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POSSIBLE EFFECTIVENESS OF ACYCLOVIR AS MEDICAL TREATMENT OPTION FOR VULVAL WARTS

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ABSTRACT

Infection with human papilloma virus is common, and associated with benign and malignant epithelial proliferations of skin and internal squamous mucosa. The mucosal human papilloma virus is oncogenic, and associated with 5 % of all cancers in men and women. A prospective study was done in Babylon Maternity and Paediatrics Teaching Hospital, for the period from February 2013 till February 2015, involved 240 women their ages ranged from 21 to 41 years. All of them were sexually active, married women, symptomatic, presented with multiple warty lesions in the vulva and eight had per-anal condylomata. History, examination ,counselling and informed consent had been performed, then 120 women treated using acyclovir cream and 120 treated by electro-diathermy, 104 from 120(87.6%) completely cleared 5 days a week for 8 weeks application compared with 110 from 120 (91.7 %) in diathermy group. Six patients from acyclovir group had less response (5%) and ten got recurrence (8.3%) while the cautery group six had recurrence(5%),two got an infection (1.66%), one had depigmentation (0.83%) and one got scarring (0.83%). Although preventive vaccines might reduce human papilloma virus associated morbidity for future generations, those with active human paapilloma virus disease still needs to be treated and treatment options either excision therapies, their aim to remove the lesion rather than target human papilloma viral infection while acyclovir target the virus itself.

KEY WORDS: ***Human papilloma virus, Acyclovir.***

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INTRODUCTION

The prevalence of genital human papilloma virus infections in the United States 10–20% of which clinical manifestations occur in 1% of the sexually active adult population, of which about 80% between the age of 17–33 [1]Treatment can remove the warts, but they do not remove the virus, so it can recur in about 50–73% [2] or spontaneously regress with or without treatment [1]Some studies say that the virus remained in the body for a lifetime, while other studies using sensitive DNA techniques have shown that through immunological response the virus can either be cleared or suppressed to levels below what polymerase chain reaction (PCR) tests can measure. Genital warts are small fleshy growths that appear on or around the genital or anal area. In England, they are the second most common type of sexually transmitted infection after Chlamydia. They are a viral skin infection caused by the human papilloma virus. Around 90% of genital warts are caused by two strains of the virus, type 6 and type 11.It's a family of over 100 different strains of viruses; its spread occurs by skin-to-skin contact during vaginal or anal sex. It can be transmitted to others when warts present. Although it's possible to pass the virus before the warts have developed and after they have disappeared. Their diagnosis based on an examination. Skin biopsy is not necessary when a diagnosis can be made on clinical examination. Biopsy is required if the woman fails to respond to treatment or there is clinical suspicion of vulval cancer [3]. Treatment of genital warts can be physically ablative or topical agents, the ablative focused on removal of visible warts, but they may regress on their own without any therapy [4]. They do not reduce transmission of the underlying HPV infection, 80% of people with HPV will clear the infection within 18 months [5] Warts can be treated depending on their number, sizes, or location. Treatments can potentially cause depigmentation, itching, pain, or scarring [4]. Physically ablative therapies are considered more effective at initial wart removal, but like all therapies have significant recurrence rates [4,6]. They are appropriate for patients with fewer numbers and smaller warts [6]. Simple excision, such as with scissors under local anaesthesia, is highly effective[4]. Liquid nitrogen cryosurgery is performed in an office visit, at weekly intervals. It is effective, inexpensive, safe for pregnancy, and does not usually causes scarring [4]. Electro cauterization is procedure with a longer history of use, and is considered effective [4]. Laser ablation has less evidence for its use. It may be less effective than other ablative methods [6]. It is expensive, and used as a last resort [7]. Surgical procedures, performed under general anaesthesia, may be needed for larger or more extensive warts, or intra-anal warts [4] . It carries a greater risk of scarring than other methods [8] . Topical agents, like podophyllotoxin (podofilox) solution in a gel or cream can be used. It is safer and more effective than podophyllin although skin erosion and pain are more commonly reported than with imiquimod and sinecatechins [9] . Its use is cycled (2 times per day for 3 days then 4–7 days off). One review states that it should only be used for four cycles.[10] Imiquimod (Aldara) is a topical immune response cream, applied to the affected area. It causes less local irritation than podofilox but may cause fungal infections and flu-like symptoms [9] . Sinecatechins (Veregen and Polyphenon E) is an ointment of catechins (55% epigallocatechin gallate [7] extracted from green tea and other components. Mode of action is undetermined [11] .It appears to have higher clearance rates than podophyllotoxin and imiquimod and causes less local irritation, but clearance takes longer than with imiquimod[9]. Trichloroacetic acid is less effective than cryosurgery [10], and is not recommended for use in the vagina, cervix, or urinary meatus [7]. Interferon can be used; it is effective, but it is also expensive and its effect is inconsistent [10]. A 5% 5-fluorouracil (5-FU) cream was used, but it is no longer considered an acceptable treatment due to the side-effects [7]. Podophyllin, podofilox and Isotretinoin should not be used during pregnancy, as they could cause birth defects in the foetus [11].Genital wart can be prevented by using human papilloma virus vaccine. Gardasil, is available for prevention of genital warts. It helps prevent infection from four types of HPV (types 6, 11, 16, and 18), which helps to prevent most cases of cervical cancer (caused by HPV 16 and 18) and genital warts (caused by HPV 6 and 11).Another vaccine, Cervarix, helps prevent infection from two types of HPV (types 16 and 18), thus it helps to prevent most cases of cervical cancer, but not genital warts [12]. Human papillomavirus (HPV) is a DNA virus from the papillomavirus family that is capable of infecting humans. Like all papillomaviruses, HPVs establish productive infections only in keratinocytes of the skin or mucous membranes. Most HPV infections are subclinical and will cause no physical symptoms; however, in some people subclinical infections will be clinically evident and may cause benign papillomas such as warts or cancers of the cervix, vulva, vagina, oropharynx and anus [13]. Acyclovir (9-[2-hydroxyethoxymethyl] guanine) has proved to be a safe and effective agent for therapy of herpes simplex and varicella-zoster infections. It's availability in topical, oral, and intravenous preparations. Acyclovir must be phosphorylated by viral thymidine kinase in infected cells, where it then acts to inhibit viral DNA replication specifically. It's well absorbed and distributed, with cerebrospinal fluid levels 50% that of plasma. Clearance is almost entirely by the renal route, with a half-life of 20 hours in the anuric patient, its major adverse effect being transient serum creatinine elevations during high-dose intravenous use. Major uses include treatment of primary and recurrent genital herpes and herpes encephalitis and prophylaxis and therapy of mucocutaneous herpes and varicella-zoster infections in immunocompromised patients. Resistance to acyclovir in herpes simplex virus is rarely encountered [14] . Common adverse drug reactions (≥1% of patients) associated with systemic acyclovir therapy (oral or IV) include: nausea, vomiting, diarrhoea, encephalopathy (with IV use only), injection site reactions (with IV use only) and headache. In high doses, hallucinations have been reported. Infrequent adverse effects (0.1–1% of patients) include: agitation, vertigo, confusion, dizziness, oedema, arthralgia, sore throat, constipation, abdominal pain, hair loss, rash and weakness. Rare adverse effects (<0.1% of patients) include: coma,

seizures, neutropenia, leukopenia, crystalluria, anorexia , fatigue, hepatitis, Stevens–Johnson syndrome, toxic epidermal necrolysis, thrombotic thrombocytopenic purpura and anaphylaxis[15]. Aciclovir classified as a Category B Drug[16], It is recommended by the Centers for Disease Control and Prevention (CDC) for treatment of Varicella during pregnancy, especially during the second and third trimesters [17] .

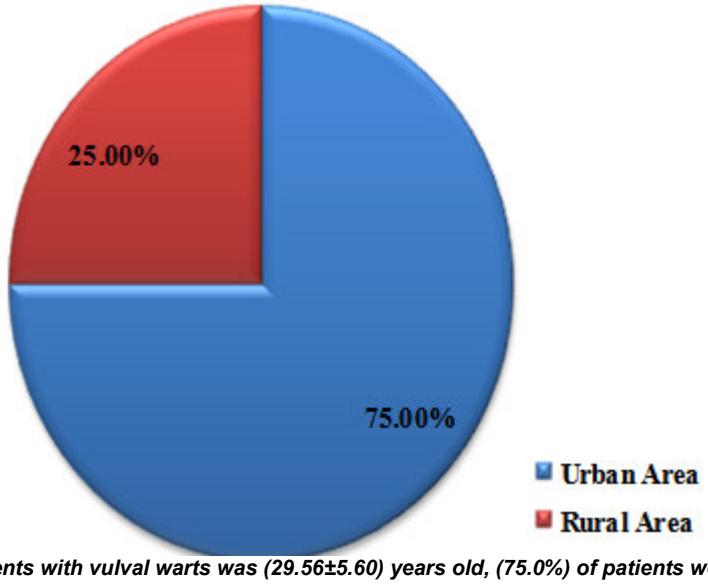
MATERIALS AND METHODS

Our study was a prospective study, performed in an outpatient clinic in Babylon Maternity and Paediatrics Teaching Hospital for the period from February 2013 till February 2015, involved 240 women their ages ranged from 21 to 41 years with a mean (29.56±5.60) years old. All of them were sexually active married women symptomatic presented with multiple warty lesions diagnosed with vulval condylomata and eight had vulval with perianal condylomata. The Ethical Committee of College of Medicine had approved it,.All women involved in the study after counselling the benefits and side effects of this medication gave informed consent for its use. Inclusion criteria were; women accepted to participate in the study, within the reproductive age group from (21 - 41) years, no history of previous use of medication to treat it. Exclusion criteria included; current pregnancy or suspicion of early pregnancy, lactation amenorrhea, a history of acute or chronic renal diseases, current use of chronic medications. A questionnaire was designed information included; demographic measurements (age, parity, weight, height, residence, education and occupation), medical history , drug intake, menstrual history , obstetrical history and contraception history and history of breast feeding. Difficulties were encountered while selecting the cases under study , the acceptance to participate in the study, the inclusion criteria, the type of medication to be used, the co-operation to re-attend back to the clinic later and to inability to visit the clinic in time for re -evaluation due to socioeconomic reason. During the study period 265 women attended having symptomatic wart lesion, after counselling 240 women accepted to participate in the study and been followed up. Their phone number was taken. Detailed history taken. Height and body weight was measured as a baseline, BMI was then measured by the following equation BMI= weight (kg) / height(m^2) Overweight is considered when the body mass index is between 25.1kg/m^2 to 29.9kg/m^2, while a body mass index ≥ 30kg/m^2 considered as obesity, both excluded in our study.Then been divided randomly into two groups. One hundred twenty women treated with electro-diathermy another 120 women received acyclovir ointment 5% w/w cream four times a day for five days a week. Maxim treatment duration was 8 weeks. ZOVIRAX is the brand name for acyclovir, a synthetic nucleoside analogue active against herpes viruses. ZOVIRAX Cream, 5% is a formulation for topical administration. The chemical name of acyclovir is 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6H-purin-6-one. Acyclovir is a white, crystalline powder with the molecular formula $C_8H_{11}N_5O_3$ and a molecular weight of 225. The maximum solubility in water at 37°C is 2.5 mg/mL. The pKa's of acyclovir are 2.27 and 9.25.Each gram of ZOVIRAX Cream, 5% contains 50 mg of acyclovir and the following inactive ingredients: cetostearyl alcohol, mineral oil, poloxamer 407, propylene glycol, sodium lauryl sulfate, water, and white petrolatum (Manufactured by GlaxoSmithKline Research Triangle Park, NC 27709 for BTA Pharmaceuticals, Inc. (subsidiary of Biovail Corporation) Bridgewater, NJ 08807 Made in India). To evaluate the safety and clinical efficacy, patients were examined and lesion areas checked on a weekly basis. All statistical analysis was done by using statistical package for social sciences (SPSS) version 21. Categorical data were described as count and percentage while numerical data were described as mean and standard error of mean. Comparisons between groups were made by using chi-square test or categorical data and t-test for numerical data. The lowest level of probability to be accepted equal or less than 0.05.

RESULTS

Distribution of Patients with Vulval Warts by Socio-Demographic Characteristics

Figure 1
Distribution of patients with vulval warts by residence



The overall mean age of patients with vulval warts was (29.56±5.60) years old, (75.0%) of patients were from urban areas (Figure 1).

Figure 2
Distribution of patients with vulval warts by occupational status

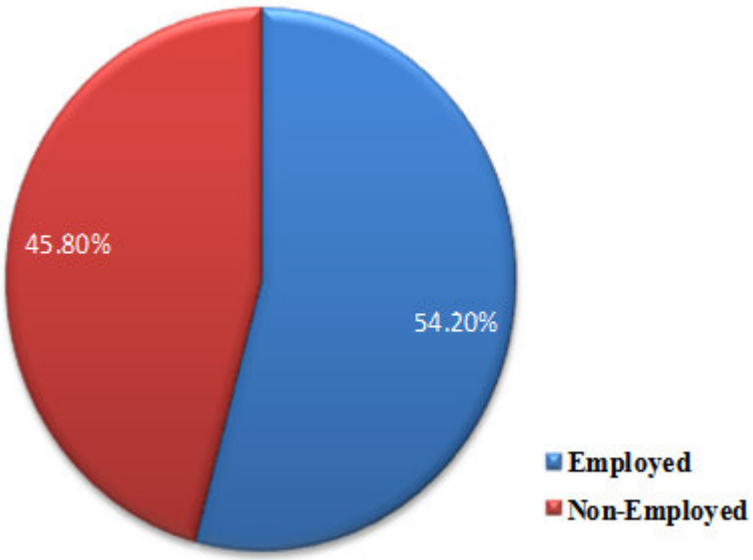


Figure (2) show distribution of patients with vulval warts by occupational status, (54.2%) of patients was employed.

Figure 3
Distribution of patients with vulval warts by educational levels

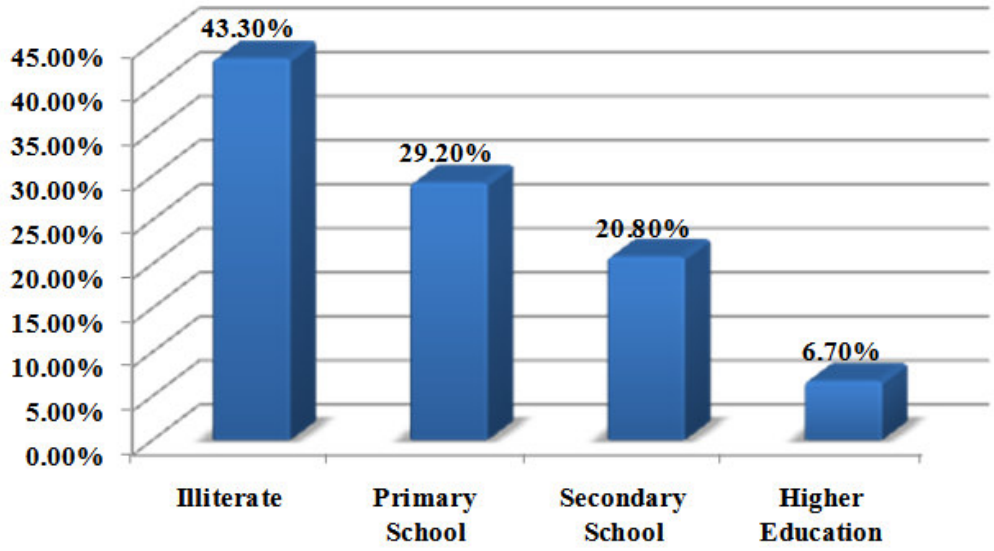


Figure 3 shows the distribution of patients with vulval warts by educational levels, (43.3%) of patients were illiterate.

Distribution of Patients with Vulval Warts by Medical History

Table 1 shows the distribution of patients with vulval warts by medical history, (81.7%) of patients were multi-Para, (72.5%) of patients had more than five wart lesions. (56.7%) of patient was not use any contraception.

Table 1
Distribution of Patients with Vulval Warts by Medical History

Variable	Frequency (%)
Parity	
Null-Para	44 (18.3%)
Multi-Para	196 (81.7%)
Clinical presentation	
> 5 wart lesions	174 (72.5%)
3-5 wart lesions	58 (24.2%)
Vulval and peri-anal lesions	8 (3.3%)
Contraception	44 (18.3%)
Combined oral contraceptive pills	34 (14.2%)
Depo-provera injection	26 (10.8%)
Intrauterine contraceptive device	136 (56.7%)
No contraception	

Distribution of Patients with Vulval Warts by Acyclovir and Cautery Treatments

Figure 4 shows the Distribution of Patients with Vulval Warts by Acyclovir and Cautery Treatments, (86.7%) and (91.7%) of patients were cured by Acyclovir and Cautery Treatments, respectively. Six patients from acyclovir group had less response (5%) and ten got recurrence (8.3%) while the cautery group six had recurrence(5%),two got infection (1.66%), one had depigmentation (0.83%) and one got scarring (0.83%).

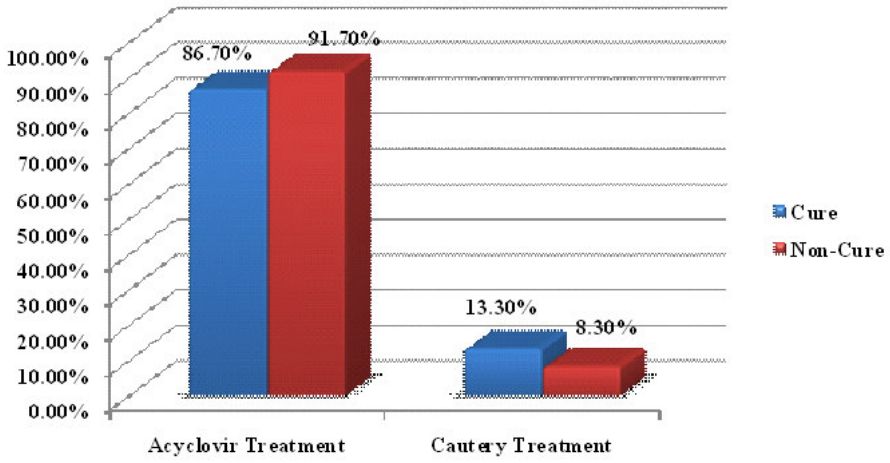


Figure 4
Distribution of Patients with Vulval Warts by Acyclovir and Cautery Treatments

Associations of Acyclovir and Cautery Treatments with Patients Socio-Demographic Characteristics
Table 2 shows the Associations of Acyclovir and Cautery Treatments with Patients Socio-Demographic Characteristics, there were no significant associations of acyclovir and cautery treatments with patients' socio-demographic characteristics; p value ≤ 0.05 is significant.

Table 2
Associations of Acyclovir and Cautery Treatments with Patients Socio-Demographic Characteristics

Variable	Acyclovir Treatment		Cautery Treatment	
	Non-Cure (%)	Cure (%)	Non-Cure (%)	Cure (%)
Age group				
< 30 years	9 (56.3)	56 (53.8)	7 (70.0)	58 (52.7)
≥ 30 years	7 (43.7)	48 (46.2)	3 (30.0)	52 (47.3)
X^2 value	0.032		1.102	
P value	0.857		0.294	
Residence				
Urban area	12 (75.0)	78 (75.0)	6 (60.0)	84 (76.4)
Rural area	4 (25.0)	26 (25.0)	4 (40.0)	26 (23.6)
X^2 value	0.0		1.309	
P value	1.000		0.253	
Occupational status				
Employed	9 (56.3)	56 (53.8)	6 (60.0)	59 (53.6)
Non-Employed	7 (43.7)	48 (46.2)	4 (40.0)	51 (46.4)
X^2 value	0.032		0.150	
P value	0.857		0.699	
Educational level				
Illiterate	4 (25.0)	48 (46.2)	1 (10.0)	51 (46.4)
Primary school	6 (37.5)	29 (27.9)	4 (40.0)	31 (28.2)
Secondary school	4 (25.0)	21 (20.2)	3 (30.0)	22 (20.0)
Higher education	2 (12.5)	6 (5.8)	2 (20.0)	6 (5.5)
X^2 value	2.968		6.585	
P value	0.392		0.068	

Associations of Acyclovir and Cautery Treatments with Patients Medical History
Table 3 shows the Association of Acyclovir and Cautery Treatments with Patients medical history, there were significant associations of acyclovir and cautery treatments with clinical presentation and complication due to vulval warts treatment as well as using of contraception, p value ≤ 0.05 is significant.

Table 3
Associations of Acyclovir and Cautery Treatments with Patients Medical History

Variable	Acyclovir Treatment		Cautery Treatment	
	Non-Cure (%)	Cure (%)	Non-Cure (%)	Cure (%)
Parity				
Null-Para	3 (18.8)	19 (18.3)	3 (30.0)	19 (17.3)
Multi-Para	13 (81.2)	85 (81.7)	7 (70.0)	91 (82.7)
X^2 value	0.002		0.992	
P value	0.963		0.319	
Clinical presentation				
> 5 wart lesions	5 (31.3)	82 (78.8)	0 (0.0)	87 (79.1)
3-5 wart lesions	9 (56.3)	20 (19.2)	8 (80.0)	21 (19.1)
Vulval and perianal lesions	2 (12.5)	2 (1.9)	2 (20.0)	2 (1.8)
X^2 value	16.850		31.072	
P value	<0.001*		<0.001*	
Contraception				
Combined oral contraceptive pills	8 (50.0)	14 (13.5)	5 (50.0)	17 (15.5)
Depo-provera injection	3 (18.8)	14 (13.5)	2 (20.0)	15 (13.6)
Intrauterine contraceptive device	2 (12.4)	11 (10.6)	1 (10.0)	12 (10.9)
No contraception	3 (18.8)	65 (62.5)	2 (20.0)	66 (60.0)
X^2 value	15.103		8.824	
P value	0.002*		0.032*	
Complication due to vulval warts tr.				
Yes	10 (62.5)	9 (8.7)	10 (100.0)	9 (8.2)
No	6 (37.5)	95 (91.3)	0 (0.0)	101 (91.8)
X^2 value	30.170		57.990	
P value	<0.001*		<0.001*	

DISCUSSION

All women in this study attended the outpatient clinic worried from multiple growths developed first time in the vulval area most of them didn't know its nature .93.3% of these patients were illiterate or had a primary or secondary school educational level and they didn't know its nature or its consequences, and their ability to recover from it. They felt difficult to leave it without consultation. So we clarify it to them that it is a viral infection which needs treatment and it is necessary to follow up. Current treatments are still unsatisfactory due to low efficacy and recurrence rate.In spite of prophylactic vaccines have been recommended for adolescent women. Appropriate treatment modalities from ano-genital warts are needed because of unavailability of the vaccine especially in developing countries as in our country or its cost. We compared the use of acyclovir cream which acts on viral DNA. Human papilloma virus is DNA virus with diathermy treatment which aimed to remove the lesions in a randomised trial 104 from 120(87.6%) completely cleared 5 days a week for 8 weeks application compared with 110 from 120 (91.7 %) in diathermy group which ended in one session but had pain of burn and complications as infection, scarring and de-pigmentation. Of the remaining sixteen in the acyclovir group six responded to acyclovir but were not completely cured (5%) and ten got recurrence (8.3%).There are many studies used different options of treatment for genital warts, whether medical or excisional each had its advantages and disadvantages.A study by Friedman M.*etal,* used the immunomodulator ammonium trichloro- tellurate 15% w/w cream to clear vulval/peri-anal condylomata acuminata,(76%) patients were considered completely cleared. Complete cure was achieved in 35 of 44 (80%) patients with vulval condylomata and in 21 of 30 (70%) patients with peri-anal condylomata. No scarring of treated areas was observed. Complete cure was achieved within a time range of 10-109 days. The most frequent side-effects observed were mild-to-moderate itching, soreness; burning and erythema while in our study no side effects from acyclovir application. In post-treatment follow up of up to 6 months, disease recurrence was observed in two patients (4%), at 105 and 144 days following completion of treatment [18] . Another study by Tatti S, *etal*, sinecatechins ointment 15% or 10% or vehicle (placebo) been used three times daily for a maximum of 16 weeks or until complete clearance of all warts: Complete clearance of all baseline and newly occurring warts was obtained in 57.2% and 56.3% of patients treated with sinecatechins ointment 15% and 10%, respectively, compared with 33.7% for vehicle (both P<.001). Significance was observed at weeks 4 and 6 and all subsequent visits. Numbers needed to treat were 4.3 and 4.4. Partial clearance rates of at least 50% were reported for 78.4% and 74.0% of patients in the sinecatechins ointment 15% and 10% groups compared with 51.5% of vehicle patients. During follow-up, recurrence of wart was observed in 6.5%, 8.3%, and 8.8% in the sinecatechins ointment 15% group, sinecatechins ointment 10% group, and vehicle patients, respectively. A total of 3.7%, 8.3%, and 0.0% developed new warts, respectively. A total of 87.7% and 87.3% of patients in the sinecatechins ointment 15% and 10% groups, and 72.1% of vehicle patients experienced application site reactions; 49.2%, 46.2%, and 65.4% of those, respectively, were mild or moderate [19] . Other study by Stockfleth E,*etal* showed About 78% of all patients treated with either Polyphenon E 15% or 10% ointment showed wart clearance rates of 50% or better. Less than 6% and 4% of patients in the Polyphenon E 15% and 10% ointment groups experienced wart recurrence during follow-up. Polyphenon E ointments demonstrated adverse effects being local application site reactions which were mild or moderate and local reactions declined during continued treatment [20] . A study by Diamantis ML,*etal*, demonstrated that imiquimod 5% cream showed complete clearance of warts occurred in up to 50% of patients treated with imiquimod 5% cream applied once-daily, 3 times per

week for up to 16 weeks. Recurrence rates ranged from up to 19% at 3 months to 23% at 6 months[21]. Akhavan S,*etal* study included six groups 42 in each group. Women aged 20-50 years: the podophyllin-, imiquimod- and cryotherapy-treated groups, and another three groups receiving 8-week combination therapy of 400 mg oral zinc sulfate with one of the above treatments. Total of 228 patients were recruited and completed the study in six treatment groups. No significant difference was observed in the response to treatment among these groups. Relapse after 6 months was significantly higher in the podophyllin-, imiquimod- and cryotherapy-treated patients compared to patients receiving these treatments in combination with oral zinc sulphate [22] . Another study y R.J.C.Gilson,*etal*: compare the efficacy and safety of combination therapy with cryotherapy and podophyllotoxin 0.15% cream versus cryotherapy alone in the treatment of anogenital warts. A randomised, double-blind, multicentre controlled trial. Patients received podophyllotoxin cream or placebo twice daily for 3 days/week for up to 4 weeks, with weekly cryotherapy continued to week 12 if required. Further treatment from week 12 to 24 was discretionary70 patients per group were randomly assigned and started treatment; 101 first-episode warts, 91 males. No treatment-related serious adverse events were reported. Follow-up at week 12 was 85%. By intention-to-treat analysis, clearances at 4 and 12 weeks were higher in the combination group (60.0% and 60.0%, respectively) than with cryotherapy alone (45.7%, 45.7%) although not statistically significant (RR 1.31, 95% CI 0.95to 1.81). By week 24 there was no difference between the groups (68.6% and 64.3%, respectively; RR 1.07, CI 0.84 to 1.35). At week 4, wart clearance was higher in men (p=0.001) and those with a past history of warts (p=0.009), but these differences were not detected at week 12. There was some evidence for a higher relapse rate in the group receiving cryotherapy alone [23] . A study by Panici, *etal* involved two hundred three patients their ages range (18- 45) years compared the use of systemic recombninant interferon intramuscular ,subcutaneous injection with electro diathermy coagulation after six months of end of treatment the overall complete and partial response was 70%,57% and82%.Fifteen and two in the cauterisation and interferon group respectively developed disease recurrence .All patients received interferon developed flue like illness for the first week and fatigue during the period of receiving the treatment [24] Excisional therapies, their aim to remove the lesion rather than specifically target HPV infection. Carrasco D,*etal* study found that Cytodestructive or surgical therapy for patients with anogenital warts is frequently associated with recurrence. In February 1997, the US Food and Drug Administration approved imiquimod as a 5% cream for the treatment of anogenital warts. Activity of the drug results primarily from interferon alfa and other cytokine induction in the skin. These cytokines stimulate several other aspects of the innate immune response. In addition, imiquimod stimulates acquired immunity, in particular the cellular arm that is important for control of viral infections and tumors. Published studies indicate that imiquimod results in complete clearance of warts in more than 50% of patients. Residual warts can be surgically excised. Their long-term follow-up (2 to 7 years) of patients who had a 16-week course of imiquimod cream with subsequent removal of remaining warts showed a much lower rate of recurrence in comparison with those patients who were treated with surgery alone. Therefore, treatment with imiquimod followed by excision of residual lesions may provide long-term clearance of anogenital warts in those patients in whom imiquimod monotherapy is insufficient [25] .

CONCLUSION

Future therapies will be directly or indirectly antiviral, targeting HPV protein functions or enhancing the ability of the immune system to resolve infection or inducing an immune response against it.

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