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The role of intralesional immunotherapy in Condyloma Acuminata

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Abstract

Intralesional immunotherapy is one of the immunotherapy modalities that can be given to patients with condyloma acuminata (CA) with a high success rate both in inhibiting progression and preventing recurrence of genital warts. Intralesional immunotherapy regimens that are currently being studied are the use of vaccines and cytokines. Some of the antigens studied for use as therapy in genital warts include *Candida albicans*, measles, mumps and rubella (MMR), and Tuberculin/Purified Protein Derivate (PPD), *Mycobacterium w*, and *Bacille Calmette-Guerin* (BCG). Vaccines and cytokines work by inducing a delayed-type hypersensitivity response to warts tissue, both through cellular and humoral immune responses, mediated by CD8+ T lymphocytes, CD4+ T lymphocytes, B lymphocytes and regulatory T cells so that this can eliminate HPV virus infection in CA. This literature review aims to provide an understanding of the use of intralesional immunotherapy as an effective alternative therapy in CA.

Keywords: Intralesional immunotherapy; Condyloma acuminata; Genital warts; Vaccines; Cytokines

1. Introduction

Anogenital warts (AGWs) are a sexually transmitted infection resulting from the Human Papillomavirus (HPV) infection. HPV can lead to the development of both malignant and non-malignant skin and mucosal tumors, including AGWs. AGWs are characterized by the appearance of one or multiple papules, typically found around the perianal, vulvar, and urethral regions [1]. Condyloma acuminata (CA) is a specific type of AGW with various features, including flat/macular, papular, keratotic, and verrucous lesions. CA may or may not cause symptoms; some individuals may experience itching and discomfort, and in certain cases, movement or sexual activity can lead to trauma. CA lesions in mucosal areas tend to be rough and pale, while skin lesions appear as dry, hyperkeratinized, and hardened growths. HPV types 6 and 11 are the primary culprits behind CA, and they are highly contagious. The incubation period for CA ranges from three weeks to eight months following infection. These benign growths have a high likelihood of recurring and pose treatment challenges due to their size, local invasiveness, and potential for recurrence [2,3].

According to Korean Health Insurance epidemiological study, the prevalence and socio-economic problems caused by CA had increased from 2007 to 2015 with the average annual change of 8.3%. However, the prevalence of CA in women decreased by 3-6% after the implementation of the routine HPV vaccination program for women. On the other hand, the prevalence of CA in men increased by 11.6%, particularly in men aged 20-49 years. This study estimated 61 cases of CA per 100,000 population in 2015 [4]. Another study in India conducted by 200 doctors in six cities in 2011 found 1.07% of 44,061 patients aged 18-60 years were diagnosed with CA with higher prevalence of males than females. Meanwhile, based on age, patients aged 25-29 years had the highest prevalence with 74.07% new cases of cases. In this study also found that 56.24% of cases of CA were recurring cases and 43.76% were resistance cases to conventional therapy [1,3–5].

Immunotherapy involves utilizing antigenic substances to activate or regulate the immune system, aiding the body in combatting cancer cells, infections, and other diseases. It can be targeted towards specific immune cells or have a

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broader impact on the entire immune system. Types of immunotherapy including the use of cytokines, vaccines, and some monoclonal antibodies. Apart from its therapeutic effects, immunotherapy was proved to be effective in preventing recurrences of recalcitrant CA. This review aims to enhance knowledge about the role of intralesional immunotherapy in the management of CA [6–8].

2. Material and methods

Literature review is research methodology or certain research and development carried out to collect and analyze related research focus on certain topics. Literature review used in this study initially obtained 89 references consist of international journal and from book. Most of it is from international journal just several reference from book.

The process for literature review can be start form finding journals by keyword such as intralesional immunotherapy, anogenital warts, condyloma acuminata, human papilloma virus. Data in this study will be collected gathered for finding definition, pathophysiology, and therapy of condyloma acuminata, definition and classification of immunotherapy.

3. Results and discussion

This review was organized into two main subtopics. The first subtopic concerns condyloma acuminata including incidence, pathophysiology, and treatment. The second subtopic concerns about definition and classification of immunotherapy.

3.1. Condyloma Acuminata

Condyloma acuminata (CA), a subtype of AGWs, characterized by several features including flat/macular, papular, keratotic, and verrucous lesions. It can remain asymptomatic or lead to discomfort and itching, with possible trauma upon movement or sexual activity. Lesions situated on mucosal areas tend to be more common, appearing macerated and pale. Additionally, mucosal lesions present as dry, hyperkeratotic, and hardened lesions. The main cause of CA is HPV types 6 or 11, both highly contagious with an incubation period ranging from three weeks to eight months post-infection. An extreme manifestation stemming from HPV infection is Giant Condyloma of Buschke-Lowenstein (GCBL), a particularly aggressive form. It may produce multiple sinus or fistula tracts that penetrate deep into the fascia, muscles, and rectum, leading to inflammation, infection, or bleeding. These benign lesions exhibit a high recurrence rate, proving difficult to manage due to their large size, local invasion, and likelihood of recurrence [3,9].

3.1.1. Incidence Rate and Recurrence Rate

Condyloma acuminata stands as the most prevalent HPV infection among young adults, with a higher incidence in women compared to men. Over 100 HPV types are known, with HPV types 6 and 11 responsible for around 90% of AGWs, and HPV types 16 and 18 linked to 70% of invasive cervical cancers. According to Korean Health Insurance epidemiological study, the occurrence and associated socio-economic challenges of CA increased from 2007 to 2015 at an average annual rate of 8.3%. Nevertheless, during this period, the prevalence of CA in women decreased by 3-6% following the implementation of a routine HPV vaccination program. Conversely, the prevalence of CA in men increased by 11.6%, particularly in those aged 20-49. The study estimated that there were 61 cases of condyloma acuminata per 100,000 individuals in 2015 [4].

In another study conducted by 200 doctors across six Indian cities in 2011, among 44,061 patients aged 18-60, 1.07% were diagnosed with CA with a higher prevalence in males than females. Notably, patients aged 25-29 had the highest incidence with 74.07% representing new cases. The study also reported that 56.24% of observed CA cases were recurring cases, while 43.76% were resistant to conventional treatment [5].

3.1.2. Pathophysiology

Condyloma acuminata (CA) has a high risk of recurring, indicating the patient's immune system inability to eliminate the HPV infection. Several studies have identified four underlying mechanisms contributing to CA: deficiencies in Langerhans cells (LCs), excessive activation of regulatory T cells (Treg), misregulation shifting from T Helper 1 (Th1) to T Helper 2 (Th2), and impaired natural killer cell (NK) function. The human immune system is categorized into innate and adaptive immunity which have role in CA. Within the adaptive immune system, the major histocompatibility (MHC) class II system plays a critical role in inducing the proliferation of Treg and Th2 cells [1,10,11].

In the context of the immune responses to HPV infection, abnormalities emerge within both innate and adaptive immune systems. Within the adaptive response, an imbalance arises between Th2 cells and Th1 cells. This imbalance, favoring

Th2 cells, plays a pivotal role in the failure to eliminate HPV. The innate immune reaction to HPV typically involves NK cells recognizing and responding to HPV-infected keratinocytes. Natural Killer cells are guided by immunoglobulin-like receptors (KIR) gene products, which either activate or inhibit them based on their recognition of reduced class I human leukocyte antigen (HLA) molecules in these infected cells. However, a lack of this recognition, particularly in AGWs, triggers a biased immune response that can perpetuate HPV infection. Furthermore, the adaptive immune response is impacted by the inadequate maturation of Langerhans cells (LCs), which are responsible for presenting peptides to T cells. This leads to faulty LCs signaling, causing T cells to bias towards Th2 stimulation bias. When coupled with reduced NK activity, this skewed response promotes persistent HPV infection and contributes to the development of disease [1,12–14].

Langerhans Cells (LCs)

Langerhans cells (LCs), a subset of dendritic cells located in the skin's epithelial tissue, function as antigen-presenting cells (APCs). It act as cells that uptake, transport, process, and present HPV antigens to T cells. Immature LCs are vital in stimulating T cell proliferation, while mature LCs aid in migration and antigen/peptide presentation to T cells in lymph nodes. Multiple studies highlight LCs as target cells for viral infections like HIV, herpes simplex virus (HSV), and HPV, each through distinct mechanisms. Human papilloma virus has evasion tactics that prevent LCs from recognizing it as a harmful entity, hindering LCs maturation and costimulation induction. HPV can also clear LCs from infected areas, thwarting T cell activation. Other studies found that there is still some debate about LCs in HPV-induced lesions that are non-functional or anergic or LCs themselves play an active role in the pathogenesis of the disease [13,15].

Clinical trials of AGWs involving imiquimod, an antiviral agent, revealed a decline in CD1a+ cells in response to treatment, indicating LCs' migration from tissues without return. The murine study confirmed that imiquimod-induced LC migration to lymph nodes impairs the formation of costimulatory factors CD80 and CD86. The interplay between cytokines from keratinocytes and LCs significantly shapes LCs function. Pro-inflammatory and anti-inflammatory cytokine IL-10 balance potentially regulates LCs migration, while TGF-β expression aids in immature LCs regulation and maturation. Langerhans Cells can induce Th1 responses and be converted to Th2 responses through IL-10 production. Th2-produced IL-10 and TGF-β impede LCs and dendritic cell (DC) differentiation. Blocking Th1 responses in IL-10 induce tolerance to AGWs and also induce LCs and DC formation from Th2 responses to antigens, showcasing LC's role as either pro- or anti-inflammatory in adaptive immunity [13,16–18].

Functional studies of LCs from tissues are complex, but monocyte-derived immature LCs derived from AGWs patients display a weak response to the pro-inflammatory cytokine IL-36γ expressed by keratinocytes, suggesting that these cells may be less functional. Similar reduced LCs response occur in active HPV infections, as demonstrated by a study with cervical cancer, which demonstrated a lack of cytokine expression when LCs were stimulated with Toll like receptor (TLR) ligand 7 or 8, suggesting that LCs may become anergic during active HPV infection. However, in 2008, a study proposed that the LCs in AGWs are not only inactive, but also a source of CCL17 and CCL22, cytokines shown to recruit Treg to local tissues. Both co-staining experiments and qPCR showed that LCs produce these cytokines. Furthermore, that antibody-induced blockade of CCL17 or CCL22 inhibited Treg migration towards tissue AGWs in culture. If it can be confirmed that LCs are the source of CCL17 and CCL22 in HPV types 6 and 11 induced papilloma, this would suggest that LCs play an active role in creating and maintaining local immune suppression by recruiting Treg cells into infected epithelial tissue [13,19–21].

Keratinocytes in persistent HPV infection increased levels of PGE2 and CCL20, while decreased in pro-inflammatory cytokine IL-36. The changes in the cytokine environment inhibit the normal activation of LCs, which reduces the number of HPV-specific Th1 cells in the lesion and increases the differentiation of regulatory T cells from Th0 T cells. In addition, local polarization of T cells toward a Th2 phenotype reduces the Th1 population in the lesion. Lack of HPV-specific Th1 cells results in low levels of HPV-specific CD8+ cells that suppress the normal immune response to HPV resulting in the production of chemokines and cytokines that favor persistent HPV infection [12,19].

T Cells (TCs)

Regulatory T cells (Tregs) were found to be increased in cancer tissue. In microscopic culture tests, FOXP3+ Tregs isolated from AGWs tissue were found to suppress peripheral blood mononuclear cells (PBMCs) proliferation. The size of the warts correlated with the relative number of Tregs (<1% of all T cells in small warts and >6% in large warts. This suggests a high proportion of Tregs in the tissue of AGWs actively suppresses the HPV-specific immune response which allows the disease progression and recurrence [22].

In lesions induced by HPV types 6 and 11, Tregs constitute a small portion of CD4+ T cells, making up approximately 6% of genital warts. Nevertheless, studies indicate that in AGWs, around half of the CD4+ T cell population exhibit very

low levels of CD127, implying these cells are present but not functioning optimally. While a comprehensive analysis of Th1 and Th2 cells within the tissue CD4+ T cell subpopulation at HPV infection sites remains incomplete, markers of Th2 cell activity such as IL-10 and TGF-β are abundant in AGWs. Other evidence points to Th2 cell-like polarization in the adaptive immune response to HPV, both at the infection site and in peripheral blood. AGWs patients have shown an elevated Th2/Th1 cell ratio in PBMCs. Adding to this, CD8+ T cell activity has been observed. These cells are likely immature cytotoxic T cells, suggesting that Th2/Treg microenvironment in AGWs affects the maturation of CD8+ T cells. This, in turn, prevents HPV clearance or suppression of HPV-infected keratinocytes [15,19,21].

Treatments

The principle of treatment for CA is divided into two. First, traditional methods that are aggressive and destructive to lesions such as using cryotherapy, electrocauterization, chemical cautery, ablative laser, and surgical excision modalities. Second, using immunotherapy modalities (topical, oral or systemic) that aim to stimulate the immune system to eliminate the virus and reduce the activity and development of the virus [2].

The choice of immunotherapy treatment depends on various factors like the patient's immune status, age, medical history, and lesion characteristics. Immunotherapy is recommended for patients with extensive or treatment-resistant CA due to its ability to treat such cases systemically. Commonly used immunomodulator regimens include antigen skin tests, interferon-α2b (IFN-α2b), and topical imiquimod agents. For instance, imiquimod can increase cytokines like Interleukin 6 (IL-6), IL-1, TNF- and IFN-, which are involved in CA development [2].

In addition to using topical and systemic regimens, an intralesional immunotherapy approach using various antigens such as MMR vaccination, *Trichophyton* skin test antigen and *Candida* extract, *Mycobacterium w* (MWV) and *Bacille Calmette-Guérin* (BCG) vaccines is also an option for CA treatment. Vaccination shows promise in treating CA and preventing cervical cancer by stimulating the immune system against the HPV type associated with CA [7,19,23–25] .

The Asian Guidelines for Condyloma Acuminatum 2022 suggest selecting therapy based on lesions number, size, and treatment efficacy. The principle of drug administration is divided into two, namely administered providers and administered patients.

Administered providers

- Therapy Photodynamic

Aminolaevulinic acid-mediated photodynamic therapy (ALA-PDT) is an effective technique in the treatment of CA. ALA-PDT is selectively destroy subclinical virus-shedding areas and activating specific immune cells in skin lesions. There was a significant difference in HPV viral load between pre- and post- therapy (one-three cycles) of ALA-PDT treatment in patients with urethral CA. All patients achieved complete clinical remission after the last session of ALA-PDT. The cervical condylomas lesions also showed significant improvement with a low recurrence rate. Pain was observed with a visual analogue scale (VAS) pain score with mean 6.96 ± 1.41 points [26].

- Lasers

Several laser modalities have been widely used in the treatment of AGWs, namely CO_2 Laser, pulsed-dye, Argon, Holmium, and Nd:YAG. Single dose of CO_2 laser is effective for vulva CA. The Nd:YAG and Thulium lasers have been used for external and urethral CA in 115 patients with complete clearance. However, 34% of patients experienced recurrence. In cases of recurrent Buschke Lowenstein tumor, CO_2 laser can achieve complete remission. The coagulation diode laser resulted in a 73% cure rate (33/45 patients) of small to large AGWs with maximum of two sessions. In a retrospective study, the Holmium laser had the highest clearance rate (92.2%) and lowest recurrence rate (14.3%) compared to cryotherapy, surgery, and podophyllin ($p = 0.001$) in the treatment of genital warts. Treatment with Holmium: YAG laser was effective in 57/60 (95%) patients with urethral warts. At a median follow-up of 26 months, recurrence occurred in 8 patients (13.3%). It is important to note that the smoke from laser treatment contains infectious particles so patient must wear masks and inhalers [27–31].

In a retrospective study of 242 women who were treated with a CO_2 laser in 2006-2007, the median time to relapse was 14.6 weeks. Systematic follow-up for a median of 3.1 years revealed at least one relapse in 68 (28.1%) of the 242 women. Women with multifocal genital warts had a 2.9 times increased risk of recurrence compared with women with unifocal lesions ($p = 0.01$). Holmium: YAG laser with ALA-PDT significantly reduced wart recurrence rate (17.6%) compared to CO_2 laser with ALA-PDT (55%). Most of the warts (88.23%) were removed after a Holmium: YAG laser pre-treatment

session. The average number of laser sessions needed to clear all warts was 1.94 in the Holmium: YAG laser plus ALA-PDT group [32,33].

- Surgical Excision

Surgical excision is considered the first choice of treatment for large stemmed AGWs. Most patients can be treated under local anesthesia using 1-2% lidocaine. The clearance rate for surgical excision is 89-93% with a recurrence rate of 18-65%. Surgical excision is probably the most effective treatment for reducing the risk of recurrence after achieving complete clearance [34].

- Electrosurgery

Electrosurgery uses high-frequency electric currents to destroy genital warts and requires local anesthesia. Similar to lasers, the vapors from electrosurgery contain infectious particles and therefore a precautionary protocol must be followed. Clinical studies have shown a clearance rate of 35-94%. At one year after treatment, a cumulative recurrence rate of 8% was observed in electrosurgical excision of anal CA in HIV-infected men [34].

- Cryotherapy

Cryotherapy mechanism of action is crystallizing the cell cytosol, resulting in cell necrosis and then activating the immune system. Cryotherapy has a clearance rate of 46-96% with a recurrence rate of 18-39%. Cryotherapy was carried out every week for 12 weeks. Cryotherapy is a cheap and simple therapeutic modality without serious side effects and considered safe for pregnant women. Then, cryotherapy also uses for patient with externally accessible urethral CA. The average number of sessions needed to clear clinically proven urethral CA without complications such as urethral obstruction is 5. Mild side effects such as blistering, local necrosis, scarring, and hypopigmentation may occur. The effectiveness of cryotherapy didn't appear to be significantly different from trichloroacetic acid, podophyllin, or imiquimod [35].

- Trichloroacetic acid (TCA)

Trichloroacetic acid (TCA) may lead to the devastating chemical burns of genital warts. TCA is used in concentrations of 33-50% three times a week or 80-90% once a week and can be given until the warts are gone. TCA is best suited for small acuminata or papular warts. Clinical studies have reported a clearance rate of 70-100%. Common side effects include local discomfort, burning, and ulceration. TCAs can be used safely during pregnancy [36].

- Immunotherapy

Immunotherapy is a treatment using an antigenic substance to stimulate or suppress the immune system to help fighting cancer cells, infections, and other diseases. Some types of immunotherapies only target certain cells of the immune system. Others affect the immune system in general. Types of immunotherapies include the use of cytokines, vaccines, and some monoclonal antibodies [7,8].

Intralesional antigen immunotherapy has been used for the treatment of genital warts. Induction of delayed-type hypersensitivity influences the regression of warts in AGWs. The use of combination therapy using immunotherapy and conventional destructive therapy is reported to reduce the recurrence rate by 30%. In a randomized controlled trial of 89 patients, the intralesional *Mycobacterium w* (Mw, new nomenclature is *Mycobacterium indicus pranii* or (MIP) vaccine showed the same efficacy and safety as 5% imiquimod cream, with a complete clearance rate of 66.7% of patients and the average reduction in the size of the warts was 83.23% [34].

The MMR vaccine is a safe and effective treatment for AGWs. The mean response of 42.4% was observed in the first three weeks after administration of the MMR vaccine, which increased to 75.8% after the second vaccine at six weeks and nearly 98% after the last vaccine at nine weeks [37].

- Podophyllin

Podophyllin 20% topical is used once a week for up to eight weeks. Podophyllin is an antimitotic and antiproliferative agent. Local side effects of edema, inflammation, and erosion may occur. The use of podophyllin is contraindicated in pregnancy. However, a recent analysis of 9229 pregnancies from January 1997 to December 2016 showed that podophyllotoxin didn't appear to be associated with an increased risk of adverse events to the fetus during pregnancy and is probably safe for use during pregnancy [38].

In 27 patients with external genital warts found that the combination of one or two cryotherapy sessions with podophyllin solution 25% as a cytotoxic agent, and post-ablation immunomodulation with 15% topical sine catechin ointment resulted in a clearance rate of 96.3%. The recurrence rate was 7.4% after six months of follow-up [39].

Patient administered

- Imiquimod 5 %

Imiquimod 5% cream is a topical immunomodulatory group, which has antiviral and anti-tumor properties by inducing the production of cytokines (interleukins, interferons, TNF-α). Imiquimod is recommended for AGWs. Imiquimod 5% is used three times per week until the warts are completely removed with maximum use of 16 weeks. In terms of complete clearance, imiquimod 5% cream has more effective compared to imiquimod 1%. Imiquimod 3.75% cream, which is approved in the US and Canada, is as effective as imiquimod 5% cream when used daily for 8 weeks with improve tolerance, reduce treatment duration, and minimal side effects [40–42].

Imiquimod 5% cream has side effects in the form of erythematous lesions and erosions which are caused by discontinuation of treatment in 40% of AGWs patients. Contraindication to the use of imiquimod 5% cream is the location of the warts which are in the area of the urethra, cervix, anus, and rectum. In a recent study, imiquimod 5% cream applied to intraanal warts was equally effective at 16 weeks. A retrospective study of 60 patients with AGWs demonstrated that the recurrence rate during long-term follow-up (up to 7 years) was lower for patients with a complete response to imiquimod 5% monotherapy (15%), or with surgical removal of remaining warts after imiquimod 5% (20%), compared with monotherapy using surgical techniques alone (65%) [36].

Imiquimod (ImiQ) is a potent immunomodulatory drug that acts as an agonist of Toll-like receptor 7 (TLR-7) which induces activation of the innate immune system. Toll-like receptor is one of the most important immunological pathways in inducing antiviral and anti-tumor responses. One of pathways is triggering the formation of interferons (IFNs). The impaired function of TLR leads to the increase the severity of clinical manifestations of viral infection [43].

ImiQ interacts primarily with TLR7 and TLR8 as a receptor agonist and also promotes TLR7 expression. It then activates the NF-κB signaling pathway, which is responsible for the production of pro-inflammatory cytokines, such as IFN-α, TNF-α, IL-1, IL-6, IL-8, and IL-12, which ultimately promotes a helper T cell immune response (Th1 type). Differentiation of T cells into Th1 subtypes is driven by the production of IL-12 and IFN-γ. The Th1 effector cytokines include IFN-γ, IL-2, and antitumor TNF-β enhance cytotoxic CD8+ T cell proliferation, while amplifying cell-mediated responses against intracellular pathogens, including viruses. In addition, ImiQ through binding to TLR 7 also has another role by inducing the activity of DC in triggering a pro-inflammatory response. What is interesting is that ImiQ can activate the caspase pathway which plays a role in inducing apoptosis of tumor cells in CA [44,45].

- Podophyllotoxin

Podophyllotoxin inhibit the proliferation of keratinocytes in the epidermis and proliferation of HPV-infected cells. Podophyllotoxin is used twice daily for 3 consecutive days each week until the warts have completely disappeared with maximum duration is 4 weeks. The clearance rate for podophyllotoxin ranges from 45-94%, with common side effects including pain, itching, burning sensation, erosion, and inflammation. One randomized control trial study compared the effectiveness of podophyllotoxin 0.5% solution applied alone and podophyllotoxin 0.15% cream, compared to clinics applying podophyllin 25% in treating AGWs. Results showed complete clearance was seen at 75%, 64.5 % and 53.1% of the patients respectively. This suggests that the use of podophyllotoxin 0.5% is more effective in AGWs [34,35].

The combination of podophyllotoxin and cryotherapy showed significantly higher efficacy compared to podophyllotoxin monotherapy after 6 weeks of treatment in genital warts in men, with significantly lower rates of recurrence and appearance of new warts than cryotherapy at 6 weeks. Several systematic review and meta-analysis stated that the use of podophyllotoxin 0.5% solution is more effective than the use of imiquimod 5% cream to achieve complete clearance at the end of treatment. Moreover, podophyllotoxin was found to be more effective than imiquimod for AGWs. In patients with dry and keratinized lesions, the complete clearance rates were 7.6% for imiquimod and 27.9% for podophyllotoxin [34,46].

- Sinecatechins and polyphenon E 10% ointment

Sinecatechin is extracted from leaves of the *Camellia sinensis* which contains the active ingredient epigallocatechingallate (EGCG; Polyphenon E). Sinecatechins have anti-viral effect in HPV infection by stimulating the formation of both innate and adaptive immunity as well as anti-carcinogenic activity. Sinecatechins was used thrice

daily until complete clearance was obtained with maximum of 16 weeks. Polyphenon E 10% ointment is generally well tolerated in adults with external and perianal genital warts. Mild local side effects when using Polyphenon E 10% ointment such as redness, burning, pain, itching and edema. Sinecatechins have a complete clearance value of 40-81% with a recurrence rate of 7-11%. In a multivariate study, use of 10% sinecatechins ointment as adjuvant therapy after ablative laser treatment with CO_2 laser was associated with lower recurrence rates of external genital warts in the short term compared with use of CO_2 laser monotherapy [36].

- Cidofovir

Cidofovir is a nucleotide analogue of deoxycytidine monophosphate. It is selectively competitive in inhibiting viral DNA polymerase. Topical cidofovir has been used successfully in the management of CA and other HPV-mediated diseases, especially in immunocompromised patients and in patients with AGWs [47–50].

- 5-Fluorouracil (5-FU)

5-Fluorouracil (5-FU) is a pyrimidine anti-metabolite that functions as an anti-neoplastic agent by blocking DNA synthesis. Daily application of 5-FU 5% cream has been reported to be effective on external genital and perianal warts. A randomized control trial including 72 patients showed no significant difference in efficacy between administration of 5-FU 1% cream and TCA 90% or between 5-FU 5% cream and TCA 90% after 7 weeks of treatment. The difference is only found in mild side effects in the administration of 5-FU 1% and 5% cream compared to 90% TCA [51].

- Interferon

In HPV infection, interferon is used as an antiviral and anti-proliferative agent. In addition, interferon can also stimulate the formation of immune system. Interferons can be administered either by the intralesional (more effective) or systemic (subcutaneous or intramuscular). A study found the effectiveness of systemic interferon administration as adjuvant therapy after ablative treatment was inconsistent. In that study, comparing the placebo, interferon alpha, beta, and gamma groups as adjuvant therapy, there were no significant differences in terms of complete clearance in the short or long term, or in relation to short- or long- term recurrence [52–54].

Other treatment modalities have been developed, such as low-dose oral cyclophosphamide therapy, systemic interleukin 2 and topical cidofovir, oral retinoids and intramuscular interferon-γ therapy, combined surgery with radiofrequency method and oral acitretin, 32P radionuclide application device for the treatment of CA in the rectum, oral pidotimod plus vitamin C after laser, chemoradiotherapy for large Buschke-Lowenstein tumors, topical nitric-zinc complex, and topical sodium nitrate with citric acid [55].

Table 1 displays a summary of CA treatment efficacy. The results are displayed based on the clearance rate and recurrence rate. Choice of therapy based on the type of lesion. In few and small lesion, the choices are Imiquimod 5% cream, 5-Fluorouracil, or Poliphenone ointment, in little and wide lesion, the choices are surgery, cryotherapy, or podophyllotoxin, in multiple lesions, the choices are immunotherapy, PDR, laser, or combination therapy [34].

Table 1 Treatment Efficacy of Condyloma Acuminata [34].

Modality Therapy	Clearance Rate (%)	Recurrence Rate (%)
Photodynamic Therapy	76-100	10-14
Laser	23-95	2.5-77
Surgery	89-93	18-65
Electrosurgery	35-94	20-25
Cryotherapy	46-96	18-39
TCA	70-100	18-36
Immunotherapy	66-98	No recurrence after 3 months
Podophyllin	42-46	46-60
Imiquimod 5%	35-75	6
Podophyllotoxin	45-94	11-100

Sinecatechins	40-81	7-12
5-Fluorouracil	10-50	50
Interferons	17-67	9-69

3.2. Immunotherapy

3.2.1. Definition

Immunotherapy is a treatment using an antigenic substance to stimulate or suppress the immune system to help fighting cancer cells, infections, and other diseases. Some types of immunotherapies only target certain cells of the immune system. Others affect the immune system in general. Types of immunotherapies include the use of cytokines, vaccines, and some monoclonal antibodies [7,8].

3.2.2. Classification

Immunotherapy modalities that can be given to patients with CA are divided into 3 administration routes: topical, systemic, and intralesional immunotherapy (Table 2).

Table 2 Immunotherapy in Condyloma Acuminata.

Agent	**Dose**	**Administration**
Topical Agent		
Imiquimod	5% Cream	3 times a week for 16 weeks
BCG	Mixed in NaCl 0.9% or sour salicylic 1 : 1	1 time 2 hours/week for 6-12 weeks
Intralesional Agent		
BCG vaccine	0.1-0.5 ml	Week 1,3,5,7,9 (5 doses)
PPD	0.1 ml	Every week for 12 weeks
Trichophyton antigens	0.3 ml	Every 3 weeks (5 doses)
Interferon alpha 2B	1-2 million units	3 times a week for 3 weeks
MMR vaccine	0.3-0.5 ml	Per week (5 doses)
Candida extracts	0.1-0.3 ml	Weeks 1 and 3 (2 doses)
Systemic interferon		

3.2.3. Topical Immunotherapy

There are numerous theories regarding the mechanism of immunotherapy for the CA treatment. The main mechanism of action focuses on antigenic competition using immunomodulators to induce allergic contact dermatitis in the given area through a delayed-type hypersensitivity reaction. The antigen acts as a hapten, which binds to an endogenous protein, forming an antigen complex. This complex is detected by APC, and activates antigen-specific T cells leading to dermatitis. At the onset of an allergic reaction, suppressor T cells are generated. The T cells that primarily express CD8+ and CD1a+, act against autonomous CD4+ and CD8+ T-cell populations, and interfere APC migration in affected keratinocyte cells. Decreased CD4+ T cells and increased CD8+ T cells in areas treated with topical immunotherapy agents resulted in a change in the perifollicular lymphocyte pattern, with a decrease in the ratio of CD4+ to CD8+ T cells from 4:1 to 1:1. MHC class I and II expression also decreased after treatment with topical immunotherapy. Topical immunotherapy can induce the expression of immunoregulatory molecules, such as cytotoxic T-lymphocyte associated protein 4, FOX P3, and indoleamine 2,3-dioxygenase. Therefore, increased local immunoregulation may promote wart regression in CA. However, all these T-cell-mediated mechanisms should be modulated by counteracting inflammatory cytokines and growth factors, so that the ratio of cytokines produced by Th1 can be increased [56–58].

3.2.4. Systemic Immunotherapy

In order to treat genital warts, therapy should not only treat the clinical manifestations but also need to build the immune system against HPV infection. This is because of no specific antiviral for HPV and the variable effectiveness of the available treatment modalities. Although the mechanism is not fully understood, systemic therapy, especially parenteral administration, is thought to be effective in inducing systemic T-cell-mediated immune responses. Cytokines released from Th1 cells such as IL-2 and IFN-γ were mostly increased in response to injection [59,60].

3.2.5. Intralesional Immunotherapy

Intralesional immunotherapy regimens that have been extensively studied are the use of vaccines and cytokines. Various vaccines have been studied for their effectiveness in terms of eliminating warts and their ability to prevent recurrence of wart lesions. Several antigens that have been studied therapy for genital warts include *Candida albicans*, measles, mumps and rubella (MMR); *Trichophyton*, and Tuberculin/ Purified Protein Derivate (PPD), *Mycobacterium w,* and *Bacille Calmette-Guerin* (BCG)[8,61].

Vaccines induce effector mechanisms (cells or molecules) that are able to rapidly control the replication of the pathogenic agent or inactivate its toxic components. Vaccine-induced immune effectors (Table 3) are basically antibodies produced by B lymphocytes, where these antibodies are able to bind specifically to a toxin or pathogen. Other potential effectors are cytotoxic CD8+ T lymphocytes which can limit the spread of infectious agents by recognizing and killing infected cells or secreting specific antiviral cytokines and CD4+ T-helper (Th) lymphocytes. These Th cells may contribute to protection through the production of cytokines and through the formation and maintenance of responsive CD8+ T lymphocytes and B lymphocytes [62].

Effector CD4+ Th cells initially divide into T-helper 1 (Th1) or T-helper 2 (Th2) subsets. These two cell types are differentiated based on the main cytokine (interferon-γ or interleukin IL-4). Th cells have increasingly been shown to include a large number of subsets with distinct cytokine-producing and homing capacities. A recent clinical study identified that vaccine-induced CD4+ Th cells are follicular T-helpers (Th cells) which are specifically equipped and located in lymph nodes to induce the activation and differentiation of B cells which secrete antibodies and directly control antibody responses [62].

Table 3 Effector Mechanisms Triggered by Vaccines.

Antibodies prevent or reduce infections by clearing extracellular pathogens through:
Binding to the enzymatic active sites of toxins or preventing their diffusion
Neutralizing viral replication (e.g., preventing viral binding and entry into cells)
Promoting opsonophagocytosis of extracellular bacteria (i.e., enhancing their clearance by macrophages and neutrophils)
Activating the complement cascade
$CD8^+$ T cells do not prevent infection but reduce, control, and clear intracellular pathogens by:
Directly killing infected cells (release of perforin, granzyme, etc.)
Indirectly killing infected cells through antimicrobial cytokine release
$CD4^+$ T cells do not prevent infection but participate in the reduction, control, and clearance of extracellular and intracellular pathogens by their homing and cytokine-production capacities. Their main subsets include:
Follicular T-helper (Tfh) cells producing mainly interleukin (IL)-21 and providing B-cell help
T-helper 1 (Th1) effector cells producing interferon (IFN)-γ, tumor necrosis factor (TNF)-α/TNF-β, IL-2, and mainly involved in protection against intracellular pathogens (viruses, *Mycobacterium tuberculosis*)
Th2 effector cells producing IL-4, IL-5, IL-13, and responding to extracellular pathogens (bacteria and helminths)
Th9 effector cells producing IL-9 and also responding to extracellular pathogens
Th17 effector cells producing IL-17, IL-22, and IL-26 and contributing to mucosal defense (*Streptococcus pneumoniae*, *Bordetella pertussis*, *Mycobacterium tuberculosis*)

Another subset of T lymphocytes that is no less important is T-helper 17 (Th17) cells which function to fight extracellular bacteria that infect the skin and mucosa, recruit neutrophils, and trigger local inflammation. Regulatory T cells (Tregs) are very important in maintaining immune tolerance. Most antigens and vaccines trigger B and T cell

responses, which supporting antibody production (humoral immunity) and T cell responses (cellular immunity) of vaccination. In addition, CD4+ T cells are required for most antibody response, whereas antibodies exert a significant influence on the response of T cells to intracellular pathogens [63].

The pharmacodynamic effects of intralesional injection have not been described. It is expected to induce a delayed type hypersensitivity response to warts tissue, and many antigens are injected. Th1 cytokines activate NK cells and cytotoxic T cells. Those cells are associated with this type of hypersensitive response. The intralesional immunotherapy will have a significant effect on the wart tissue and other tissues around lesion [8,64,65].

Peripheral mononuclear cell proliferation tests were significant in response to intralesional immunotherapy compared to those that did not respond. Several cytokines, including IL-2, IL-4, IL-5, IL-8, IL-12, TNF-α, and IFN-γ are released during intralesional immunotherapy, thereby eliciting a strong immune response. Intralesional injection may also play a role in centralizing the local immune response. However, some argue that injection trauma alone may be sufficient to induce an adequate immune response in immunocompetent patients [66].

Current researches of immunotherapy administration using intralesional antigens (autogenous vaccine, *Candida* antigen, mumps antigen, *Trichophyton* skin test antigen, and tuberculin) or vaccines (BCG and MMR vaccines), *Mycobacterium w* vaccine) have been tried to treat warts. Intralesional immunotherapy significantly recognize viral antigens that induce a delayed-type hypersensitivity response. Hypersensitivity reactions not only to antigens but also to HPV. As a result, the stimulated immune response eliminates all lesions in other parts of the body and can reduce the recurrence rate in cases of CA [7,65].

In immunocompetent patients, Th1 (CD4+) cells secrete a variety of cytokines, the most important of which are IFN-γ, IL-2, and IL-12. IL-2 stimulate killer T cell maturation and enhances natural killer cell cytotoxicity. A critical function of killer T cells is cytotoxicity, which means recognizing and destroying virus-infected cells. Several observations have shown that a predominant CD4 immune reaction in HPV-infected tissues is associated with a high probability of eliminating HPV infection[7,8].

In conclusion, the mode of action of intralesional immunotherapy is fundamentally related to its ability to induce robust cell-mediated immune reactions to alter the balance between Th1 and Th2 responses ultimately leading to HPV eradication.

Bacille Calmette-Guerin (BCG)

Bacille Calmette-Guerin (BCG) is a type of vaccine containing live attenuated *Mycobacterium bovis*. This vaccine is one of the vaccines that has been widely used both against tuberculosis (TB) and as an immunotherapy modality for various diseases, especially those related to tumors/cancer [23].

The pathogenesis of CA cell mediated immunity (CMI) is an immune response that is very important in the elimination process of warts, this is what is used as the basis of immunotherapy. *Bacille Calmette-Guerin* (BCG) has the ability to stimulate the proliferation of macrophages, T and B lymphocytes, and NK cells, and increase the production of IL-1 [7]. Immunotherapy both topical and intralesional have been shown to be associated with the release of various cytokines such as IL-2, IL. -4, IL-5, IL-8, IFN-γ, and TNF-α, which stimulate a strong immune response against HPV [8,65,67]. It has also been reported that antigen injection is associated with peripheral blood mononuclear cell proliferation that drives the respons of Th1 cytokines which in turn activate cytotoxic T cells and NK cells to eliminate HPV-infected cells [8].

The administration of intralesional BCG vaccine is 0.1-0.5 ml in a week as many as 5 doses. In a study conducted by Deepika *et al.* in 2016 stated that in 7 cases of AGWs who were given a single dose of BCG immunotherapy, 85.7% of warts experienced regression and 28.6% experienced complete resolution [25]. Contraindications (Table 4) vary between countries and often reflect different health care facilities. In the United States, the BCG vaccine is contraindicated in immunocompromised persons, including HIV patients, congenital immunodeficiency, leukemia, lymphoma, malignancy, and those who are pregnant. Special monitoring is needed when giving BCG to people at high risk of HIV infection [10]. Side effects of intralesional BCG immunotherapy include local side effects including local edema and regional lymphadenopathy. However, it is possible to find abscesses and multiple lymphadenitis [10,25].

Table 4 Indications and Contraindications of BCG Vaccine Intralesional Administration [68].

Who should have BCG	Who should not have BCG
*Neonates who have a family history of Tuberculosis	*People who have been vaccinated with in the las five years. BCG, and people with a history of TB
*Neonates, infants, and children below 16 years who born or whom their parent born in a country with an incidence of T.B > 40 per 100,000	*People with a positive TST (Mantoux)
*Contacts aged under 36 years of those with active respiratory TB	*People who have had a history of anaphylactic reaction to any of the substances used in the vaccine
*Healthcare workers and laboratory staff (irrespective of age) who have contact with patients	*Neonates in a household where a case of TB is suspected or confirmed
*New immigrants aged 16 - 35 years from Sub-Saharan Africa or a country with an incidence of TB > 500 per 100,000	*People who are seriously unwell or have a septic condition at the site of injection
	*Immunocompromised people
	*Pregnant women

Tuberculin Purified Protein Derivate (PPD)

Mycobacterium indicus pranii or *Mycobacterium w* is a fast growing non tubercular mycobacteria which induce a strong proinflammatory response when injected intralesional. There is a prominent delayed-type hypersensitivity response with increased Th1 cytokines such as IL2, IL4, IL6, and IFN-γ and activation of NK and cytotoxic T cells. The HPV-laden cells are caught in the crossfire leading to wart clearance both at the injection site and distally [69].

PPD injection is given in two ways either with an intradermal sensitizing dose or without a sensitizing dose. In the first method, a sensitizing dose of 0.1 ml is administered intradermal in the deltoid area followed by 2-4 intralesional injections per week in multiple warts (maximum 0.1 ml per injection) for up to 10 doses. After the sensitizing dose, direct intralesional injection was initiated. The responses varied with an average success rate of 54-93% for cutaneous warts and 89% for AGWs, and 86% prevented recurrences [68,70].

Side effects that can occur after administration of PPD vaccine intralesional immunotherapy are divided into mild and severe side effects, mild side effects in the form of reddish spots and induration found within 48-72 hours after injection. While the serious side effects are lymphadenitis, systemic anaphylactic reactions and foreign body reactions (Table 5) [68,71].

Table 5 Adverse Reaction to Intralesional PPD Vaccine Administration [68].

Nature of reaction	BCG	MWV	PPD
Mild	Papule at the injected site (2 - 4 weeks) Ulceration (1 - 2 months) Scar (2 -5 months)	Papule at the injected site, Induration, ulceration, scar formation.	Redness, Induration 48 - 72 hr
Severe	Local: abscess, keloid, suppuration 2 - 6 months. Systemic: Cutaneous lesions, osteitis, disseminated BCG, immune reconstitution syndrome	Local: abscess, adenitis Systemic: fever 2 days after intradermal injection, pain and paraesthesia distal to the injected site lasting for one week	Local: lymphadenitis Systemic: anaphylactic reaction, foreign body reaction

Measles, Mumps and Rubella (MMR) Vaccine

The vaccine is a freeze-dried preparation of live attenuated measles, mumps, and rubella virus which is available in a single dose vial of 0.5mL. In patients with genital warts, 0.5 mL of MMR vaccine diluted with water for injection is

injected intradermal into the largest single wart. Intralesional MMR vaccine can be given in doses of 0.1-0.5 ml which are given at 2-week intervals for a maximum of 5 doses. In a study conducted by Pushpinder *et al.* in 2019 stated that in 51 cases of AGWs who were given 5 doses of MMR immunotherapy, 98% of warts had regressed and 82.4% experienced complete clearance [72] .

The MMR and MMRV vaccines are not recommended in people with primary or acquired immune deficiencies (including AIDS or severe immunosuppression associated with HIV infection) or in people with leukemia, lymphoma, or other malignant neoplasms affecting the bone marrow or lymphatic system. This vaccine also should not be used in people under systemic immunosuppressive therapy, including corticosteroids at a dose of more than 2 mg/KgBW or more than 20 mg/day of prednisone, given for 2 weeks or longer [10,37].

The MMR vaccine should not be given to pregnant women or women who are planning a pregnancy. If the vaccine is given to a woman who is planning a pregnancy, it is advisable not to get pregnant for 28 days after vaccination. If the MMR vaccination is accidentally given during pregnancy, this is not an indication for termination of pregnancy [10]. Side effects that can occur after administration of intralesional immunotherapy using the MMR vaccine include flu-like syndrome, erythema at the injection site, and other reactions may appear such as fever, restlessness, lymphadenopathy, cough, diarrhea and conjunctivitis [10].

Candida albicans Extract

Candida albicans is the main pathogenic flora of the skin. The primary defense against *C. albicans* involves the delayed hypersensitivity immune system. Delayed hypersensitivity to *C. albicans* occurs in 60% to 78% of healthy adults. Therefore, intralesional injection of *C. albicans* extract into warts may be able to trigger the formation of a host cell immune response through the cell-mediated immunity (CMI) pathway leading to warts regression [73].

Several studies regarding immunotherapy using *Candida* immunotherapy (CI) stated that this modality can be given only if conventional therapy using cryotherapy or keratolytic agents fails, the number of warts is >3, mosaic warts, or intolerance to pain caused by other therapies. Preparation for CI is necessary to carry out a sensitivity test which conducted 15 minutes before the first CI treatment to identify the presence of a rapid type hypersensitivity reaction to *C. albicans*. The choice of injection site is based on the largest lesion (mother wart/MW) [74–76].

Immunotherapy treatment using the *C. albicans* skin test antigen (CAST) can be carried out in 3 ways: the first solution is 0.1 mL of CAST diluted with 0.1 mL of 1% plain lidocaine solution in MW. The second solution with 0.1 mL of pure CAST. Third solution with 0.1 mL of *C. albicans* allergen extract (CAE [1:1000]). The MW was injected intralesional, using a BD one-piece insulin syringe. The syringe is held parallel to the surface of the skin, and the needle is injected with the bevel facing up. Patients who use CI are instructed to wait 15 to 30 minutes after injection to screen for signs and symptoms of hypersensitivity that may occur. Patients then were instructed to discontinue all other wart treatments during therapy. In another study, a dose of 0.2 ml of CAST was injected using a 30 G needle. In order to reduce pain during injection, nitrogen liquid spray can be given for 2-3 seconds in the area to be treated [8,77].

Therapy can be discontinued if there is complete clearance of the CA lesions after the second dose. If there is a partial response after the third injection, then therapy can be continued until complete clearance is achieved. If there is no response after the third injection then the treatment is considered failed and discontinued. In a study conducted by Munoz *et al.* in 2015, the results showed that 70.9% of respondents achieved complete clearance, 34% responded to warts in other areas that did not receive CI injections. This study also stated that there were several side effects that could occur in patients who were given CI immunotherapy in the form of bullae, edema, desquamation, fever, and pain at the injection site [8,77,78].

The efficacy of single-agent intralesional immunotherapy varies. In CI showed 43-100% complete responses in 2-4 weeks, Mumps or CI showed 72-74% complete responses in 3-4 weeks. MMR showed 27-81% complete responses in 1-2 weeks, PPD showed 29-76% complete responses in 1-3 weeks, MWV showed 55-93% complete responses in 1-2 weeks, and BCG showed 100% complete responses in 2 weeks [79]. Side effects include flu-like symptoms, fever, myalgia, erythema, edema, pain during injection, blisters in injection site, and hypopigmentation [6,79].

Interferon alpha 2B

Interferon alpha (IFN-α) is a glycoprotein with antitumor, antiviral, and immunomodulatory activities, currently used extensively in the treatment of viral infections such as hepatitis B and C, CA, shingles, etc. [80,81]. After IFN-α and IFN-γ bind to their receptors, a specific tyrosine kinase (tyk2) is phosphorylated, along with other tyrosine kinases: Janus-activated kinase (JAK-1 and JAK-2). When activated tyrosine kinase induces the formation of protein subunits, the IFN-

stimulated gene factor (ISGF)-3 complex is guided to the nucleus, thereby establishing a DNA-binding complex specific for IFN-stimulated response element (ISRE). The formation of transduced signals includes IFNAR1, IFNAR2, JAK1, JAK2, STAT1, and STAT2. A similar sequence of events occurs when the IFN- γ receptor is activated, but the STAT-1 homodimer binds to a DNA element called a gamma-activated site (GAS). IFN-γ signaling events include the actions of several proteins: IFNGR1, IFNGR2, JAK1, JAK2, and STAT1 [82–84].

With major advances in proteomics and gene microarrays techniques, the IFN mechanisms of action are becoming easier to discern. Interferons exert their effects via binding to cell surface receptors and activating members of the JAK kinase family. Activated JAK kinases phosphorylate the STAT family transcription factors. The antitumor effect results from a direct action on the proliferation or antigenic composition of tumor cells, or from a modulatory effect on an immune effector cell population with tumor cell specificity. Interferons can affect cell proliferation or induce tumor cell differentiation. In addition, they can have indirect effects, such as modulation of the immune response and inhibition of tumor angiogenesis. Interferons regulate gene expression and modulate the expression of proteins on the cell surface. If there are any changes in gene expression can modulate cytokine receptors and other enzymes that control cell function. These changes can affect cell differentiation, proliferation rate, and apoptosis. All effects of IFN, whether direct or indirect, are the result of regulation of gene expression. IFN-α and IFN-β can act in all phases especially mitotic cells [83,84].

It was recently shown that the binding affinity of interferon to IFNAR1 and IFNAR2 receptors correlates with antiviral and antiproliferative effects, Tumor-associated macrophages can become tumoricidal under the influence of IFN, producing substances that can exert antiproliferative effects on tumor cells. Apoptosis is genetically regulated cell death. It is important in the control of many physiological events such as embryonic development and immune regulation for eliminating gene defects, i.e. avoiding uncontrolled cell proliferation with genotypic changes and disease, among them cancer, being an attractive mechanism for the antitumor action of IFNs. The molecular mechanisms that control apoptotic cell death can be enhanced through the management of CA using IFN alone, combination or adjuvant treatment. Mutations in p53, the first tumor suppressor gene found to be associated with apoptosis [85–87].

Immunomodulation and inhibition of angiogenesis are indirectly mediated by apoptosis in antitumor effect. With regard to immunomodulation, IFNs can have antitumor effects via increasing cytotoxic T cells, NK cells and DCs. Inhibition of angiogenesis may occur as a result of endothelial cell apoptosis which is important in inhibiting the formation of warts [86–89].

Intralesional alpha 2B interferon can be given a dose of 1-2 million IU which is given 3 times in a week for 3 weeks or the equivalent of 9 doses. In a study conducted by Noval *et al.* in 2013 stated that in 40 cases of AGWs who were given 9 doses of Interferon alpha 2B, 85% of warts experienced regression and 79% experienced complete clearance. Some of the side effects that can occur in patients who are given interferon alpha 2B immunotherapy include bullae, edema, desquamation, fever, and pain at the injection site, but this can still be tolerated [77].

4. Conclusion

Immunotherapy is a promising therapeutic modality in the management of CA. Current intralesional immunotherapy has proven effective in the management of CA, especially in recalcitrant CA. There are several advantages of intralesional immunotherapy compared to conventional therapy, such as simple application techniques, promising therapeutic effectiveness, high safety profile, cost-effectiveness, and no movement restrictions, scarring and pigmentation changes. In addition, intralesional techniques play an important role in reducing or even preventing recurrence after successful therapy. Although it is undeniable that intralesional immunotherapy has some limitation such as the lack of standardization in various aspects of intralesional immunotherapy which are the concentration and amount of antigen injected, number of treatment sessions, interval between sessions, follow-up period required to evaluate adequate recurrence rates, and side effect for the child. Children are seen from the pain effect caused by the injection, so it is better for children to prefer topical applications that don't cause pain.

Compliance with ethical standards

Disclosure of Conflict of interest

The authors assure that there is no conflict of interest with the publication of the manuscript or an institution or product mentioned in the manuscript and/or important for the result of the presented study.

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