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Review Article

Treatment of cutaneous and genital warts in immunocompromised patients

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Abstract

Immunocompromised patients are usually more predisposed to widespread resistant wart lesions and have higher risk of relapse and malignant transformation of untreated lesions. In this review, we decided to evaluate the treatment of cutaneous and genital warts in immunocompromised patients. We searched Pubmed, Medline, Web of Science, and Google Scholar with related keywords. Inclusion criteria were articles that evaluated efficacy of different treatments on cutaneous or genital warts in immunocompromised patients since January 2010 to September 2023. Eventually, 30 articles were chosen for this review. Based on literature review, the most common treatment approaches were replacement/dose reduction of immunosuppressive drugs and immunotherapy methods. Combination of destructive methods (such as lasers) with antiproliferative therapies (such as cidofovir, retinoids and podophyllotoxin) can lead to superior results. Surgical excision especially is recommended in patients with giant condyloma acuminata. Administration of oral retinoids, cidofovir (topical or intralesional) and topical imiquimod should be precluded in renal transplant recipients or patients with impaired renal function. Replacement of traditional immunosuppressive drugs with novel immunomodulators such as sirolimus and leflunomide can be the first step against widespread recalcitrant lesions in immunocompromised patients. Intralesional immunotherapy can be recommended as the first-line of therapy in immunosuppressed patients with resistant warts.

Key words
Human papillomavirus; Warts, Immunocompromised; Immunosuppression; Solid organ transplant.

Introduction

Human papillomavirus (HPV) is a deoxyribonucleic acid (DNA) virus which can infect any mucocutaneous surface. Spontaneous clearance of warts might occur in immunocompetent individuals after approximately two years. However, immunocompromised patients due to impairment of cellular immune system and down-regulation of T helper (TH)-1 cytokines are more predisposed to various types of infections including HPV.[1-3] In addition, these patients usually have more resistant lesions, and are more likely to have widespread lesions which can cause disfigurement and psychological distress. On the other hand, there is a higher risk of malignant transformation of untreated wart lesions in immunosuppressed patients which can lead to significant morbidity and mortality in these patients. Most of the existing evidence and reviews evaluate efficacy of various treatment modalities on immunocompetent subjects.[1,2] In this review, we

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decided to evaluate the treatment of cutaneous and genital warts in immunocompromised patients.

Methods

We searched Pubmed, Medline, Web of Science, Google Scholar with related keywords including "wart" OR "verruca" AND "immunosuppression" OR "immunocompromised" OR "solid organ transplant" OR "human immunodeficiency virus" OR "immunosuppressive drug" AND "treatment". Inclusion criteria were articles that evaluated efficacy of different treatments on cutaneous or genital warts in immunocompromised patients since January 2010 to September 2023. Exclusion criteria were letters to editor, short communication and brief reports or articles which were not performed on humans or those which were not in English language. Initially, 85 articles were found, that after investigation of title and abstract, 43 articles were excluded. Then, eventually based upon evaluation of full texts of articles, 30 articles were chosen for final review. Flowchart of the literature review is demonstrated in **Figure 1**. Details of articles including number of patients, age, sex, study design, type of immunosuppression, previous treatments, current treatment modality, efficacy, side effects, follow up duration and relapse rate are stated in **Table 1**.

Results

Thirty articles evaluated efficacy of different treatments on 69 immunocompromised patients (including 33 males and 36 females). The articles included twenty-five case reports, two case series, one randomized controlled trial, one retrospective observational study and one retrospective cohort study.[2,4-32] The most common therapeutic approaches were

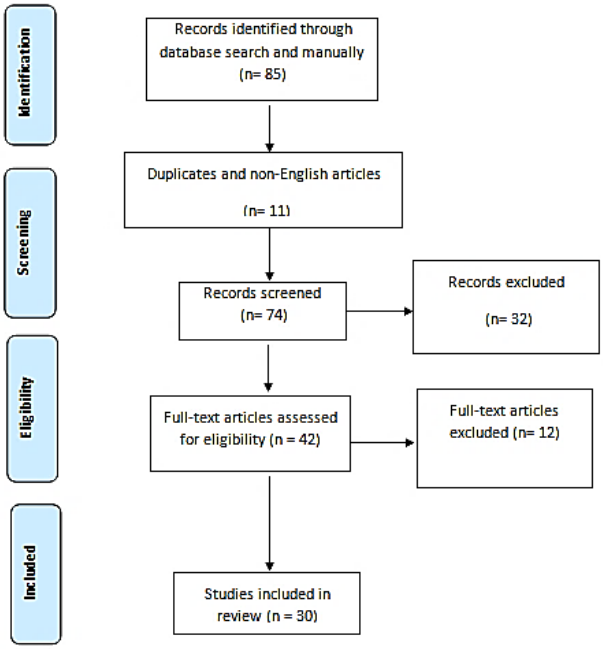

Figure 1 Schematic of the search strategy.

immunotherapy methods and replacement/ dose reduction of immunosuppressive drugs.[2,4-11,14-19] Three case reports demonstrated substantial reduction or complete remission of verruca vulgaris (VV) with three doses of nonavalent HPV vaccine with no recurrence over 15-22 months follow up in immunosuppressed patients with multiple recalcitrant warts on extremities for many years.[4-6] Another case report described a patient with acquired immunodeficiency syndrome (AIDS) and numerous verrucous lesions on hands and feet that were unresponsive to various types of treatment. All of the lesions disappeared after the second dose of vaccine of Corona virus disease 2019 (COVID-19, Moderna). No relapse was reported during 8 months follow up. It has been postulated that COVID-19 vaccine can stimulate local immune system in skin by recruitment of plasmacytoid dermal dendritic cells, activation of CD4+ and CD8+ T lymphocytes and up-regulation of interferon (IFN)-1 and release of other cytokines associated to TH-1 that help the regression of viral warts.[7]

Santos-juanes *et al.* reported a renal transplant recipient (RTR) who was treated with topical 5% imiquimod cream (every other day) for widespread recalcitrant wart lesions on face and upper extremities. Over one month after treatment, he developed acute tubular necrosis (ATN) that responded to discontinuation of imiquimod, along with intravenous pulse of corticosteroid and hemodialysis.[8]

Moscarelli *et al.* reported complete remission of periungual wart in a RTR with twice a day application of topical vitamin D (calcitriol) for three months without any recurrence at 9 months follow up.[9]

Two case reports demonstrated marked-to-complete remission of refractory wart lesions in immunocompromised patients with combination of intralesional (IL) *candida* antigen (0.2 cc every 2-4 week) with either cryotherapy or oral retinoid (20 mg/day) during 6-9 weeks.[10,11]

Two case reports demonstrated the efficacy of combination of oral retinoid with surgical methods (surgical debulking or laser).[12,13] One case report showed complete cure of extensive perianal warts in a patient with systemic lupus erythematosus (SLE) with combination of surgical excision with oral isotretinoin (20 mg/kg/ day for 8 months) and discontinuation of azathioprine (AZT).[12] Snast *et al.* in a retrospective cohort study evaluated the efficacy of combination oral acitretin (10-30 mg/day) and pulsed dye laser (PDL, 3-14 treatment sessions) on 10 solid organ transplant recipients (SOTRs) which had recalcitrant hypertrophic wart lesions. Marked-to-complete clearance of warts was reported in 60% of cases. Only one patient experienced elevated liver enzymes which were normalized by decreasing acitretin dosage from 25 mg/day to 10 mg/ day.[13]

Six articles demonstrated marked improvement in recalcitrant wart lesions with either replacement or discontinuation/ reduction in dosage of immunosuppressive drugs. Mycophenolate mofetile (MMF), AZT, adalimumab, tacrolimus and infliximab were replaced by leflunomide, methotrexate (MTX), cyclosporine and sirolimus.[2,14-18] In contrast, one case report showed exacerbation of plantar warts in a patient with Crohn's disease during immunosuppressive therapy with AZT. Nevertheless, withdrawal of the immunosuppressive drug did not improve warts, and patient was candidate for laser surgery.[19]

Das *et al.* in a retrospective observational study evaluated the efficacy of high dose of cimetidine (30-40 mg/kg) for 3-6 months on multiple wart lesions in eight immunosuppressed pediatric patients. Complete remission was achieved in 87.5% of cases. Two cases showed recurrences, that one of them responded to commencing of cimetidine. Gynecomastia was reported in one patient.[20]

Ingenol mebutate cream is a plant-based topical drug that is extracted from Euphorbia peplus. It is a cytotoxic drug that shows apoptotic effects on infected epidermal cells and induces irritant reaction by activation of protein-kinase C delta and recruitment of neutrophils. Mrad *et al.* showed complete resolution of large plantar warts in a RTR patient with application of topical ingenol mebutate cream (500 µg/g) over three cycles (in two subsequent days) of treatment at 6-week interval.[21]

One case report revealed complete improvement of recalcitrant plantar warts with triple combination of shave therapy, imiquimod and cantharidin-podophyllotoxin-salicylic acid (CPS) following 19-treatment sessions over 16 months.[22]

Three articles investigated the efficacy of cidofovir (topical or IL) in treatment of various types of warts.[23-25] One case report demonstrated

Table 1 Results of the studies regarding treatment of cutaneous and genital warts in immunocompromised patients.

Author	*Design*	*Age*	*Sex*	*Type of IS*	*Clinical type/ Site*	*Previous treatments*	*Study*	*Result*	*S/E*	*F/UP (RR, %)*
Smith (2017)[4]	CR	17	1 M	Innate	VV	Cryotherapy, Imiquimod, OTC	HPV vaccine (Gardasil, quadrivalent), 3 doses	CC	No	2 Y (0)
Ferguson (2017)[6]	CR	77	1M	UC	VV	Cryotherapy, SA Shave removal	HPV vaccine, (nonavalent), 3 doses	Marked reduction in numbers	No	15 mo (0)
Silling (2014)[5]	CR	72	1 F	CLL Breast cancer	VV	SA podophyllotoxin, 5-FU Iimiquimod 5% Cryosurgery Surgical curettage, Electrocautery, CO2 laser therapy	HPV vaccine (Gardasil, quadrivalent), 3 doses	CC	No	15 mo (0)
Bressler (2023)[7]	CR	63	1M	HIV	VV	Cryotherapy, Topical, 5-FU, Topical imiquimod, IL belomycin, Topical cidofovir, Acitretin	COVID-19 vaccine (Moderna) 3 doses	CC	No	8 mo (0)
Santos-Juanes (2011)[8]	CR	44	1 M	RTR	VV	Cryotherapy Glutaraldehyde solution Electrocoagulation SA	Topical 5% imiquimod cream (3 times/w) for 42 d	No improvement	ATN, Fever , Malaise Oropharyngeal pain, Dizziness Asthenia, Back pain	2 y
Moscarelli (2011)[9]	CR	41	1 F	RTR	PU	Cryotherapy Electrocoagulation	Topical activated vitamin D (calcitriol, 0.5 µg solution, II/d, 3 mo)	CC	No	9 mo (0)
Acharya (2023)[10]	CR	7	1M	RTR	PP PU	SA Topical retinoid 5-FU	IL *candida* immunotherapy (2 monthly sessions) + cryotherapy (2 monthly sessions)	CC	De novo BK viremia, Elevated, level of plasma donor derived cell-free DNA	10 mo (0)
Herold (2019)[11]	CR	60	1 M	BTR CRF	VV	40% salicylic acid Candida immunotherapy Cryotherapy Acitretin + Candida immunotherapy	IL *candida*, immunotherapy (0.2 cc every 2 w) + isotretinoin (20 mg/d) +	Significant improvement in 6 w	No	6 w
Herold (2019)[11]	CR	40	1 M	HTR CRF	VV CA	Imiquimod sinecatechins Candida immunotherapy HPV Vaccination Cryotherapy	IL *candida* immunotherapy (0.2 cc every, 2 w) + Isotretinoin, (20 mg/d)	Marked improvement in 9 w	Cheilitis Xerosis	9 w
Das (2018)[20]	Retrospective Observational	7-18	6 F 2M	HTR	VV CA PP	NS	Cimetidine (30-40 mg/kg/d, for 3-6 mo)	CC: 87.5% NR: 12.5%	Gynecomastia : 12.5% (resolved after 2 w) Severe pruritus : 12.5%	1 y (25%)
Nguyen (2012)[14]	CR	15	1F	RTR CF	VV	Laser therapy	Replacement of MMF with leflunomide for 7 mo	Dramatic improvement	No	7 mo
Nguyen (2012)[14]	CR	8	1 F	RTR	VV	SA, Cryotherapy, Cantharidin	Replacement of MMF with leflunomide for 5 mo	CC	No	7 mo (0)
Nguyen (2012)[14]	CR	18	1 F	RTR Granulomatosis with polyangitis	VV	Cryotherapy Injections	Replacement of tacrolimus/MMF with tacrolimus/leflunomide for 2 mo	CC	No	2y (0)
Georgala (2012)[15]	CS	26	1F	IS drug for psoriasis	CA	No	Replacement of infliximab with MTX + 3 sessions cryotherapy	CC	NS	NS
Georgala (2012)[15]	CS	25	1 M	IS drug for psoriasis	VV CA	No	Discontinue of infliximab + 3 sessions of cryotherapy	CC	NS	NS

Author	*Design*	*Age*	*Sex*	*Type of IS*	*Clinical type/ Site*	*Previous treatments*	*Study*	*Result*	*S/E*	*F/UP (RR, %)*
Georgala (2012)[15]	CS	22	1M	IS drug for psoriasis	CA VV	No	Discontinue of infliximab + 3 sessions of cryotherapy	CC	NS	NS
Timmer (2013)[19]	CR	29	1 M	IS drug for CD	PP	Cryotherapy, SA Coagulation therapy	Discontinue of AZT	No improvement	No	No
Ash (2017)[2]	CR	51	1 F	RTR	PP VV	Acitretin, SA, Zinc sulfate, Cryotherapy, IL 5-FU, IL candida antigen, Topical Sinecatechins, TCA	Reduction in MMF dose	Marked reduction in size and number, CC in most lesions	No	Few mo
Campoli (2019)[16]	CR	18	1F	Psoriasis	CA	No	Replacement of cyclosporine with adalimumab	CC after 2 mo	No	1y (0)
Maor (2018)[17]	CR	45	1 F	RTR	VV CA PP	Cryotherapy, SA, DPCP, Cantharidin, Podophyllin, TCA IL belomycin, Acitretin	Discontinue of MMF and tacrolimus, Reduction in prednisolone dosage	CC	No	6 mo (0)
Shahidi (2011)[18]	CR	21	1 M	RTR SLE	VV	Topical therapy Cauterization	Replacement of cyclosporine with sirolimus	CC	No	NS
Shahidi (2011)[18]	CR	18	1 F	RTR	VV	Topical therapy Cauterization	Replacement of cyclosporine with sirolimus	CC	No	Less than 1 y, (0)
Yew (2013)[12]	CR	27	1 F	SLE	CA	Topical imiquimod cream + Cryotherapy	Oral isotretinoin (20 mg/d) for over 8 mo+ surgical debulking (3 sessions) + discontinue of AZT)	CC	No	2 y (0)
Snast (2020)[13]	R/Cohort	22-67 (46)	5M 5 F	RTR LTR PTR	VV PW PP	Cryotherapy, PDL, PDT, SA Topical retinoid Systemic retinoid	Acitretin (10-30 mg)+ PDL [8 (3-14) sessions, spot: 5 mm, PD: 1.5 ms, fluence: 12-14 j/cm^2, stack: 2-3, interval: 4-8 w]	CC: 30%	Increased liver enzymes (10%) Mild pain Mild xerosis	7-59 mo (10)
Blouin (2012)[24]	CR	23	1 M	RTR	PP	Cryotherapy, SA, Cantharidin, Imiquimod, Podophyllin, DNCB, Cimetidine, IL Bleomycin, CO2 laser, Replacement of MMF with rapamycin, Topical cidofovir	IL cidofovir (7.5 mg/cc) 7 monthly sessions Volume: 0.2 -1.5 cc/session	CC: 95%	No	2 y (0)
Oh (2020)[25]	CS	16	1F	LTR	PP	NS	IL cidofovir, 15 mg/ml, Maximum: 5 cc/day, Monthly interval, 2 sessions	CC	No	2 mo (100)
Oh (2020)[25]	CS	46	1M	IS drug for MG	PP	NS	IL cidofovir 3 sessions	CC	No	2 mo (100)
Kralund (2011)[23]	CR	13	1 M	RTR	PP	Keratinolytics Cryotherapy Curettage Topical 5% imiquimod	Curettage+ CO_2 laser+ topical 1% cidofovir (75 mg/ml, 2 hours under occlusion, two 5-d cycles , every 2 w, 3 mm margin)	CC	NS	3 y (0)
Mrad (2018)[21]	CR	30	1 M	RTR	PP	Cryotherapy, Topical 5-FU, Imiquimod, Topical podophyllin CO2 laser Electrocoagulation	Topical ingenol mebutate cream, 500µg/g, (3 courses during 2 subsequent d at 6 w interval)	CC	No	12 mo (0)
Ghafari-Saravi (2023)[22]	CR	34	1 F	CF LuTR	PP	Cryotherapy Silver nitrate Topical cidofovir IL Candida antigen Bleomycin Topical 5-FU SADE immunotherapy, Cantharidin	Shave removal + cryotherapy+ CPS (12 hours, 19 sessions over 16 mo)	CC	No	33 mo (0)

Author	*Design*	*Age*	*Sex*	*Type of IS*	*Clinical type/ Site*	*Previous treatments*	*Study*	*Result*	*S/E*	*F/UP (RR, %)*
Sparsa (2012)[26]	RCT	4-24 (52.3) y	9M 7 F	RTR	PW VV	NS	A: keratolytic (30% SA during 8 days) + , MAL-PDT, (3 sessions every week+ Red light: 75 J/CM^{2,} Fluence: 150mw/cm^2 WL: 570-670 nm) B: keratolytic (30% SA during 8 days	Case vs. control: 48.4% vs. 18.4% Reduction in area Reduction in number: 41% vs. 19.4%, Patients' satisfaction: 87.5%	Acceptable pain Crusting Persistent burning sensation	1 y (0)
Caucanas (2010)[27]	CR	64	1M	PTR	VV	Cryotherapy	PDT , (3 sessions, every 10 days, 5-ALA: 3h under occlusion, Red light: 634 nm,37 j/cm^2, Time : 9 min)	CC	Pain (1-2 h) Erythema/swelling (2-3 days) Healing: 8 days	1 y (0)
Zhang (2016)[28]	CR	23	1 F	IS drug for nephritic syndrome	VV Mucosal	No	Local hyperthermia, (44° C, 3 consecutive day, 30 min, 3 sessions during 10 days, then once a week over 9 w)	CC	Blister (3 d) Burning sensation Stabbing pain PIH	3 mo (0)
Evruke (2023)[32]	CR	25	1 F	RTR	CA	No	Wide surgical excision	CC	No	6 mo (0)
Atkinson (2014)[30]	CR	29	1 F	AIDS	CA	No	Wide surgical excision	CC	No	6 mo (0)
Atkinson (2014)[30]	CR	24	1 F	AIDS	CA	No	Wide surgical excision	CC	No	6 mo (anal wart)
Rachman (2016)[29]	CR	42	1 F	SLE	CA	No	Surgical excision	CC	No	1 mo (cervical wart)
Makbul (2023)[31]	CR	65	1 M	IS drug for psoriasis	VV	No	Electrodessication	CC	No	1 mo (0)

Abbreviations: IS, immunosuppression; S/E, side effect; F/UP, follow up; RR, relapse rate; CR, case report; M, male; VV, verruca vulgaris; OTC, over-the-counter; HPV, human papilloma virus; CC, complete clearance; Y, year; UC, ulcerative colitis; IL, intralesional; SA, salicylic acid; mo, month; F, female; CLL, chronic lymphocytic leukemia; 5-FU, 5- fluorouracil; CO_2 laser, carbon dioxide laser; HIV, human immunodeficiency virus; COVID, Corona virus disease; 6-MP, 6-mercaptopurine; RTR, renal transplant recipient; D, day; W, week; ATN, acute tubular necrosis; BTR, bowel transplant recipient; CRF, chronic renal failure; HTR, heart transplant recipient; CA, condyloma acuminata; SLE, systemic lupus erythematosus; R, retrospective; MG, Myasthenia gravis; LTR, liver transplant recipient; PTR, pancreas transplant recipient; PW, plane wart; PP, palmoplantar; AIDS, acquired immunodeficiency syndrome; PDL, pulsed dyed laser; PDT, photodynamic therapy; CF, cystic fibrosis; LuTR, lung transplant recipient; MMF, mycophenolate mofetile; CS, case series; MTX, methotrexate; NS, not stated; CD, Crohn's disease; AZT, azathioprine; TCA, trichloroacetic acid; DPCP, SADE, squaric acid dibutylester ; CPS, cantharidin-podophyllotoxin-salicylic acid; DNCB, dinitrochlorobenzene; MAL, methylaminolevulinic acid; HCV, hepatitis C virus; PR, partial response;

complete remission of verrucous palmar lesions with combined curettage, carbone dioxide (CO_2) laser and topical cidofovir (two cycles of 5-day, for 2 hours under occlusion, every 2 weeks) with no recurrence during 3 years follow up.[23] Two studies evaluated the efficacy of IL cidofovir (7.5-15 mg/ml, 2-7 treatment sessions, and monthly intervals) on widespread verrucous palmoplantar warts in immunocompromised patients. Complete remission was reported in 95-100% of the cases.[24,25] While no recurrence was reported in one case over 2 years follow up, two other cases showed rapid relapse two months after cessation of treatment.[25]

Two studies revealed significant reduction or complete remission of VV or plane warts with photodynamic therapy (PDT) as monotherapy or combined with topical keratolytic agents.[26,27] Sparsa *et al.* in a randomized controlled trial showed significant reduction in total warts' surface area with combination of 30% salicylic acid (SA, during 8 days) and PDT (three weekly sessions) compared to topical 30% SA as monotherapy in RTRs. Although, number of warts were decreased in combination therapy group compared to monotherapy group; however, the difference was not statistically significant.[26]

One study reported complete remission of VV and mucosal warts with local hyperthermia during three months treatment in a patient with nephritic syndrome which has been under treatment with immunosuppressed drugs.[28] Four studies revealed complete improvement of VV or condyloma acuminata (CA) lesions with wide surgical excision or electrodessication in immunosuppressed patients.[29-32]

Discussion

Traditional therapeutic methods such as cryotherapy or keratolytic agents are the first-line of treatment of warts in immunocompetent individuals; however, these types of treatments as monotherapy are usually insufficient to induce remission of warts in immunosuppressed patients due to their impaired cellular immunity.[1,33-35]

Degree and duration of immunosuppression as well as type of the used immunosuppressant drugs are essential factors that can influence prevalence and resistance of warts to treatment.[2] Several immunosuppressive drugs can exacerbate existing HPV infection and lead to spreading of lesions or their resistance to treatment. Tumor necrosis factor-α (TNF-α) particularly has an essential role in antiviral activity of immune system. It also prevents epithelial cell dysplasia and malignant transformation by inducing under-expression of oncogenic genes (E6/E7) in infected epithelial cells by carcinogenic HPVs.[15] Therefore, TNF-α inhibitors and immunosuppressive drugs (such as cyclosporine, MMF and AZT) can promote HPV replication via reduction in TH-1 related cytokines such as TNF-α.[2] In contrast, novel immunosuppressive drugs (such as leflunomide and sirolimus) regarding their antiviral and antiproliferative properties via blocking the synthesis of HPV E7 oncoprotein and suppression of phosphorylation of the translation inhibitorof 4E-BP1, are better alternative immunosuppressive drugsin SOTRs.[14,18]

Beside replacement/ dose reduction of immunosuppressive drugs, immunologic therapies are generally the first-line of treatment in immunocompromised patients. They can activate the immune system against HPV, and can lead to regression of treated and untreated distant warts via up-regulation of TH-1 cytokines [i.e. interleukin (IL)-2 TNF-α, IFN-gama, and IL-12). They are safe treatment options in immunosuppressed patients due to low risk of occurrence of serious adverse effects. Based upon literature reviews, immunomodulators which have been used in the treatment of immunosuppressive patients with

wart lesions were including HPV vaccine, IL candida antigen, systemic cimetidine and topical imiquimod.[4-11,20]

Emerging evidences recently proposed HPV vaccine for the treatment of cutaneous and genital warts. Structural similarities between L1 protein capsid of various types of HPV which exists in vaccine and in those viruses causing warts, can stimulate immune system and recruits activated lymphocytes to eradicate warts. Advantages of treatment with HPV vaccine include the short-term treatment course and a good safety profile.[4-6] Regarding the scarce number of the studies which evaluated efficacy of HPV vaccine on warts, and relatively high treatment cost; larger studies are required before any conclusion can be made.[4-6]

Cimetidine is a histamine-2 (H2) blocker that shows immunomodulatory effects at high doses. It suppresses the activation of T inhibitory cells. Cimetidine might interact with immunosuppressive drugs (such as tacrolimus and cyclosporine), and lead to an increase in their serum levels via inhibitory effects on cytochrome p450. Thereby, its administration with other medications which are metabolized by this enzyme should be precluded.[20]

Imiquimod activates toll-like receptor-7 (TLR-7), and up-regulates inflammatory cytokines associated to TH-1. Imiquimod might be absorbed systemically, which might aggravate renal function (by production of IFN-α and other inflammatory cytokines), especially in RTRs. In addition, there is a possible risk of organ rejection and graft-versus-host disease (GVHD) with administration of imiquimod in transplant recipients.[8] Therefore, administration of it in immunocompromised patients should be with precaution.

Oral retinoids including acitretin and isotretinoin can be good alternative options in immunosuppressed patients with extensive recalcitrant lesions. They reduce replication of HPV through modulation of proliferation and differentiation of keratinocytes. In order to maximize their efficacy, they can be adjunct to other topical medications. Moreover, their administration prior to laser treatment can enhance penetration of laser's beam into the skin; due to a decrease in hyperkeratosis and thickness of lesions. Caution should be taken in prescribing oral retinoids in child-bearing age subjects or patients with impaired renal function.[11-13]

Cidofovir is a nucleoside analogue that has antiproliferative effects against DNA viruses such as HPV by suppressing HPV DNA polymerase, and as a result inhibition of viral replication. It also can directly induce local inflammation and apoptosis of infected epithelial cells which results in death of infected keratinocytes. One of the main advantages of topical cidofovir is rapid remission of warts over 2-weeks therapy that leads to better adherence of patients to treatment which also consequently reduces risk of spreading HPV to normal surrounding skin; while other topical agents such as imiquimod require long-term treatment courses (16-week) to eradicate warts.[23-25] It is recommended to monitor renal function regularly during the treatment course (prior to injections and 12 hours after) due to the risk of nephrotoxicity, especially in patients with impaired renal function, RTRs and patients who are receiving other nephrotoxic drugs simultaneously.[23-25] Application of cidofovir in patients with AIDS should be with high level of caution, and the patients should be warned about the increased risk of human immunodeficiency virus (HIV) transmission due to the high occurrence of mucosal erosions after treatment.[24]

Surgical therapeutic methods such as lasers, PDT, local hyperthermia, electrocoagulation and

wide surgical excision are other alternative approaches that can be used in the treatment of recalcitrant warts in immunosuppressed patients.[13,26-31]

PDL leads to necrosis of HPV-infected keratinocytes through coagulation of the feeding vasculature of warts in papillary dermis. It also augments immune system response against virus through immunomodulatory effects. However, monotherapy with PDL might have limited efficacy on recalcitrant hyperkeratotic warts. Therefore, combination with other treatment modalities such as topical keratolytics or oral retinoid is recommended to improve light penetration and increased effectiveness.[13,33]

PDT induces apoptosis and destruction of infected keratinocytes via releasing free oxygen radicals. It also modulates immune system, has anti-inflammatory properties, and prevents replication of HPV. It is a non-invasive therapeutic modality that has a good safety profile and results in a good outcome in immunocompromised patients. It is possible to treat large numbers of warts during one session; therefore, it can reduce the risk of recurrence and viral spreading to nearby areas between sessions. No serious side effect has been reported following PDT; the only drawback is the pain during and after treatment, which is tolerable. Treatment with methylaminolevulinic acid (MAL) is more efficient and less painful than 5-aminolevulinic acid (5-ALA), due to higher lipophilicity and better penetration of the former compared to the latter into wart lesion.[26,27]

Regarding high percentage of recurrence rate and high risk of malignant transformation in immunocompromised patients with giant condylomas acuminata, radical surgical excision of the lesions is recommended as the first-line of treatment in these patients. Moreover, regular follow up sessions are suggested for early detection of relapse.[29-32]

The main limitation of this review was scarcity of high-quality studies such as randomized controlled trials that evaluated efficacy of treatments in immunocompromised patients. Future clinical trials are recommended to evaluate efficacy of various treatment modalities in immunocompromised patients.

Conclusion

Replacement of conventional immunosuppressive drugs with immunomodulators such as sirolimus and leflunomide can reduce or clear recalcitrant wart lesions in immunocompromised patients. Due to low risk of adverse effects, intralesional immunotherapy can be suggested as a first-line of treatment in immunosuppressed patients with wart lesions resistant to conventional treatment methods. Other suitable alternatives are PDT and PDL. Oral retinoids, cidofovir (topical or intralesional) and topical imiquimod should be prescribed with caution especially in patients with impaired renal function or RTRs.

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Author's contribution

MK: Substantial contribution to study design, acquisition of data, manuscript writing, has given final approval of the version to be published.

RK: Substantial contribution to analysis and interpretation of data, critical review, has given final approval of the version to be published.

BI: Substantial contribution to analysis and interpretation of data, critical review, has given final approval of the version to be published.

FG, MA: Substantial contribution of acquisition of data, drafting of manuscript, has given final approval of the version to be published.

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