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Management of Large Size Wartsasia

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Abstract

Large warts are difficult to treat as they need repeated treatment for a longer duration compared to small warts. They are associated with higher viral load and significantly more cell mediated immune suppression. There are no standardized guidelines for management of large warts. Intralesional immunotherapy like Candida antigen, Cadi-05 and antiviral like Cidofovir are found to be useful in achieving complete remission as a monotherapy and can be tried as first line treatment. Quadrilateral HPV vaccine is also useful in achieving complete remission as a first line therapy. Combination of ablation therapy and topical therapy may be useful in quicker resolution of mass and achieving complete resolution.

Keywords: Wart; Large wart; Immunomodulators; Combination therapy; Immune profile; Cidofovir; Immunosuppressant; Surgery

Abbreviations: HPV: Human Papilloma Virus (HPV), HIV: Human Immunodeficiency Virus (HIV), PD-1: Programmed Cell Death Protein 1, RR: Risk Ratio, IFN: Interferon, CI: Confidence Interval, PDL: Pulsed Dye Lasers, NSCLC: Non-Small Cell Lung Cancer, PDT: Photo Dynamic Therapy (PDT), TNF: Tumor Necrosis Factor

Introduction

Warts are caused by the Human Papilloma Virus (HPV) mainly by low risk HPV. Human papilloma viruses (HPVs) essentially induce skin and mucosal epithelial lesions [1-3]. Immune compromised individuals are more prone to HPV infection. HPV infection is almost six times more common in patients with human immunodeficiency virus (HIV) [4,5]. Low-risk HPV types behaving more aggressively in immune compromised patients [4]. Each HPV type is typically associated with infections of specific areas (location) on the body and induces distinct histological lesion [6-9].

Common warts (*verruca vulgaris*)

HPV types 2 and 4 (most common); also types 1, 3, 26, 29, and 57 and others. Clinically they appear as slightly raised rough surface epithelial proliferations. They are most often seen on hands but can grow anywhere on the body.

Flat warts (verruca plana)

HPV types 3, 10, 28, 38, and 49. Clinically they appear as a small (1-2mm), smooth flattened, skin colored wart [10]. They can occur in large numbers. They are most common on the face, neck, hands, wrists and lower part of legs but never in the soles of hands. Very rarely they assume large size. They usually regress and get cleared on their own within 2 months with resolution of infection.

Plantar warts (*verruca plantaris*) (myrmecia)

HPV type 1 (most common) also types 2, 3, 4, 27, 28, 58, 66 and others. A plantar wart is a wart occurring on the bottom of the foot or toes [11], usually on pressure points on the soles of the feet.

Anogenital warts (condylomata, acuminata or venereal warts)

HPV types 6, 11(most common), 16, 18, 42, 44 and also others; a wart that occurs on the genitalia, anal region. They can be confluent or large size.

Butcher's warts of the hands and fingers (HPV 7)

Butcher's wart is a cutaneous (skin) condition with a prevalence of 8.5% to 23.8% among butchers and other meat-handling professions [12,13].

Natural Course and Immune Profile

Like majority of viral diseases almost 75% of warts regress spontaneously [8] with 30% regressing within four months [14]. Rest persist, progress with increase in no. and size. Immune response to HPV infection is responsible for spontaneous regression of warts. Spontaneously regressing warts have epidermal and dermal influx of CD^{4+} activated memory lymphocytes, low level of Il-10, high level of Interferon and Th1 response [4,15,16]. CD^{4+ve} lymphocytes within the wart

stoma and the surface epithelium [5] along with macrophage predominate [2,17] in regressing wart. There is a significant change in the ratio of CD^{4+} to CD^{8+} cells [17].

The failure to develop effective cell-mediated immunity to clear or control infection is associated with systemic or local immune dysfunction or defects [18]. There is a down regulation of major histocompatibility complex I and II in local lesions, alternation of the ratio of CD^{4+} and CD^{8+} T lymphocytes, decrease in expression of tumor necrosis factor (TNF) α, GM CSF, interleukin (IL) 1α and IL 1β, increased expression of IL 10, the dysfunction and decreased number of langerhans cells and expression defects of co stimulatory molecules [4,8]. There is a marked increase in Tregs expressing expression Foxp3, TGF β1, IL 10, CTLA4, GITR and PD 1 [18,19]. Increase Tregs are induced by epithelial cell expressing E7 protein [20]. NK cell activity is suppressed due to reduction in expression of NKG2D and NKp46 [18]. There is a decreased ratio of Th1/Th2 and Tc1/Tc2 [19,21]. There is decrease in Th1 cytokine (IL 2, IL 12 and IFN γ) and increase in Th2 cytokines (IL 4 and IL 10) [18,21]. Persisting warts can be divided into small (<5mm) medium (5 to 8mm) or large (>8mm) as per size. Intralesional cell mediated immune suppression is proportionate to size of wart. FoxP3 expressing Treg cells (immune suppressive cells) are highest in large wart and absent in small warts [22]. This cell seems to be responsible for decreased expression of IFN and IL-2 and increased expression of IL-10 and TGF-beta in large wart compared to small warts [22].

Response to Therapy and Immune Changes

Like spontaneous regression, increased cell mediated immune response of Th1 type with infiltration of immune cells [16,23-34] are important for treatment induced regression of warts. There is no change in immune profile of non-responders/ per sisters. In spite of clearance with therapy, recurrence is seen in large no (25%-67%) within three months. Reactivation at the site of previous infection, and persistence following are believed to be responsible for recurrence [8]. Cell mediated immune suppression as revealed by decrease in Th1 cytokine and CD4 T cells, suppression of delayed type hypersensitivity and increase in 12. Programmed cell death protein 1(PD-1) expressing T cells is found in recurrent warts [24, 35,36]. Predominant Th1 or mixed Th1/Th2 cytokine profile is seen in non- recurrent warts [24].

Therapeutic Options

Warts are superficial lesions harboring virus. One of the options is to get rid of tissues harboring viruses and include surgical removal, cryotherapy, laser therapy, pulsed laser therapy etc. as provider administered or office procedures. Uses of topical medications to be self-administered for removal of tissues include salicylic acid, podop etc. The other options include use of immune modulators to correct immune dysfunction for persistence of infection. Immunomodulators like imiquimod, Sinecatechins are topical medications while isotretinoin, cyclophosphamide are oral medication for self-administrations. Immunomodulators can be administered intralesional as office procedure. Intralesional immune modulators include allergens (antigen) like candida used for determining dermal hypersensitivity, CADI-05. Quadrilateral HPV vaccine approved for prevention of HPV vaccine is also found useful in treatment of warts. Cidofovir is antiviral agent active against cytomegalovirus infection. It is found useful in management of warts when administered topically or intralesional.

With multiple options available, treatment in a given patient is determined by number, size, and location of lesions [2] and preference of a physician as well as patients. Large warts are difficult to treat due to their size and associated cell mediated immune suppression. The management may require repeated treatments over a prolonged time period [37]. Their size makes it difficult for topical therapies to achieve desired tissue concentrations. First-line treatment is not always successful in achieving complete clearance [37]. Current evidence is also not adequate to suggest best option for treatment of large warts [37]. CO2 laser therapy, are generally associated with higher probabilities of complete clearance at the end of treatment for large warts [37]. Very large wart lesions, including Buschke-Löwenstein tumors, can be considered for surgical treatment [37]. However surgical treatment is generally not recommended as first line therapy due to scar formation following it and or need for anesthesia and another specialist [37]. Review of literature suggests that some of the immunotherapeutic agents are useful in management of large wart as a monotherapy and include Candida antigen, CADI-05, Quadrivalent HPV vaccine. Of these, CADI-05 is found to have antiviral properties and viral load, as well. Cidofovir is also described as useful in management of large warts as a monotherapy.

Compared to smaller warts, large warts are associated with increased viral load and cell mediated immune suppression and so targeting both may be useful. This can be achieved by combining two or more therapeutic options. For decreasing viral load by removing tissue, cryotherapy, surgical excision/ debulking, Laser therapy, photodynamic therapy can be used. The advantage of these procedures is immediate decrease in viral load. Disadvantages include need for multiple treatment session for complete cure, high recurrence rate and scar formation. Cidofovir, an antiviral agent, can be administered topically or intralesional. For improving immune profile, Imiquimod, Sinecatechins, CADI-05, Quadrilateral HPV vaccine, cyclophosphamide are found useful. . Combination therapies described to be useful in management of large warts include ablative procedure like cryotherapy/ laser therapy with topical immunotherapy like Imiquimod, Sinecatechins. Ablative procedure is also combined with isotretinoin and cyclophosphamide. Combination of ablative procedure with antiviral cidofovir is also found useful.

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Candida Antigen

Sensitivity testing by intradermal injection of an antigen (allergen) is a measure of delayed cell mediated immunity. Candida antigen injection in patients sensitive to Candida antigen is associated with complete resolution of warts in (54% -76%] of patients [38-43]. Clearance of distant untreated warts is seen in (57% -78%) of patients [38-43]. Candida antigen is useful irrespective of size (small or large) or no. of warts [38-43]. It is effective in newly diagnosed warts as well as warts resistant to standard treatment in immune compromised individuals also [38-45]. Intradermal injection of Candida antigen up regulates the cell-mediated immune response, augmenting the overall clearance of the HPV [46].

The baseline immune status as determined by IFN-gamma levels seems to predict outcome with higher levels seen in responders [41]. The response is associated with HPV L1 peptide specific cell mediated immune response [47].

The recommended dosing regimen is 0.1-0.3mL of Candida antigen injected intradermally into the largest lesion every two to three weeks until complete clearance of the wart or a maximum of three to five treatments [39,41,42]. Side effects include mild erythema and pain at the site of injection. There is one reported case of vitiligo and another case of painful, purple discoloration at the site of injection [40,48,49]. Like Candia antigen, other skin sensitizing agents used include mumps, trichophyton and tuberculin [50].

CADI-05

CADI-05 is a potent TLR 2 agonist which induces pure potent systemic Th1 response [51]. It induces prominent delayed hypersensitivity response by increasing innate as well as adaptive immune response [52-54]. Unlike other immunotherapy it decreases immunosuppressive T cells like Treg also [52,56]. Effect on immune suppression is significant and manifests as improved CD4 count in HIV positive individuals [55]. The systemic immune response generated is strong enough to work as monotherapy in bladder cancer [56] and melanoma [57]. It is approved for treatment of advanced Non-small cell lung cancer (NSCLC) along with chemotherapy in India.

In management of wart it is administered intradermally or intralesional or combination of two [58-66]. It generates systemic immune response following intralesional administration and clears remote (distant, non-injected) warts [61-63,65]. Its administration is associated with clearance of HPV virus also [64]. It achieves complete clearance in small as well as large warts, cutaneous as well as anogenital warts [58-66]. It is effective in newly diagnosed as well as recalcitrant wart which has not responded to other therapies or recurred following other therapies [58-62]. No. of administration for achieving complete response seems to be related to size and/or no. of warts [63]. New warts following clearance, if seen are at a different location [63].

Following therapy with CADI-05 of large refractory extra-genital warts, complete clearance of treated warts was seen in 66.7% (20/30) of the patients with clearance of 46.2% of distant warts [61]. Complete clearance is also seen in large anogenital warts [58,66]. The reported systemic side effects include flu-like symptoms, fever, and lymphadenopathy [60,62,63,65]. Injection site reaction include pain, modularity, ulceration, scarring at the site of injection [60,62,63,65].

Quadrivalent HPV Vaccine

Quadrivalent HPV vaccine, GARDASIL, is approved for prevention of diseases caused by HPV types 6,11,16,18. It is also found useful in management of wart as a therapeutic vaccine [67-76]. It induces complete clearance of chronic warts, warts not responding to other therapies irrespective of its size [67,68,70-76]. It works in immune compromised individuals also [67,69,72,75]. The decrease in size is evident following first injection. Complete clearance is achieved three months after third dose. Clearance of warts caused by other (not included in vaccine) e.g. HPV 2 type is also seen [68,72]. Surprisingly anogenital warts are not cleared while cutaneous warts are cleared following administration of quadrivalent vaccine [69].

The major drawback of quadrilateral vaccine is time required for administration of three dose (0, 2 and 6 months) and time taken for complete resolution of warts. Quadrivalent vaccine is now replaced by nine talent vaccine providing prophylaxis against HPV type 31, 33, 45, 52, and 58 also. This should provide better efficacy than quadrilateral vaccine. It will be useful to evaluate it in recalcitrant large size warts.

Cidofovir

Cidofovir is approved for treatment of cytomegalovirus infection by intravenous route of administration [77,78]. Cidofovir has been shown to reduce E6 and E7 expression in HPV +ve cells and thereby reducing proliferation of infected cells leading to apoptosis, and virustatic control of HPV infection [78,79]. Cidofovir works on HPV transformed cells having compromised DNA repair [80]. It has no effect on normal cells. In animal studies of HPV infections, systemic administration is not found useful [81]. Topical treatment is useful in small/medium size lesions [81]. Intralesional cidofovir cures even large papilloma [81]. Recurrences following intralesional cidofovir can be eliminated by combining it with immunotherapy [82].

Topical and intralesional cidofovir has been successfully used in treatment of warts [78,79,83-93]. Best results with topical cidofovir are seen with 3% cidofovir applied twice daily. Treatment should be stopped if there is no response after 10 weeks [83]. It is found useful for warts on the oral mucosa, hands and anogenital region [84]. Complete response following topical cidofovir range from 47%-57.5% [94,95]. Complete response is also possible in a large wart a [83]. Female gender, younger age and genital warts are likely to have complete response following topical cidofovir [95].

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The most common side effects of topical cidofovir are pain, pruritus and rash at the application site [96].

Intralesional cidofovir 7.5mg to 25mg/mL is administered once a month [84,91,92]. This achieved complete wart clearance 276 of 280 patients (98.5%) in recalcitrant warts with no recurrence [85]. Intralesional cidofovir is found useful in management of a large wart [92]. The most common adverse events with these injections were pain, burning sensation, itching, erythema, and post-inflammatory hyper pigmentation [85]. Topical cidofovir 3% is found useful in management of large warts in immune compromised hosts with surgical debulking in anecdotal cases [97,98].

Cryotherapy

Cryotherapy, an inexpensive and simple provider administered procedure using liquid nitrogen in a spray or cryoprobe. The temperatures involved with cryotherapy are cold to the point that there is permanent dermal and vascular damage leading to necrosis and clearance of the abnormal cells and is frequently used to destroy warts by cold-induced cytolysis. It does not treat subclinical lesions in the surrounding skin and can account for recurrence. A recent systematic review of randomized controlled trials (RCTs) on local treatments for immune competent and HIV infected patients globally concluded that ablative techniques are clinically more effective at completely clearing warts immediately.

(-Health assessment-) Cryotherapy is considered a first-line provider administered therapy due to its relative ease of administration and cost. Cryotherapy efficacy did not appear to differ from that of topical therapies [99-101] and is very effective for multiple and small warts [102]. Recurrence rates are estimated between 25% and 42% [102-105]. Combining it with interferon (IFN) - alpha does not improve clearance rate as well as recurrence rate [105] outcome. Electro surgery was weakly associated with better AGW clearance than cryotherapy (risk ratio (RR) 0.80, 95% confidence interval (CI) 0.65-0.99) [100]. Cryotherapy is associated with more immediate adverse events (erythema, stinging, or irritation; RR 3.02, 95% CI 1.38-6.61) and immediate pain requiring oral analgesics (RR 2.11, 95% CI 1.07-4.17) [99,100,106]. Local tissue destruction with blistering, ulceration, infection, and loss of pigmentation manifest later. There is also a risk for permanent scarring [102]. Cryotherapy is not popular as a monotherapy in management of large warts as treatment of a widely involved area is not tolerated well by patients due to pain and multiple visits needed for complete clearance.

Surgical Excision

Warts may be removed surgically via shave excision, scissor excision, curettage, and/or electro cautery [102]. Surgical intervention provides immediate results, which is useful in patients with large, obstructive or extensive warts [102]. It also provides opportunity for histopathological assessment for lesions suspicious of malignancy. Recurrence following surgical excision is described in 19% to 29% of cases [107-109]. The high recurrence rates may be attributed to the clinically unapparent surrounding tissue that continues to harbor the HPV virus. Disadvantages include bleeding, longer healing course, and pain. It can be combined with other topical therapies to improve outcome. This is not the procedure of choice for majority of patients with large wart.

Laser therapy

Carbon dioxide laser

Carbon dioxide (CO^2) laser has been a valuable tool as a destructive therapy for genital warts that uses infrared light energy to vaporize targeted areas [110-112] to provide bloodless removal. Clearance rates range between 23% and 52% with recurrence rates as high as 77%. HIV-negative patients responded better to treatment with a 71% cure rate versus 58% for HIV-positive patients. Scarring, hypo pigmentation, are some of the disfiguring adverse effects of CO^2 laser treatment of warts [113,114]. Postoperative pain and prolonged wound healing are other complications [113,114]. Scarring has been reported in up to 61% of patients treated for recalcitrant warts and appeared unrelated to wart duration or location [113]. Immune suppressed patients are especially susceptible to scarring and delayed wound healing [115]. This can be combined with other therapies to improve the outcome. Its side effect profile is better than cryotherapy [100].

Pulsed Dye Lasers

Pulsed dye lasers (PDL) emit a wavelength from 585 to 595nm, consistent with a hemoglobin absorption peak. It is hypothesized that PDL destroys the characteristically dilated superficial capillaries that supply warts, thereby starving the epidermal cells that host viral molecules [116-118]. Furthermore, it has been suggested that PDL destroys the HPV virus itself as a result of the virus's heat-sensitive properties [116,119-121]. PDL therapy has been used to treat simple and recalcitrant common, palmar, plantar, and flat warts, with studies reporting remission rates ranging from 47% to 100% [116,117,120-127]. Palmar warts may have higher response rates than plantar warts (75% palmar vs 20% plantar [125]; 93% palmar vs 69% plantar) [126]. PDL can treat warts in cosmetically important area. PDL is combined with other modalities to improve outcome. In recalcitrant warts, PDL followed by intralesional bleomycin (0.5 IU/mL; median, 0.3mL/wart) achieved 89% remission in recalcitrant hand warts [127] with 80% in an immune compromised patients. Adverse effects of PDL therapy include local pain during and after the procedure, bullae, crusting, scarring, and temporary pigment changes [117,118,124]. PDL has significantly fewer adverse effects than the CO2 laser [122]. Compared with cryotherapy, PDL has a lower incidence of pain and bulla formation [122]. It is found useful in management of large warts also as a monotherapy.

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Photodynamic Therapy

5-aminolevulinic acid is a photosensitive which accumulates in HPV-infected cells in greater quantities than in adjacent normal skin following topical application [28] and is used for destruction of tissue harboring HPV by phototoxic reaction in photodynamic therapy (PDT). There is a significant, up to 10 fold increase of interleukin (IL)-1 alpha and a 2.5-fold increase of tumor necrosis factor-alpha [128] following photodynamic therapy (PDT). Response to therapy is associated with increase in CD8+ cells [28,128], CD4+ cells [129], dendritic cells, and decrease in Treg cells [130] with achievement of normal Treg level by three weeks. 5-aminolevulinic acid can be injected into lesion to enhance penetration and increase its effectiveness e.g larger or thicker lesions [131,132].

The main advantages of PDT are a high degree of effectiveness and safety, a short recovery period, good cosmetic results and the ability to treat a large surface area with minimal scarring and low recurrence rate [133-140] irrespective of site of lesion in general complete clearance rates of 56%–100% in recalcitrant hand and foot warts have been reported [135]. The reported recurrence rates with PDT are best amongst all ablative procedures as a monotherapy. PDT has been proposed for treating refractory lesions and lesions that recur despite the correct administration of another treatment. However, ALA-PDT was not shown to be beneficial as an adjunctive treatment to ablation of condyloma acuminata with a CO2 laser [141]. The adverse effects, all local, include pain [142], a burning sensation, and erythema [143]. Photodynamic therapy is ls better than cryotherapy for wart clearance and adverse events [140].

Imiquimod

Imiquimod (an imidazoquinoline amine), is an immune response modifier licensed for the topical treatment of external genital and perianal warts. Imiquimod acts through a Toll-like receptor (TLR7) [144,145]. Treatment with Imiquimod [32,34] activates cell mediated immune response of Th1 type as revealed by significant increases in mRNA for interferon (IFN)-alpha, IFN-gamma, 2'5' AS , TNF-alpha, CD4 and CD8. Imiquimod is associated [33,146] with a decrease in HPV DNA and in mRNA expression. Wart clearance [33] following treatment with Imiquimod is associated with evidence of tissue production of interferon-alpha, -beta, and -gamma and tumor necrosis factor-alpha. A significant correlation between the presence of circulating, pre-existing HPV specific T lymphocytes and regression of HPV positive lesions has also been observed [147,148].

In clinical studies, wart clearance has been reported in 35-68% of patients with treatment courses up to 16 weeks [144,145,149-155]. The reported clearance rates are higher in women than in men, and also women have a shorter median time to clearance than men. Clearance is seen between 8-12 weeks for small cutaneous warts [156]. Recurrence rates (6-26%) after successful clearance are low [144,145,151,152,155]. Erythema is often seen as a side effect with Imiquimod therapy [156] and sometimes appears to precede clinical resolution [50]. Occasionally severe inflammation is seen necessitating discontinuation of therapy [50]. Rare side effects include psoriasis form eruptions, mucosal ulcerations, hyper pigmentation [157,158].

It is combined with other therapies like laser [159-162], cryo therapy [163] salicylic acid [163,164] to improve clearance rates and minimize recurrences it has been successfully used as a combination therapy in management of large warts [164].

Sinecatechins

Sinecatechins (Polyphenon E) Polyphenon E is a standardized extract of green tea leaves (Camellia sinensis). Sinecatechins inhibits proliferation of HPV infected cells and also induces apoptosis in vitro [165]. Sinecatechins use is associated decreased viral load in warts. The decreased viral load is associated with changes in genes involved in regulation of cell signaling, immune response and apoptosis processes [166-168]. Sinecatechins inhibits MMP-2, MMP-7, MMP-9; lipoxygenases and cyclooxygenases [COX-1, COX-2]); epidermal growth factor [169].

An ointment containing Sinecatechins at a concentration of 15% and 10% are available as approved products for the treatment of external anogenital wart. Both have similar results. The dosage is 3 applications daily for up to 16 weeks. Randomized controlled trials in patients of both sexes has shown overall lesion clearance rates of between 54% and 65% compared to an average clearance rate of 35% in placebo groups [170-174]. Recurrence rates were between 6% and 12% after 12 weeks of follow-up. The effect of this substance is not evident clinically until approximately the third week of treatment and becomes more apparent in the fourth to sixth weeks [170].

The most common undesirable effects (80%) are local ones, particularly erythema and pruritus that begin to appear in the second or third week of treatment [170-173]. Although a large percentage of patients have adverse reactions, they are well tolerated. Inflammation, indicative of the drug's activity, arises from a local immune response mediated by pro-inflammatory cytokines. The incidence of local skin reactions has been reported to be higher in responders than nonresponders [171]. The efficacy in immune compromised individuals is not known. Recurrence rate (6.5%) is identical to placebo group [173]. Use of Sinecatechins following cryotherapy for warts, improves response rate of cryotherapy [175]. Response rate can be as high as 96.3% with a recurrence rate of 7.4% [176]. The combination may be useful on management of large tumors.

Isotretinoin

Retinoic Acid suppresses transcription of HPV [177]. Oral isotretinoin is used successfully in management of warts as a single agent [178-181]. Oral low dose (0.5mg/day) is also useful [182-184]. Complete clearance is seen in 31.2% -100%

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[178,183-186]. Topical isotretinoin is not as effective as oral isotretinoin [181]. It can be combined with topical podophyllin for achieving complete response in partial responding/ recurring warts with topical podophyllin alone [187]. It is safe for use in immune compromised individuals [179,188]. It is found useful in treatment of large wart as a monotherapy seen in B-cell lymphoma following Rituximab [179]. It has been possible to achieve complete remission of large wart in immune compromised individual after surgical debulking [188]. Combining with interferon alpha does not seem to offer any additional advantage [186].

Cyclophosphamide

Large warts are associated with significant immune suppression via increased Treg cells and are believed to be responsible for partial response/recurrence following therapy. Oral cyclophosphamide (50mg/day for a week) is found useful in depleting Treg cells. Anecdotal case reports suggest its usefulness in achieving complete response as a standalone therapy for newly diagnosed and recurrent anogenital warts [189]. When used with laser therapy for large wart it helps in achieving and maintaining response. Recurrences are amenable to re-administration of oral cyclophosphamide [190]. This is achieved by altering milieu of lesion to normal.

Conclusion

Large warts are difficult to treat. There are no guidelines for its management. It is possible to achieve complete response with intralesional immunotherapy like Candida antigen, CADI-05 or antiviral Cidofovir. Quadrilateral HPV vaccine is also useful. Combination of ablation of lesion using various modalities with topical immunotherapy or antiviral is also useful.

Conflict of Interest

I have no conflict of interest since it is a review of published information. However, I am an employee of Cadila Pharmaceuticals limited who is a manufacturer of CADI-05.

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