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Systematic Review of Imiquimod for the Treatment of External Genital Wart

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Abstract: The objective of this review is to assess whether imiquimod provides a therapeutic advantage over placebo (vehicle) or other active therapy used in the treatment of adult patients with external genital and perianal warts/condyloma acuminata. We searched MEDLINE (1966 -March 2006), EMBASE (1988-March 2006) and the Cochrane database for randomized controlled trials. Eight RCTs were identified that met the inclusion criteria. None of them compared imiquimod to other active therapy. Seven trials compared imiquimod (1, 2 or 5% cream) to placebo in immunocompetent patients of which only two trials used the recommended dose and dosing regimen with a follow up of 12 weeks duration. Mortality and serious adverse events were not reported. The effectiveness of imiquimod over other existing therapies for the treatment of external genital/perianal warts has not been established. In immunocompetent patients, there is sufficient evidence to conclude that imiquimod 5% cream applied three times a week for a maximum duration of 16 weeks compared to placebo provides a short term efficacy advantage in terms of complete clearance with no recurrence at the end of 12 weeks of follow up (ARR = 27%, NNT = 4). There were significant increases in several adverse events (erythema ARI = 43%, NNH = 2; erosion ARI = 24%, NNH = 4; excoriation ARI = 22%, NNH = 5; edema ARI = 15%, NNH = 7; scabbing ARI = 13%, NNH = 8 and induration ARI = 6%, NNH = 17). Based on one trial in immunocompromised patients (HIV positive) we conclude that there is insufficient evidence that imiquimod provides a therapeutic advantage compared to placebo.

Key words: Imiquimod, external genital wart, systematic review

INTRODUCTION

External Genital Warts (EGW), caused by the Human Papilloma Virus (HPV) infection, are the most common sexually transmitted disease. Genital HPV infections are primarily transmitted by sexual contact with an infected individual; in some cases, maternal/fetal transmission occurs. The incubation period varies from 2 weeks to 8 months (Ting and Dytoc, 2004). EGW are commonly asymptomatic but depending on the size and anatomic location, they can be painful, friable and pruritic.

Epidemiologists estimate that the incidence of HPV infections is approximately 5.5 million per year in the USA and up to 75% of sexually active men and women have developed an antibody response to this virus (Ting and Dytoc, 2004). The estimates of prevalence of HPV infection vary by population studied and testing procedure used. About 10 to 20% of sexually active adults exhibit molecular evidence of current genital HPV infection, in 50 to 75% of which the infection is from high-risk types. Serological evidence suggests that over 50% of sexually active women have had a past infection with at least one HPV type. The rate of infection by any HPV type among sexually active young women within three years was 44% in a recent study. However most of these infections are transient. Women under 25 to 30 years have higher rates of infection although a second peak has been described in postmenopausal women" (Koliopoulos, 2005). A HPV prevalence survey in women in Ontario has reported the highest prevalence of HPV i.e., 24%, in women 20 to 24 years old and a progressively lower prevalence in older age groups, reaching 3.4% in women 45 to 49 years (Sellors *et al*., 2000). Follow up HPV testing one year later showed 11.1% (28/253) incident HPV infection in the women overall, with the highest rate, 25.0% (6/24), in the 15-19-year age group. Of the previously HPV-positive women, 51.9% (28/54) had cleared the infection (Sellors *et al*., 2003).

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Of the HPV infected population, only 1-2% manifest active EGW lesions. There are over 80 different HPV types and approximately 30 of them have been associated with genital epithelial infection (Ting and Dytoc, 2004). HPV types 6 and 11 usually cause EGW. These types are rarely associated with invasive squamous cell carcinoma of the external genitalia. However, HPV types 16, 18, 31, 33 and 35 are found occasionally in visible genital warts and have been associated with external genital (i.e., vulvar, penile and anal) squamous intraepithelial neoplasia (i.e., squamous cell carcinoma in situ, bowenoid papulosis, erythroplasia of Queyrat, or Bowen's disease of the genitalia). These HPV types also have been associated with vaginal, anal and cervical intraepithelial dysplasia and squamous cell carcinoma. Patients who have visible genital warts can be infected simultaneously with multiple HPV types (STD Guideline, 2002).

Infection of the uterine cervix with the high-risk types of HPV is necessary for the development of cervical cancer, although the HPV infection alone is usually not sufficient to cause cancer and the presence of additional co-factors is required. Other risk factors for cervical cancer (sexual behavior, oral contraceptives, smoking, parity, circumcisional status of the male partner) are effect modifiers that influence the association between HPV infection and carcinogenesis (development of cancer) (Koliopoulos, 2005; Sanclemente and Gill, 2002). Squamous cell anal cancer is associated with a history of genital warts, which suggests that papilloma virus infection is a cause of anal cancer (Habif, 2004; Daling *et al*., 1987). Seventy-three percent of the nonmalignant, clinically and histologically normal tissue 2 to 5 cm from the tumors contained HPV-16. This implies that HPV can persist latently in tissue that appears normal (Habif, 2004; Macnab *et al*., 1986).

The primary goal of treating visible genital warts is the removal of symptomatic warts. In most patients, treatment can induce wart-free periods. Without treatment, genital warts regress spontaneously (10-30% complete regression in placebo treated patients within 3 months), remain unchanged or multiply and increase in size (Perry and Lamb, 1999; Stone, 1995). Immunocompromised patients are more likely to experience symptomatic disease and typically have larger warts for a longer duration than immunocompetent HPV infected patients. The immune system may play a key role in the control of HPV infection (Coleman *et al*., 1994). Both nonspecific (natural killer cells) and antigen-specific (humoral and cell-mediated) immunity are involved in the defense against HPV. Serum IgG and secretory IgA block the attachment of the virus to the epithelial cells. However, once the infection has occurred, the antibodies cannot usually eliminate the virus. The cell-mediated immunity is essential at this stage as CD4+ and CD8+ lymphocytes are activated and destroy infected cells and produce cytokines such as interferons which have antiviral properties (Koliopoulos *et al*., 2005; Sanclemente and Gill, 2002). The changes in regression of genital warts are consistent with a delayed -type hypersensitivity reaction to foreign antigen. Regressing warts contained more lymphocytes and macrophages than did nonregressing controls (Coleman *et al*., 1994).

Determining whether treatment of genital warts will reduce transmission is difficult, because no laboratory marker of infectivity has been established and because clinical studies evaluating the persistence of HPV DNA in genital tissue after treatment have shown variable results. Existing data indicate that currently available therapies for genital warts may reduce, but probably do not eradicate, infectivity (STD Guidelines, 2002).

Treatment of genital warts should be guided by the preference of the patient, the available resources and the experience of the health-care provider. Because of uncertainty regarding the effect of treatment on future transmission and the possibility for spontaneous resolution, an acceptable alternative for some patients is to forego treatment and await spontaneous resolution. No single treatment is ideal for all patients or all warts (STD Guidelines, 2002).

This systematic review was performed to assess the benefits and harms of the recommended dose of imiquimod (5%, 3 times a week, up to a maximum of 16 weeks) in the treatment of EGW. Its potential therapeutic advantage over placebo (vehicle) or other existing therapies was assessed based on the published randomized controlled trials.

Imiquimod, an immune response modifying agent, is indicated for the treatment of external genital and perianal warts/condyloma acuminata in adults" (Aldara ™ product monograph, 2004). Imiquimod is to be applied 3 times per week, prior to normal sleeping hours and left on the skin for 6-10 h, until there is total clearance of the genital/perianal warts or for a maximum of 16 weeks.

The recommended dose was chosen on the basis of no significant difference in efficacy in terms of wart clearance rate but a significant increase in the incidence of local adverse events (erythema, vesicle formation, ulceration and excoriation) with frequency of application greater than 3 times per week. This recommendation is supported by the findings from three open label dose escalating clinical trials that compared imiquimod 5% application once a day, twice a day, three times a day or three times a week for 4 or 16 weeks or up to complete clearance of warts (Fife *et al*., 2001, 2004; Trofatter *et al*., 2002; Gollnick *et al*., 2001).

The precise mechanisms of action of imiquimod in regression of genital warts, primary superficial basal cell carcinoma and treatment of actinic keratoses, the three

approved indications, are not known. Imiquimod has not been shown to have direct anti-viral activity in tissue culture, suggesting that its mechanism of action *in vivo* is indirect. Release and/or synthesis of a range of cytokines from monocytes/macrophages and keratinocytes is induced by imiquimod. The precise pattern of cytokines depends on the cell type and includes interferon-α, tumour necrosis factor-α, IL-1, IL-6, IL-8, IL-1 receptor antagonist, GM-CSF, macrophage inflammatory protein 1a and IL-12 (which in turn can stimulate interferon-α). Interferon-α activates macrophages, cytotoxic T-cells and natural killer cells. The cytokine profile is consistent with enhancement of a Th1 immune response, the type of immune response generally required for antigen-specific anti-viral and anti-tumour responses. Since binding of imiquimod to responding cells is a saturable event (i.e., finite), a membrane receptor exists. Recently it has been shown that imiquimod binds to and activates the toll-like receptor (TLR) 7. The toll gene was originally described in Drosophila melanogaster and plays a role in antifungal defenses (Hurwitz *et al*., 2002). Toll-like receptors are transmembrane receptors that recognize pathogen-associated molecular structures such as peptidoglycans, bacterial DNA, viral double stranded RNA, lipopolysaccharides and bacterial flagellin. So far, eleven subtypes of toll-like receptors have been identified in humans. Each identified subtype of receptor binds a specific microbial product (e.g., TLR-4 recognizes bacterial lipopolysaccharide; the natural ligand for TLR7 has not been identified). Upon binding of ligand, toll-like receptors initiate the synthesis of pro-inflammatory cytokines through an adaptor protein MyD88 that binds the receptor along with downstream signaling proteins.

TLR7 is expressed in murine heart, spleen, bone marrow and lymph nodes (Hemmi *et al*., 2002). Immunological cells that express TLR7 include monocytes/macrophages, B cells and dendritic cells. Dendritic cells participate in the presentation of antigen to T-cells. Peritoneal macrophages from mice deficient in TLR7 (or MyD88) do not produce cytokines in response to imiquimod, suggesting that imiquimod activates macrophages through TLRs (Hemmi *et al*., 2002). *In vivo* responses to R-848, a more potent imidazoquinoline than imiquimod are also absent in TLR7 deficient mice. TLR7 deficient splenocytes (containing B cells) do not proliferate in response to imiquimod suggesting that activation of B cells also occurs via TLRs. To date, expression of TLR7 has not been reported in keratinocytes or Langerhans cells. It is therefore not known whether imiquimod exerts its effect only through TLR7 or whether TLR7 is the only receptor imiquimod binds to. The clinical relevance of activation of TLR7 in genital wart or actinic keratosis treatment is not yet known.

MATERIALS AND METHODS

The inclusion criteria for this review were published randomized controlled trials (single, double blind or open label) comparing imiquimod to placebo or other standard therapy used in the treatment of external genital and perianal warts/condyloma accuminata in adult patients. Open label trials were included since the local adverse effect of the imiquimod treatment results in high frequency (82-100%) of local skin reactions and blinding can be potentially broken. Also it is not possible to maintain blindness for some therapies such as cryotherapy or electrosurgery.

Other standard therapies include:

- Pharmacologic treatment:
  - Cytotoxic agents: Podophyllin, Podofilox, Trichloroacetic acid (TCA), 5-fluorouracil (5-FU), Retinoids and Bleomycin.
  - Immunomodulating agents: Intralesional Interferon-α 2b
- Nonpharmacologic treatment:
  - Physical ablation: Cold steel surgery, cryotherapy, electro-surgery and lasers

The following outcome measures from each trial were summarized with most weight given for the outcomes highest on the list.

- All-cause mortality
- Other serious adverse events -including, anogenital cancer, cervical/vaginal cancer and intraepithelial dysplasia.
- Total adverse events including systemic and local events (e.g., local skin reactions, systemic events such as flu-like symptoms, etc).
- Complete clearance rate with no recurrence at the end of follow-up (ideally over a period of 8 months). This is defined as 100% clearance of identified baseline wart lesion followed by development of no new wart lesion at the same site at the end of the follow up period.

For proper conclusion on the benefit versus harm of imiquimod therapy for genital wart, RCTs require long-term (preferably several years) assessment of efficacy and safety outcomes. Conference abstracts or posters were not considered since they do not contain sufficient detail to assess the validity of the findings and the quality of the study.

Conclusions were based on critically appraised and/or summarized trials meeting the inclusion criteria.

Search strategy and findings: The search included electronic databases: MEDLINE (1966-March 2006-), EMBASE (1988-March 2006), the Cochrane database. In addition, retrieved clinical trials and some review articles were hand searched for references. Keywords used were: 'Imiquimod', genital wart or condyloma acuminata" and 'randomised or randomized'.

RESULTS

Eight RCTS met the inclusion criteria (Edwards *et al.*, 1998; Beutner, Spruance *e t al.*, 1998; Beutner, Tyring *et al.*, 1998; Syed *et al.*, 1998, 2000; Tyring *et al.*, 1998; Arican *et al.*, 2004; Gilson *et al.*, 1999). None of the trials compared imiquimod to other standard therapy used in treatment of adult patients with genital and perianal warts/condyloma accuminata. Two trials in immunocompetent patients (Edwards *et al.*, 1998; Tyring *et al.*, 1998 and one trial in immunocompromised patients (Gilson *et al.*, 1999) used imiquimod at the recommended dose and duration compared to placebo.

Seven trials included a total number of 885 immunocompetent patients aged≥18 years (seronegative for HIV) with 2-50 EGW lesion and total wart coverage area of at least 10 mm^2. Gilson *et al.*, 1999 trial has evaluated 100 patients of age≥18 years with a laboratory confirmed diagnosis of HIV.

Benefit: In this review, efficacy (benefit) from all trials is reported as complete clearance of warts with no recurrence and is calculated based on an intention-to-treat analysis of all randomized patients at the end of follow up in each trial. Those patients who were lost to follow up were considered to not have achieved the efficacy measure (Table 3-7).

Harm: Harm has been reported according to the hierarchy of outcome measure defined in methods. Long term adverse events beyond 16 weeks of treatment and 12 weeks of follow up are not known. Short-term adverse events have been summarized in Table 3-7). Mortality and serious adverse events were not reported. Commonly

Table 1: Summary outline of 6 double blind randomized controlled trials included in this review using imiquimod 5% cream compared to placebo

Trial	Interventions	Duration of Rx Follow-up	Patients N (%), M = Males, F = Females
Trials in immunocompetent patients			
Tyring *et al.* (1998)	Imiquimod 5% Placebo 3 times a week applied overnight (8±2 h)	16 weeks Rx 12 weeks follow up	N = 22, M = 12 (55), F = 10(45)
Edwards *et al.* (1998)	Imiquimod 5% Imiquimod 1% Placebo 3 times a week applied for 6-10 h	16 weeks Rx 12 weeks follow up	N = 311, M = 180 (58), F = 131 (42)
Ferenczy *et al.* (1998) (a second follow up study of Edwardset *el al.* (1998)	Imiquimod 5% Placebo once-daily application during follow up.	Rx duration = NR FU duration = NR	N = 94 (subgroup), M = 52 (55), F = 42 (45)
Beutner, Tyring *et al.* (1998)	Imiquimod 5% Placebo Imiquimod 1% Daily application applied for 8±2 h (at bedtime)	16 weeks Rx 12 weeks follow up	N = 279 M = 154 (55), F = 125 (45)
Arican *et al.* (2004)	Imiquimod 5% Placebo 3 times a week applied for 8±2 h 8±2 h	12 week RX 24 week follow up	N = 45, M = 32 (71), F = 13 (29)
Beutner Spruance *et al.* (1998)	Imiquimod 5% Placebo 3 times a week applied for 24 h	8 weeks Rx 10 week follow up	N = 108, M = 98 (91), F = 10(9)
Trial on immunocompromised patients (HIV positive)			
Gilson *et al.* (1999)	Imiquimod 5% Placebo 3 times a week applied for 8±2 h (at bedtime)	16 weeks Rx 12 weeks follow up	N = 100, M = 97 (97), F = 3 (3)

Table 2: Summary outline of 2 double blind randomized controlled trials included in this review using imiquimod 2% cream

Trial	Interventions	Duration of Rx Follow-up	Patients N (%), M = Males, F = Females
Syed *et al.* (1998)	Imiquimod 2% Placebo Twice daily for 5 consecutive days applied only on warts	6 weeks Rx 11 months follow up	N = 60 only, F (100)
Syed *et al.* (2000)	Imiquimod 2% Placebo once daily for 3 consecutive days per week applied at bedtime.	4 weeks Rx (maximum 12 applications in 4 weeks). In patients who were not cured at 4 weeks treatment was continued and patients were examined weekly up to 16 weeks. Treatment was stopped in patients who were considered cured at the weekly examination. 17 months follow up	N = 60 only, M (100)

Table 3: Summary of the efficacy and safety data of the two trials with the indicated dose/duration (Imiquimod 5%, 3 times per week, for a maximum duration of 16 weeks)

Trial	Benefit I = imiquimod 5%; P = Placebo	Harm
Edwards *et al.* (1998) 16 weeks Rx 12 weeks FU N = 311 Imiquimod applied for 6-10 h	Complete clearance and no recurrence I = 39/109 (36%) P = 9/100 (9%) p<0.05 ARR = 27% NNT = 4 New lesions were tracked separately and were not included in the analysis of the baseline warts.	Mortality not reported SAE not reported Total withdrawals = 4 Total WDAE = 4 One due to rhabdomyolysis (it is not clear in I or P group) and 1 due to lightheadedness, insomnia, fatigue (it is not clear this patient has received imiquimod 5% or 1%) I = 2 due to local skin reactions Total AE : not reported Most common adverse events (the denominator does not include all randomized patients) Erythema I = 71/106 (67%); P = 23/95 (24%) Erosion I = 34/106 (32%); P = 8/95 (8%) Excoriation I = 26/106 (24%); P = 2/95 (2%) Edema I = 17/106 (16%); P = 1/95 (1%) Scabbing I = 16/106 (15%); P = 2/95 (2%) Induration I = 9/106 (9%); P = 3/95 (3%) Total number of patients experiencing ≥1 local AE not reported Flu-like symptoms "no difference in incidences among groups" but numbers NR
Tyring *et al.* (1998) 16 weeks Rx 12 weeks FU N = 22 Imiquimod applied overnight (8±2 h)	Complete clearance and no recurrence could not be calculated Trial reports complete clearance rate I = 7/19 (37%) P = 1/3 (33%) p value = not significant	Mortality not reported SAE =1 (diabetic coma) Lost to follow up = 3 WDAE = 1 I = due to diabetic coma Adverse events with imiquimod and placebo : NR

FU = Follow Up, ARR = Absolute Risk Reduction, NNT = Number Needed to Treat, WDAE = Withdrawal Due to Adverse Events, AE = Adverse Events, SAE = Serious Adverse Events, NR = Not Reported

reported adverse events at application site among all trials were tenderness, itching, burning, erythema, edema, erosion and excoriation. Available data on adverse events could not be pooled because of inconsistency in reporting of these outcomes in different trials.

Systemic exposure to imiquimod is one potential safety concern during 16 week treatment for EGW. Systemic adverse events similar to those associated with interferon treatment (e.g., flu-like syndrome, headache and myalgia) have been reported in the available RCTs. However, the incidence of such events was not statistically significantly different than the control groups in Arican *et al.* (2004) and in other trials.

Table 4: Summary of the efficacy and safety data of trials using more frequent or longer duration of application of imiquimod 5% cream that is not recommended according to the product monograph

Trial	Benefit I = Imiquimod 5%; P = Placebo	Harm
Beutner, Tyring *et al.* (1998) Different frequency of application of imiquimod 5% cream 16 weeks Rx 12 weeks FU N = 279 Daily application for 8±2 h	Complete clearance and no recurrence I = 40/94 (43%) P = 3/95(3%) p<0.05 ARR = 40%, NNT = 3	Mortality not reported SAE = 0 Total withdrawals = NR WDAE I = 1 due to local skin reactions P = 0 Most common Itching I = 32/92(35%); adverse events I = 30/92 (33%); P = 17/92 (19%) Pain (p<0.001) P = 2/92 (2%) Burning (p<0.0003) I = 15/92 (16%); P = 1/92 (1%)Tenderness (p<0.01) I = 11/92 (12%); P = 2/92 (2%) Other symptoms HeadacheI=27/92(29%); P = 30/92(33%) Upper respiratory tract infection I = 13/92(14%); P = 25/92(27%)
Beutner, Spmance *et al.* (1998) Different duration of Rx 3 times per week for 8 weeks applied for 24 h N = 108	Complete clearance and no recurrence N = 108 I = 10/51 (20%) P = 0/57 (0%) p<0.05 ARR = 20% NNT = 5	Mortality not reported SAE not reported Total withdrawals = NR WDAE: 0 Adverse events Skin irritation at wart site at week 8 I = 20/35 (57%); P = 41/45 (91%) p<0.002
Arican *et al.*, (2004) Different duration of Rx 3 times per week for 12 weeks N = 45	Complete clearance with no recurrence or new lesion I = Could not be calculated Placebo = 0/10(0%) Trial reports complete clearance rate I =23/33(70%) Placebo = 1/10(10%) p<0.05 ARR = 60, NNT = 2	Mortality not reported SAE not reported Total withdrawals = 2 (I = 1, Placebo = 1) WDAE = 0 Adverse events Total AE: I = 18/33(55%); Placebo = 4/10 (40%) Application site reaction I = 17/33 (52%); P = 4/11(36%) Flu like symptoms I = 1/33 (3%); P = 0

FU = Follow Up, ARR = Absolute Risk Reduction, NNT = Number Needed to Treat, WDAE = Withdrawal Due to Adverse Events, AE = Adverse Events, SAE = Serious Adverse Events, NR = Not Reported

Table 5: Summary of the efficacy and safety data of trials using different dose and/or duration of imiquimod treatment that is not indicated according to the product monograph

Trial	Benefit I = Imiquimod; p = Placebo	Harm
Syed *et al.* (1998) Imiquimod 2% twice daily for 5 consecutive per week days N = 60	Complete clearance and no recurrence I = 21/30 (70%) P = 0/30 (0%) p<0.05 ARR = 70%, NNT = 2	Mortality not reported SAE not reported Total withdrawals = NR WDAE = 0 Adverse events I = 8/30 (27%) P = 0 Nausea I = 2/30(7%), P = 0 Tenderness I3/30 (10%), P = 0 Erythema I = 2/30 (7%), P = 0 Burning sensation I = 1/30 (3%), P = 0
Beutner, Tyring *et al.* (1998) Imiquimod 1% daily application for 16 week N = 279 Imiquimod 1% = 90 P = 95	Complete clearance and no recurrence I = 10/90 (11%) p =3/95 (3%) p<0.05 ARR = 70%, NNT = 2	Mortality not reported SAE not reported Total withdrawals = NR WDAE = 1 in imiquimod group due to local skin reaction Most common adverse events (denominator does not include all randomized patients)

Table 5: Continued

Trial	Benefit I = imiquimod; p = placebo	Harm
		Itching I = 20/86(23%; P = 17/92 (19%) Pain (p<0.0001) I = 11/86(13%); P = 2/92 (2%) Burning (p<0.0003) I = 12/86 (14%; P = 1/92 (1%) Tenderness (p<0.01) I = 11/86(13%); P = 2/92 (2%) Other symptoms Headache I = 26/86 (30%); P = 30/92 (33%) Upper respiratory tract infection I = 23/86 (27%); P =25/92 (27%)
Edwards *et al.* (1998) Imiquimod 1% three times a week for 16 week N = 311 Imiquimod 1% =102 P =100	Complete clearance and no recurrence I = 18/102 (18%) P = 9/100 (9%) p<0.05 ARR = 9%, NNT = 12 New lesions were tracked separately and were not included in the analysis of the baseline warts.	Mortality not reported SAE not reported Total withdrawals = NR Total WDAE =? One due to rhabdomyolysis (it is not clear in I or P group) and 1 due to lightheadedness, insomnia, fatigue (it is not clear this patient has received imiquimod 5% or 1%) Most common adverse events Erythema I = 25/97 (26%); P = 23/95 (24%) Erosion I = 5/97 (5%); P = 8/95 (8%) Excoriation I = 4/97 (4%); P = 2/95 (2%) Edema I = 3/97 (3%); P = 1/95 (1%) Scabbing I = 3/97 (3%); P = 2/95 (2%) Induration I = 4/97 (4%); P = 3/95 (3%)
Syed *et al.* (2000) Imiquimod 2%applied at bedtime once daily for 3 consecutive days per week for 4 weeks. (Maximum 12 applications in 4 weeks) N = 60	Complete clearance and no recurrence I = 20/30 (66%) P = 1/30 (3%) p<0.05 ARR = 63%, NNT = 2	Mortality not reported SAE not reported Total withdrawals =? WDAE = 0 No drug related anticipated side effects = 49/60 (82%) The number of no adverse symptoms" has been reported as I = 48, P = 1 in table 1 of the article. Common adverse events Erythema I = 4 (13.3%); p = 0 Erosion I = 4 (13.3%); p = 1(3.3%) Edema I = 2 (6.7%); P = 0

FU = Follow Up, ARR = Absolute Risk Reduction, NNT = Number Needed to Treat, WDAE = Withdrawal Due to Adverse Events, AE = Adverse Events, SAE = Serious Adverse Events, NR = Not Reported

Table 6: Summary of the systemic adverse effects data of eight included trials of this review

Trial	Systemic adverse events
Tyring *et al.* (1998)	NR
Edwards *et al.* (1998)	2 WDAE, one due to familial rhabdomyolysis (it is not clear in I or P group) and 1 due to lightheadedness, insomnia, fatigue (which is not clear this patient has received imiquimod 5% or 1%)
Beutner, Tyring *et al.* (1998)	Headache I = 27/92(29), P = 30/92 (33) p = 0.0892 Upper respiratory tract infection I = 13/92(14), P = 25/92 (27) p = 0.053
Gilson *et al.*(1999)	Diarrhea I = 18.5% P = 5.7% Herpes simplex infection I = 12.3%, P = 8.6%
Beutner, Spmance *et al.* (1998)	NR
Syed *et al.* (1998)	Nausea I =2, P = 0
Syed *et al.* (2000)	NR
Arican *et al.* (2004)	Influenza-like symptoms I = 1, P = 0

WDAE = Withdrawal Due to Adverse Events, NR = Not Reported, I = Imiquimod, P = Placebo

Table 7: Summary of Gilson *et al.* (1999) randomized controlled trial using imiquimod for treatment of anogenital warts in HIV-infected patients

Trial	Benefit I = Imiquimod 5%; P = Placebo	Harm
Gilson *et al.* (1999) 16 weeks Rx and possibility of extended treatment for 8 additional weeks 12 weeks FU N = 100 M = 97 F = 3 Imiquimod applied for 8±2 h every other day followed by two consecutive days without treatment, three times a week for a maximum of 16 weeks	Complete clearance and no recurrence I = 7/65 (11%) P = 2/35 (6%) p = not significant New wart lesions I = 12/62 (19%) P = 7/30 (23%) p = not significant 3/12 lesions in imiquimod group and none in the placebo group cleared. p = not significant	Mortality not reported SAE not reported Total withdrawals I = 27/65 (42%); P = 20/35 (57%) Severe adverse events I = 3/65 (1 severe pain at wart site, 1 severe pruritis and burning at wart site and 1 required circumcision after swelling and soreness of the prepuce and glans). Total WDAE, I = 1/65 (1.5%); P = 1/35 (2.8%) Total AE, I = 45/62(69%); P = 23/30(66%) At least one moderate to severe adverse event I = 34/62(52%); P = 23/30 (66%) Three most frequent adverse events Application site reaction (pmritis, pain and soreness at wart site) I =15.4%; P = 20% (p = NS) Diarrhea I = 18.5% P = 5.7% (p = NS) Herpes Simplex infection I = 12.3%; P = 8.6% (p = NS) HIV disease progression-5 patients receiving 5% imiquimod; 0 in P group (p = NS)

FU = Follow Up, ARR = Absolute Risk Reduction, NNT = Number Needed to Treat, WDAE = Withdrawal Due to Adverse Events, AE = Adverse Events, SAE = Serious Adverse Events, NR = Not Reported, NS = Not Significant

DISCUSSION

- There are no head to head RCTs comparing imiquimod with other existing therapies in the treatment of EGW in adult patients.
- None of the trials reported mortality. Serious adverse event and other adverse event reporting was inadequate in most trials
- There are no trials using the recommended dose and duration of imiquimod with a long-term follow up data. Two trials using the recommended drug regimen had a short follow-up period of 12 weeks. Three trials using imiquimod 5% but not the recommended frequency or duration of treatment had a follow up period of 10-24 weeks. Two trials (Syed *et al.*, 1998, 2000) with a follow up period of 11 and 17 months, respectively compared 2% imiquimod with placebo treatment for duration of 4-6 weeks, which is not the recommended dose, or duration of treatment as stated in the product monograph.
- None of the trials have clearly stated the practical method of distinguishing new wart lesions from recurrence of the previous lesion. Also data of new lesions have not been reported in detail in many trials and this could potentially weaken the validity of the reported data on recurrence rate in both imiquimod and placebo groups.
- Another relatively minor limitation regarding AE is the fact that in some of the trials the total numbers of patients with application site reactions are not reported (e.g., these are divided into several categories in Edwards *et al.* (1998). Some patients may experience more than one reaction

In the only available RCT in HIV-infected patients using the recommended drug regimen with short-term follow up period of 12 weeks, recurrence rate has not been reported so complete clearance rate with no recurrence could not be calculated. There was no significant difference between imiquimod and placebo-treated patients in terms of complete clearance rate.

CONCLUSIONS

Imiquimod versus other standard therapy

- There are no available RCTs comparing the effect of imiquimod with other existing therapies for the treatment of external genital/perianal warts in adult patients. Therefore, the effectiveness of imiquimod over other existing therapies for the treatment of external genital/perianal warts has not been established.

Imiquimod versus placebo

- There is evidence from one published randomized controlled trial (N = 885) that imiquimod 5% cream applied three times a week for a maximum duration of 16 weeks provides a short-term efficacy advantage compared to placebo in terms of complete clearance rate with no recurrence during 12 weeks of follow-up (ARR = 27%, NNT = 4) in immunocompetent adult patients with external genital or perianal warts/condyloma accuminata. Serious adverse events were not reported. There was a significant increase in local adverse events in the imiquimod

group compared to placebo-erythema (ARI = 43%, NNH = 2); erosion (ARI = 24%, NNH = 4); excoriation (ARI = 22%, NNH = 5); edema (ARI = 15%, NNH = 7); scabbing (ARI = 13%, NNH = 8); induration (ARI = 6%, NNH = 17) (Edwards *et al*., 1998).

- One published randomized controlled trial (N = 100) with 12 weeks follow up showed that imiquimod 5% cream applied three times a week for a maximum duration of 16 weeks was not statistically significantly different compared to placebo in terms of complete clearance rate in adult HIV-infected patients with external genital and perianal warts/condyloma accuminata. Complete clearance rate with no recurrence could not be calculated in this trial (Gilson *et al*., 1999). Mortality and serious adverse events were not reported. There was no significant difference between imiquimod and placebo groups in other adverse events.

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