced by using adjunctive topical or intralesional anesthetics (27).

4) Podophyllin and podophyllotoxin
Although they are a standard treatment for anogenital warts, their evaluation in cutaneous warts has been limited. The side-effects of this treatment include an intense inflammatory reaction with blistering, which can be very painful (28).

5) 5-Fluorouracil (Intralesional and Topical):
5-Fluorouracil (5-FU) is an antimetabolite that interferes with DNA synthesis and inhibits RNA formation, resulting in cytotoxicity. Side effects include local pain, irritation and potential ulceration (29).

6) Retinoids:
Retinoids are vitamin A derivatives. Retinoids affect epidermal proliferation and differentiation and so can reduce wart volume and alter stratum corneum quality and quantity (3).

Tretinoin 0.05% is a good option for flat facial warts (24).

Their main side-effects skin dryness and skin irritation, which could influence inflammatory reactions in the skin and contribute to the drug immunomodulatory effects (3).

7) Occlusotherapy (Duct tape):
The mode of action of duct tape is not well-understood, but it has been suggested that duct tape occlusion may produce a macerating and keratolytic environment, which may stimulate an immune response. However, it has also been suggested that it may have a psychological effect that works better in children than adults (30).

D) Immunological therapy:
Immunotherapy is defined as a type of biological therapy that uses substances to stimulate or suppress the immune system to help the body fight cancer, infection, and other diseases. Topical and systemic immunotherapy has now found a significant place in the treatment of warts because of its non-destructive action, ease of use, and promising results (31).

1- Topical immuthery: a) Imiquimod:
Imiquimod, a synthetic imidazoquinoline derivative that is FDA approved for the treatment of external genital and perianal warts. It is thought to have both antiviral and anti-tumor effects. Its side effects include burning sensation, pain, erythema, and vitiligo-like depigmentation. It is effective and safe in children and pregnancy (32).

b) Topical Bacillus Calmette-Guerin (BCG):
Topical immunotherapeutic BCG is an effective and safe treatment option for children with common and plane warts. No recurrences or side effects were observed (33).

2- Contact immunotherapy:

Contact immunotherapy with dinitrochlorobenzene (DNCB), diphenycyprone (DPC) or squaric acid dibutyl ester (SADBE) induces a local delayed hypersensitivity reaction at the wart site triggering a local immune response. Diphenycyprone (DPC) is a more potent contact sensitizer than dinitrochlorobenzene (DNCB) for the same concentration (3).

3- Intralesional immunotherapy:

Intralesional Candida, mumps and tuberculin antigens have been used to induce wart clearance through antigenic stimulation of the host-cell mediated immune system. There is no evidence to support the use of this type of intralesional immunotherapy but reported clearance rates range from 47% to 87% (3).

Tuberculin Antigen:

It is an inexpensive, effective, and safe modality with good cure rates for treatment of cutaneous warts in previously immunized patients. Most side effects had been reported were Local redness, tenderness, and edema, which subsided four days after injection without any medications (34).

b) Candida albicans antigen:

It stimulates Th1 cytokines such as IFN-γ and IL-2 which activate cytotoxic and natural killer cells to eradicate HPV infection not only at the injected site but also all over the body. Adverse effects that have been reported with candida immunotherapy include febrile reactions, myalgia, pain, erythema, and edema at the injection site. However, this form of therapy is inexpensive (35).

c) Measles, mumps, rubella vaccine:

The mechanism of action of Measles, mumps, rubella (MMR) vaccine is still obscure. It has been postulated that a functional host immune system, particularly CMI, is a necessary prerequisite for successful intralesional antigen immunotherapy. This may be achieved through the direct effect of the trauma itself, a strong nonspecific inflammatory response against the HPV-infected cells, and through an interaction of stimulated macrophages, T-helper cells, neutrophils and natural killer cells (36).

d) Mycobacterium:

It induces a strong pro inflammatory response while injected intralesionally. There is a prominent delayed hypersensitivity response. The reported side effects include pain, nodularity, ulceration, scarring at the site of injection, flu-like symptoms, fever, and lymphadenopathy (37).

e) Bacillus Calmette-Guerin vaccine:

The principle behind using Bacillus Calmette-Guérin (BCG) vaccine is the same as that of the Mycobacterium vaccine. The delayed hypersensitivity response against the antigen is the key to clinical response against warts. It increases the serum levels of IL-12 and decreases the level of IL4. One to three doses are administered 1 month apart (31).

III. SYSTEMIC THERAPY:

a) H2 receptor antagonists:

H2 receptor antagonists are widely used in the treatment of gastroesophageal reflux. They increase IL-2 expression from T lymphocytes, enhancing cell-mediated immune responses (3).

b) Zinc oxide and zinc sulfate:
It acts as an immune modulator. It is crucial for all highly proliferating cells in the human body, especially the immune system, and innate and acquired immunity can be compromised by zinc deficiency. Zinc could counteract viral infections by having an effect on the synthesis of cytokines. In vivo, not only oral zinc sulfate but also topical zinc oxide has shown therapeutic efficacy in the treatment of viral warts (38).

5) Complementary and alternative treatments:
Most cultures have a history of charms, herbal treatments and other remedies for warts. Modern complementary therapies are often derived from these treatments.

a) Hypnosis:
Hypnosis has been used to treat warts in children and adults for years. It stimulates the immune system, leading to the resolution of lesions. (24).

b) Herbal treatment:
Plants used include mayapple (Podophyllum peltatum) (the source of podophyllin) and greater celandine (Chelidonium majus) (3).

Dermoscopic picture of Cutaneous Warts:
According to their anatomic location, warts are commonly classified as common warts (verruca vulgaris), palmpplanter warts, plane warts and anogenital warts. Although their diagnosis is usually based on typical clinical features, clinicians may sometimes be faced with features that overlap with other skin lesions or that make it difficult to accurately diagnose based on clinical criteria only (39).

Verruca vulgaris dermoscopically displays multiple densely packed papillae (100 %), each containing a central red dot or loop, which is surrounded by a whitish halo (64.4%). Hemorrhages represent a possible additional feature, appearing as irregularly distributed, small, red to black, tiny dots or streaks giving a so-called frogspawn appearance (64.4%) (40).

HPV vaccine
Human papillomavirus vaccines have been available since 2006. Currently available vaccines are sub-unit vaccines made from the major protein of the viral coat or capsid of HPV (major capsid protein L1). Virus-like particles (VLPs) are prepared from recombinant proteins grown in either yeast or baculovirus infected insect cells (the latter derive from a type of moth). VLPs mimic the structure of the native virus but do not contain any viral DNA. Thus, they cannot infect cells, reproduce or cause disease (41).

The available vaccines differ in the number of HPV genotypes that they contain, the way that they are manufactured and the adjuvant that they contain. There are currently three HPV vaccines licensed in Europe: the bivalent vaccine (Cervarix) that contains virus-like-particles (VLPs) of HPV types 16 and 18, the quadrivalent HPV vaccine (Gardasil/Silgard) that includes VLPs of HPV types 6, 11, 16 and 18 and the nonavalent vaccine (Gardasil 9), that contains VLPs of HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58 (42).

Immunogenicity
The bivalent and quadrivalent vaccines induce strong immune responses against vaccine HPV types and some phylogenetically related non-vaccine types. The main effector of protection is believed to be the IgG antibody, which can reach the site of infection by transudation from serum into the vaginal milieu and by exudation at sites of trauma that expose the basement membrane to infection (43).

Duration of antibodies has been assessed through about 10 years, and sustained high concentrations have been reported during this time, suggesting that antibodies against both vaccines are likely to last for decades (44).

Dosage and schedule for HPV vaccines:
1- For children and adolescents aged between nine years old and below 15 years of age (Two dose schedule):
Schedule for Gardasil® (containing HPV types 6, 11, 16, 18), Gardasil®9 (containing HPV types 6, 11, 16 18, 31, 33, 45, 52, 58) and Cervarix® (containing HPV types 16, 18)

- First dose of 0.5ml of HPV vaccine.
- Second dose of 0.5ml 6 to 24 months after the first dose.

For adolescents aged less than 15 years of age, the Joint Committee on Vaccination and Immunization (JCVI) recommends a schedule of 0, 6-24 months for all HPV vaccines. Any gap between doses of between six and 24 months is clinically acceptable. As long as the first dose was received before the age of 15 years the two-dose schedule can be followed. If the course is interrupted, it should be resumed (using the same vaccine) but not repeated, even if more than 24 months have elapsed since the first dose. Whenever possible, immunizations for all individuals should follow the recommended 0, 6-24 months schedule, but there is some clinical data that the interval between the two doses can be reduced to five months for Cervarix. For Gardasil® the minimum interval between the two doses should be 6 months. For Gardasil®9 the minimum interval between the two doses can be 5 months (45).

2- for those aged 15 years and above (Three dose schedule):

Schedule for Gardasil® (containing HPV types 6, 11, 16, 18) or Gardasil®9 (containing HPV types 6, 11, 16 18, 31, 33, 45, 52, 58)

- First dose of 0.5ml of HPV vaccine.
- Second dose of 0.5ml at least one month after the first dose.
- A third dose of 0.5ml at least three months after the second dose.

Schedule for Cervarix® (containing HPV types 16, 18)

- First dose of 0.5ml of HPV vaccine.
- Second dose of 0.5ml, one to two and a half months after the first dose.
- A third dose of 0.5ml at least five months after the first dose A.

Vaccination schedule of 0, 1, 4-6 months is appropriate for the HPV vaccine for those commencing the course at age 15 years and above. All three doses should ideally be given within a 12-month period. If the course is interrupted, it should be resumed (using the same vaccine) but not repeated, ideally allowing the appropriate interval between the remaining doses. There is no clinical data on whether the interval between doses two and three can be reduced below three months. Where the second dose is given late and there is a high likelihood that the individual will not return for a third dose after three months or if, for practical reasons, it is not possible to schedule a third dose within this timeframe, then a third dose can be given at least one month after the second dose. This applies to all the currently licensed HPV vaccines (46).

IV. ADMINISTRATION:

Vaccines are routinely given intramuscularly into the upper arm or anterolateral thigh. This is to reduce the risk of localized reactions, which are more common when vaccines are given subcutaneously (47).

However, for individuals who have a bleeding disorder, vaccines should be given by deep subcutaneous injection to reduce the risk of bleeding. HPV vaccines can be given at the same time as other vaccines such as MMR, Influenza, and hepatitis B. The vaccines should be given at a separate site, preferably in a different limb. If given in the same limb, they should be given at least 2.5cm apart. The site at which each vaccine was given should be noted in the individual’s records. In treatment of warts the vaccine could be injected locally in the warts (48).
Disposal:

Equipment used for vaccination, including used vials, ampoules or syringes, should be disposed of by placing them in a proper, puncture-resistant ‘sharps’ box.

Mechanism of action of Cervarix:

The mechanism of action of HPV vaccines in the treatment of warts is not yet established. This might be mediated by the development of IgG neutralizing antibodies directed against the major and minor capsid proteins, L1 and L2 of human papillomavirus generated as a result of vaccination. It has also been reported that Cervarix is associated with increased levels of IL-2 and TNF-α and proinflammatory cytokines (IL-6, IL-1α, IL-1β) following 1st and 3rd vaccinations. Furthermore, Cervarix induces long-term immune protection through stimulation of circulating B memory cells that produces antibodies in response to further antigenic challenges (49).

Adverse reactions and contraindications:

The most common adverse reaction observed after HPV vaccine administration is mild to moderate short-lasting pain at the injection site. An immediate localized stinging sensation and redness. Other reactions commonly reported are headache, malagia, fatigue, and low-grade fever (50).

Syncope (vasovagal reaction), or fainting, can occur during any vaccination, most commonly in adolescents and adults. Some individuals may also experience panic attacks before vaccination. Fainting and panic attacks occurring before or very shortly after vaccination are not usually direct side effects of the vaccine, but events associated with the injection process itself. Anaphylaxis is a very rare side effect (51).

The vaccine should not be given to those who have had a confirmed anaphylactic reaction to a previous dose of HPV.

vaccine, or a confirmed anaphylactic reaction to any components of the vaccine. Yeast allergy is not a contraindication to the HPV vaccine. Even though Gardasil® is grown in yeast cells, the final vaccine product does not contain any yeast. Minor illnesses without fever or systemic upset are not valid reasons to postpone immunization. If an individual is acutely unwell, immunization may be postponed until they have fully recovered. This is to avoid confusing the differential diagnosis of any acute illness by wrongly attributing any signs or symptoms to any possible adverse effects of the vaccine (52).

REFERENCES


