The Egyptian Journal of Hospital Medicine (April 2022) Vol. 87, Page 1173-1176

Role of HPV Vaccines in Multiple Recalcitrant Warts Treatment: Review Article

Esam Alfetori Abdulsalam*, Ahmad Nofal, Mohamed Ibrahim El-Ghareeb
Department of Dermatology, Venereology and Andrology, Zagazig University Hospital, Egypt.
***Corresponding author:** Esam Alfetori Abdulsalam, **E-Mail:** alwershefanye1980@gmail.com

ABSTRACT

Background: When warts appear on the skin, they can cause substantial pain and embarrassment since they are caused by human papillomavirus. Cryotherapy, laser vaporisation and surgical excision are some of the current techniques for treatment of skin cancer There are a number of ways to address these issues, but some of them are more invasive and may result in scarring. A huge number of warts makes local methods impractical for patients. Combining a targeted strategy with an increase of the host immune system has proven successful in treating various lesions. To evaluate the numerous vaccine antigens which was intralesionally injected for tratment of anogenital warts as well as , a comprehensive literature review was conducted. These non-specific intralesional immunotherapies include Candida albicans, mumps, and rubella; Trichophyton; and tuberculin antigens such as pure protein derivative, Mycobacterium w vaccine, and Bacillus Calmette-Guerin. Warts, particularly refractory and anogenital warts, can be treated safely, effectively, and comfortably using intralesional vaccine injection. Bivalent and guadrivalent HPV vaccines are currently available for primary prevention of HPV infection, which includes both types 16 and 18. There has been a dramatic reduction in the incidence of cervical neoplasia as well as genital warts due to HPV vaccines; however, they do not target genotypes that are specific to other skin locations.

Objective: To evaluate the potential role of role of HPV vaccines in multiple recalcitrant warts treatment.

Conclusion: Several previous studies have demonstrated that recent studies and case reports have shown promising efficacy of HPV vaccines in the treatment of warts.

Keywords: HPV Vaccines, Multiple Recalcitrant Warts.

INTRODUCTION

HPV is the virus that causes warts, which are harmless skin and mucosal growths. Prevalent warts, Genital Warts, Flat Warts, and Deep Palmoplantar Wraths are the most common HPV-infected clinical presentations (myrmecia) . More uncommon HPV-related conditions include epidermodysplasia verruciformis and localised epithelial hyperplasia [(1)].

Cutaneous viral warts are a prevalent skin ailment that affects nearly everyone at some point in their lives in some shape or form [(2)].

Between 7% and 13% of children and adolescents and between 25% and 34% of adults between the ages of 25 and 34 have cutaneous viral warts [(3)].

Verrucae vulgaris (common warts) and verrucae plantaris (plantar warts) are the most frequent forms of wart. Despite the fact that cutaneous warts have a benign course, they are a substantial source of physical and mental discomfort [(4)].

Methods:

A search strategy has been performed to determine the related literature. Initially, the objective of review was identified: To evaluate the potential role of role of HPV vaccines in multiple recalcitrant warts treatment. Relevant keywords included: HPV Vaccines, and Multiple Recalcitrant Warts, more synonymous key words had been used.

These databases were searched for articles published in English in 3 data bases [PubMed – Google scholar- science direct] and Boolean operators (AND, OR, NOT) had been used such as [HPV Vaccines AND Multiple Recalcitrant Warts OR Warts Treatment] and in peer-reviewed articles between January 2001 and January 2020; a 19-year date range was selected, and no language limitations, and filtered in selected data basis for the last 19 years, however, the range of time interval for researches is wide as there's scarcity of data on the particular reviewed, accurate and depth in the retrieved literature. Documents in a language apart from English have been excluded as sources for interpretation was not found. Papers apart from main scientific studies had been excluded: documents unavailable as total written text, conversation, conference abstract papers and dissertations.

HPV Vaccines:

This virus is responsible for many dangerous disorders, including cancer of the female reproductive tract and squamous cell carcinomas of the head and neck in adults and children. The goal of developing a preventive HPV vaccination is to eliminate the risk of female sexually transmitted cancer in women [(5)].

Vaccination of women between the ages of 9 and 26 was suggested by the Advisory Committee on Immunization Practices (ACIP) back in 2007 [(6)]. FDA and ACIP approved Cervarix, a vaccine that protects against both HPV 16 and 18 strains, in 2009 [(7)].

In October 2009, the FDA approved the use of a quadrivalent HPV vaccine for boys aged 9 to 26 years, while the ACIP advised vaccination in 2010 for males [(8)]. Over 100 countries have granted vaccination approval for HPV since 2006. HPV vaccination has been incorporated in immunisation regimens in more than 40 nations as of 2012 [(9)].

Received: 11/11/2021
Accepted: 23/12/2021

The HPV vaccine was rigorously tested for safety during its development and distribution. For the quadrivalent and bivalent vaccines, there were no significant differences in major adverse events, autoimmunity or death between the vaccine and control groups during prelicense trials including over 20,000 women. More than 144 million quadrivalent vaccines and 41 million bivalent vaccines were administered worldwide by the end of 2013. Passive surveillance, active monitoring, and demographic research have found no indication of vaccine-related major impacts from HPV vaccinations. The most common side effect following a vaccine is syncope [(10)].

There are currently three commercially available HPV vaccines: the Gardasil, Merck quadrivalent vaccine against HPV types 6, 11, 16, and 18; the Cervarix, GlaxoSmithKline bivalent vaccine against HPV types 16 and 18; and the nine-valent vaccination against HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 (Gardasil 9, Merck) **[(11)].**

Biology:

An impressive level of efficacy in protecting against HPV infection has been demonstrated for HPV vaccinations based on L1 VLPs. One of the key proteins in the papillomavirus capsid, L1, is capable of assembling itself spontaneously into virus-like particles (VLPs). Vaccine-like particles (VLPs) make it possible to produce vaccines in a safe and simple manner, and they also elicit a significant immune response. Recombinant L1 VLPs, which are highly immunogenic, induce a high level of the initial serum anti-HPV type-specific antibody response **[(12)].**

Intramuscular injections of commercial HPV VLP vaccines induce adaptive immune responses. Endocytosis into the epithelial basal cells is prevented by the antibodies, which neutralise the HPV virus. An exudate induced by tissue injury to the epithelium may bring antibodies to the basement membrane. Bacterial L1-binding is prevented by neutralising antibodies present at the infection site [(13)].

Indications:

The FDA has currently approved three L1 vaccines: Cervarix, Gardasil, and Gardasil 9. Prophylactic L1 vaccines are designed to protect children from HPV infection before they are sexually active. With Gardasil and Gardasil 9, the risk of HPV-related precancerous/cancerous lesions and genital warts can be reduced. Male patients between the ages of 9 and 26 are also eligible for Gardasil and Gardasil 9, respectively. Women between the ages of 9 and 25 are eligible to use Cervarix exclusively as a preventative measure against cervical cancer [(14, 15)].

It has also been claimed that pregnant women with condyloma who are vaccinated may passively protect their newborns from acquiring RRP by increasing their HPV-neutralizing antibodies. Reduced rates of HPV infection and condyloma in pregnant women, as well as the consequent reduction in horizontal transmission of HPV to vulnerable children, are most likely to be the largest benefits of the HPV vaccine for RRP [(16)].

L1 vaccines now on the market are designed to be administered over a six-month period in three doses. The three-dose regimen is still widely used in certain nations, although many are experimenting with two-dose regimens instead in an effort to cut costs and boost adherence. Cervarix has been studied for four years and found to offer the same protection against HPV 16/18 in women who received two doses of the drug as those who received three [(17)].

All around the world, the recommended quantity of vaccinations and the immunisation requirements (gender, target age, and so on) differ. Three shots of Gardasil are still recommended in the United States despite World Health Organization recommendation of two doses. HPV vaccination methods differ from state to state within the United States [(17)].

Efficacy:

It was found that both vaccines, Gardasil and Cervarix, prevented almost all cervical infections with HPV 16 and 18 when tested by the FDA. As of this writing, Gardasil 9 is 97% effective in protecting against the five new HPV strains **[(18)].**

Cervical malignancies caused by HPV 16 and 18 infections account for 70–95 percent of HPV-related non-cervical cancers, which can be prevented with L1 vaccinations **[(19)].**

About 90% of genital warts are caused by HPV 6/11 infection, which Gardasil also protects against, along with RRP [(20)].

Most Australian girls receive Gardasil vaccinations as part of the national HPV immunisation campaign. As a result, genital warts were less common in women who had been vaccinated and even in men who had not been [(21)].

The risk of HPV-related disorders will be reduced if men and women take preventative measures against HPV. Vaccination against HPV-related genital warts has been shown to protect males from HPV-related illness [(22)].

Low antibody concentrations have been shown to protect animal models immunised with commercial L1 vaccinations [(23)].

Gardasil and Cervarix have been demonstrated to protect humans for at least eight and nine years, respectively, in long-term studies **[(24)].** Common warts have also been shown to disappear after receiving anecdotal reports of HPV vaccines that target specific HPV strains. SCC may be caused in part by the human papillomavirus (HPV), according to new research [(25)].

Combining systemic and intratumoral HPV vaccine delivery for the first time in 2018, numerous cutaneous SCCs disappeared [(26)].

How HPV vaccines for warts on the skin work:

HPV illness in the cervix or genital warts appears to be unaffected by a bivalent or quadrivalent vaccine, despite evidence to the contrary [(14)]. Vaccination as a treatment for cutaneous warts has only sporadic anecdotal evidence [(27)].

HPV types 1–4 or 26–29 are the most common causes of extragenital cutaneous warts, and since the quadrivalent HPV vaccine contains HPV 6, 11, 16 and 18, a possible cross-protective effect is expected. Common epitopes and considerable similarity of L1 amongst HPV types have been hypothesised to result in vaccine crossprotection against HPV strains that are not specifically targeted by the vaccine. According to research, some verruca vulgaris may be caused by the vaccine's target species [(28)].

Cross-reactive immunological responses may occur between HPV 2 subtypes (27 and 57) and HPV 6, because of the similarities in their genomes. It's possible that the vaccine or its adjuvant causes a general increase in the body's ability to fight infection, allowing it to be eliminated. Evidence suggests that prophylactic HPV vaccination can activate responsive lymphocytes against virally infected cells, perhaps leading to immune clearance directed at specific cells that have been infected [(29)].

For therapeutic HPV vaccination, treatment with synthetic long peptides for HPV vaccination has revealed that alterations to the local cytokine milieu and/or the stimulation of interferon gamma producing T lymphocytes may be involved [(30)].

This trial was conducted on six children who had intractable extragenital warts for more than two years that had failed to respond to other treatments. A total of three intramuscular injections were performed in the deltoid area of the upper arm. All six of the children had warts completely removed [(31)].

HPV vaccine has been shown to completely eradicate HPV warts in patients with immunosuppression in prior investigations. During the two years of follow-up, no new warts appeared. The immunisation had no negative effects on the patients [(28)].

In 2020 **Nofal *et al.*** [(32)] reported research Bivalent human papillomavirus vaccination used intralesionally versus intramuscularly to treat resistant common warts. Two-weekly intralesional injections of 0.1 to 0.3mL of bivalent HPV vaccination were given to 22 adults with numerous persistent common warts, while the other 22 received intramuscular injections at 0, 1, and 6 months or until warts were totally eliminated or for a maximum of six sessions..

The findings of the Nofal research In 18 patients (81.8 percent) of the intralesional group and 14 patients (63.3 percent) of the intramuscular group, warts were completely cleared of the skin. Both groups experienced only brief and negligible side effects, and no recurrences were found [(32)].

Both groups experienced modest and temporary side effects. The injection location was tolerable for both groups of patients. Ninety-nine percent of patients treated with intralesional injection reported itching in their warts, compared to 95.5 percent of patients treated with intramuscular injection. Two patients in each group reported feeling tired or drowsy (9.1 percent) [(32)].

CONCLUSION

Several previous studies have demonstrated that Recent studies and case reports have shown promising efficacy of HPV vaccines in the treatment of warts.

Financial support and sponsorship: Nil.
Conflict of interest: Nil.

REFERENCES

1. **Leto M, Santos Júnior G, Porro A *et al.* (2011):** Human papillomavirus infection: etiopathogenesis, molecular biology and clinical manifestations. Anais Brasileiros de Dermatologia, 86(2): 306-317.
2. **Sterling J, Hand F, Hudson P (2001)**: Guide Line For the management of cutaneous warts. Br Journal Dermatol., 144(1):4-11.
3. **Lynch M, Cliffe J, Morris R *et al.* (2014):** Management of cutaneous viral warts. BMJ., 27: 348-53.
4. **Bruggink S, De Koning M, Gussekloo J *et al.* (2012):** Cutaneous wart-associated HPV types: Prevalence and relation with patient characteristics. J Clin Virol., 55:250–255.
5. **Guo T, Eisele D, Fakhry C (2016):** The potential impact of prophylactic human papillomavirus vaccination on oropharyngeal cancer. Cancer, 122(15): 2313–2323.
6. **Markowitz L, Dunne E, Saraiya M *et al.* (2014):** Human papillomavirus vaccination: recommendations of the Advisory Committee on Immunization Practices (ACIP). Morbidity and Mortality Weekly Report: Recommendations and Reports, 63(5): 1-30.
7. **Handler M, Handler N, Majewski S *et al.* (2015):** Human papillomavirus vaccine trials and tribulations: Clinical perspectives. Journal of the American Academy of Dermatology, 73(5): 743-756.
8. **Castle P, Maza M (2016):** Prophylactic HPV vaccination: past, present, and future. Epidemiology and Infection, 144(3): 449-468.
9. **Markowitz L, Tsu V, Deeks S *et al.* (2012):** Human papillomavirus vaccine introduction–the first five years. Vaccine, 30: 139-148.
10. **Herrero R, González P, Markowitz L (2015):** Present status of human papillomavirus vaccine development and implementation. The Lancet Oncology, 16(5): 206-216.
11. **Wei M, Wang D, Li Z *et al.* (2018)**: N-terminal truncations on L1 proteins of human papillomaviruses promote their soluble expression in Escherichia coli and self-assembly in vitro. Emerging Microbes & Infections, 7(1): 160.
12. **Schiller J, Lowy D (2018)**: Explanations for the high potency of HPV prophylactic vaccines. Vaccine, 36(32): 4768–4773.

13. **Harper D, Vierthaler S, Santee J (2010):** Review of Gardasil. Journal of Vaccines and Vaccination, 1(107): 107-112.
14. **Hildesheim A, Herroro R, Wacholder S *et al.* (2007):** Effect of human papillomavirus 16/18 L1 virus-like particle vaccine among young women with pre-existing infection: A randomized trial. JAMA., 298: 743–53.
15. **Ahn J, Best S, Tunkel D (2018):** Advances in Vaccine Technology. In: Recurrent Respiratory Papillomatosis. eds Campisi P. Springer: Cham, Pp. 45-58. https://link.springer.com/book/10.1007/978-3-319-63823-2
16. **Shah K (2014)**: A case for immunization of human papillomavirus (HPV) 6/11–Infected pregnant women with the quadrivalent HPV vaccine to prevent juvenile-onset laryngeal papilloma. The Journal of Infectious Diseases, 209(9): 1307-1309.
17. **Kreimer A, Rodriguez A, Hildesheim A *et al.* (2011):** Proof-of-principle evaluation of the efficacy of fewer than three doses of a bivalent HPV16/18 vaccine. Journal of the National Cancer Institute, 103(19): 1444-1451.
18. **Chatterjee A (2014):** The next generation of HPV vaccines: nonavalent vaccine V503 on the horizon. Expert Review of Vaccines, 13(11): 1279-1290.
19. **Gillison M, Chaturvedi A, Lowy D (2008):** HPV prophylactic vaccines and the potential prevention of noncervical cancers in both men and women. Cancer, 113(10): 3036-3046.
20. **Koutsky L, Ault K, Wheeler C *et al.* (2002):** A controlled trial of a human papillomavirus type 16 vaccine. New England Journal of Medicine, 347(21): 1645-1651.
21. **Fairley C, Hocking J, Gurrin L *et al.* (2009):** Rapid decline in presentations of genital warts after the implementation of a national quadrivalent human papillomavirus vaccination programme for young women. Sexually Transmitted Infections, 85(7): 499–502.
22. **Giuliano A, Palefsky J, Goldstone S *et al.* (2011):** Efficacy of quadrivalent HPV vaccine against HPV Infection and disease in males. New England Journal of Medicine, 364(5): 401-411.
23. **Day P, Kines R, Thompson C *et al.* (2010):** In vivo mechanisms of vaccine-induced protection against HPV infection. Cell Host and Microbe, 8(3): 260-270.
24. **Lowy D, Schiller J (2012):** Reducing HPV-associated cancer globally. Cancer Prevention Research, 5(1): 18-23.
25. **Martin J, Mateo E, Ramón D (2018):** Spontaneous regression of a recalcitrant wart after bivalent papillomavirus vaccination. The Journal of Pediatrics, 194: 259-259.
26. **Nichols A, Gonzalez A, Clark E *et al.* (2018):** Combined systemic and intratumoral administration of human papillomavirus vaccine to treat multiple cutaneous basaloid squamous cell carcinomas. JAMA Dermatology, 154(8): 927-930.
27. **Smith S, Baxendale H, Sterling J (2017)**: Clearance of recalcitrant warts in a patient with idiopathic immune deficiency following administration of the quadrivalent human papillomavirus vaccine. Clinical and Experimental Dermatology, 42(3): 306–308.
28. **Smith S, Baxendale H, Sterling J (2017)**: Clearance of recalcitrant warts in a patient with idiopathic immune deficiency following administration of the quadrivalent human papillomavirus vaccine. Clinical and Experimental Dermatology, 42(3): 306–308.
29. **Smolen K, Gelinas L, Franzen L *et al.* (2012)**: Age of recipient and number of doses differentially impact human B and T cell immune memory responses to HPV vaccination. Vaccine, 30: 3572–79.
30. **Kenter G, Welters M, Valentijn A *et al.* (2009):** Vaccination against HPV-16 oncoproteins for vulvar intraepithelial neoplasia. New England Journal of Medicine, 361(19): 1838-1847.
31. **Abeck D, Fölster-Holst R (2015):** Quadrivalent human papillomavirus vaccination: A promising treatment for recalcitrant cutaneous warts in children. Acta Dermato Venereologica, 95(8): 1017– 1019.
32. **Nofal A, Marei A, Al-shimaa M *et al.* (2020):** Intralesional versus intramuscular bivalent human papillomavirus vaccine in the treatment of recalcitrant common warts. Journal of the American Academy of Dermatology, 82(1) : 94–100.