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Imiquimod, a Patient-Applied Immune-Response Modifier for Treatment of External Genital Warts

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Genital human papillomavirus infection is one of the most common sexually transmitted diseases. Imiquimod is a new agent, an immune-response modifier, that has been demonstrated to have potent in vivo antiviral and antitumor effects in animal models. The present prospective, multicenter, double-blind, randomized, vehicle-controlled trial evaluated the efficacy and safety of daily patient-applied imiquimod for up to 16 weeks for the treatment of external genital warts. Wart recurrence was investigated during a 12-week treatment-free follow-up period. In the intent-to-treat analysis, baseline warts cleared from 49 of 94 (52%) patients treated with 5% imiquimod cream, 13 of 90 (14%) patients treated with 1% imiquimod cream, and 3 of 95 (4%) vehicle-treated patients; the differences between the groups treated with vehicle and imiquimod were significant ($P < 0.0001$). For subjects who completed the follow-up period, recurrence rates after a complete response were 19% (9 of 48 patients) in the 5% imiquimod cream group, 17% (2 of 12) in the 1% imiquimod cream group, and 0% (0 of 3) in the vehicle-treated group. There were no systemic reactions, although local skin reactions (generally of mild or moderate severity) were common, particularly in the 5% imiquimod cream group. Local reactions caused two patients to discontinue treatment. The most frequently reported local skin reactions were erythema, excoriation or flaking, and erosion. Patient-applied 5% imiquimod cream is effective for the treatment of external genital warts and has a favorable safety profile.

Genital human papillomavirus (HPV) infection is a common sexually transmitted disease. The most frequent clinical manifestation of infection is genital warts. An estimated 30 to 50% of sexually active adults in the United States are infected with HPV, although only 1% may have visible genital warts (16, 21). The natural history of genital warts in humans appears to be that they may persist, progress, or regress (33). Regression of genital warts is thought to be due to an immune response (17).

Most treatments currently available for genital warts (e.g., cryotherapy, excision, electrosurgery, coagulation, laser surgery, trichloroacetic acid treatment, and podophyllin resin treatment) are directed at the lesions and not at the etiologic agent, HPV (33, 34). Interferons (IFNs) (8, 9, 28, 36) and patient-applied podofilox (podophyllotoxin) (5, 10, 19, 37) are currently available therapies that have been evaluated in well-controlled trials.

Imiquimod, 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (also known as R-837 and S-26308), is a nonnucleoside heterocyclic amine that belongs to a class of products known as immune-response modifiers. In vivo studies have demonstrated that imiquimod is a potent inducer of alpha IFN (IFN-α), tumor necrosis factor alpha (TNF-α), and interleukin-6 (IL-6) (20, 25, 29, 38, 39) and that it has adjuvant properties greater than those of Freund's complete adjuvant (4). In animal models, imiquimod has been demonstrated to have potent antiviral (2, 3, 7, 12–14, 17, 25) and antitumor (6, 30, 31) effects. The current study was designed to evaluate the efficacy and safety of imiquimod for the treatment of external genital warts.

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MATERIALS AND METHODS

This seven-center, double-blind, randomized, parallel-group study assessed the efficacy and safety of daily applications of imiquimod cream versus vehicle cream in patients with external genital warts. Otherwise healthy males and females, aged 18 years and older, were enrolled if they had at least 2 but not more than 50 external genital warts (defined as warts in the genital, anal, perineal, or perianal area) with a biopsy diagnostic or suggestive of condyloma acuminatum and a bidimensional wart area of at least 10 mm^2. All patients were seronegative for the human immunodeficiency virus. Female patients could not be pregnant or lactating and had to agree to use effective birth-control measures. Exclusion criteria included genital wart therapy in the 4 weeks prior to treatment initiation and, for female patients, a prestudy Pap smear showing a high-grade squamous intraepithelial lesion. All patients gave written informed consent before enrollment. The protocol and consent forms were reviewed and approved by appropriate institutional review boards at each institution.

Patients were randomized by study center and gender to receive daily applications of either 5% imiquimod cream, 1% imiquimod cream, or vehicle cream for a maximum of 16 weeks. Before bedtime patients rubbed the study cream into clean, dry, wart-area skin until it disappeared and washed the area with soap and water 8 ± 2 h after application. To investigate wart recurrence, patients who had complete clearance of their baseline warts at any time during the treatment period stopped treatment and entered a 12-week treatment-free follow-up period.

Patients were evaluated weekly for the first 4 weeks and every 2 weeks thereafter for the remainder of the 16-week treatment period as well as during the 12-week follow-up period. A detailed wart assessment, including photographs,

TABLE 1. Baseline patient and wart characteristics

Characteristic	5% Imiquimod cream group	1% Imiquimod cream group	Vehicle group
No. of patients	94	90	95
Gender			
Male (no. [%])	52 (55)	49 (54)	53 (56)
Female (no. [%])	42 (45)	41 (46)	42 (44)
Mean ± SD age (yr)	30 ± 10	33 ± 11	30 ± 9
Race			
White (no. [%])	89 (95)	84 (93)	93 (98)
Black or other (no. [%])	5 (5)	6 (6)	2 (2)
Wart area (median mm^2 [range])	137 (2–9,588)	148 (10–13,461)	121 (4–2,603)
No. of warts (median [range])	7 (1–47)	8 (1–50)	8 (1–45)
Duration of current outbreak (median no. of mo [range])	7.3 (0.2–484.3)	12.2 (0.3–388.1)	8.7 (0.3–246.8)
Time since initial onset (median no. of mo [range])	21.7 (1.0–485.3)	24.1 (0.3–491.4)	19.9 (0.6–318.3)
No previous wart treatment (no. [%])	31 (33)	24 (27)	23 (24)
Wart location[a] (no. [%])			
Female			
Vulvar	35 (83)	37 (90)	38 (90)
Perianal	17 (40)	21 (51)	21 (50)
Perineum	1 (2)	2 (5)	1 (2)
Other	4 (9)	2 (4)	0 (0)
Male			
Penile	50 (96)	41 (84)	47 (89)
Perianal	4 (8)	12 (24)	5 (9)
Scrotum	2 (4)	3 (6)	4 (8)
Groin	2 (4)	7 (14)	3 (6)
Other	4 (8)	8 (16)	4 (8)

[a] Some patients had warts in more than one location.

measurements, counts, and location, was completed before the study treatment was initiated and at each evaluation visit. New warts that developed during the treatment period were treated with study medication and were followed separately from the baseline target warts. Both the patient and study personnel assessed local skin reactions at the treatment sites using a four-point scale of from 0 (no reaction) to 3 (severe). Clinical laboratory tests (e.g., hematology, blood chemistry, and urinalysis) were performed before treatment, at week 8, and after treatment. All patients were asked about adverse experiences at each evaluation visit.

The primary efficacy comparison was the proportion of patients in each treatment group who had complete clearance of their baseline warts during the treatment period. The intent-to-treat analysis included all randomized patients. The subset evaluable for efficacy analysis excluded patients who discontinued treatment for administrative reasons (e.g., for personal reasons, loss to follow-up, or insufficient baseline wart area), were noncompliant, had intercurrent illness, or otherwise failed to meet the study criteria. The clearance rates among the treatment groups were compared by Fisher's exact test for both analyses.

RESULTS

A total of 279 patients, 154 males and 125 females, entered the study. Patient demographic and wart characteristics were similar among treatment groups (Table 1). The primary locations of warts in the female patients were vulvar (88%) and/or perianal (47%), and in men they were penile (90%) and/or perianal (14%).

Of the 279 patients, 72 (26%) did not complete treatment (25 in the 5% imiquimod cream group, 19 in the 1% imiquimod cream group, and 28 in the vehicle group). Seventeen patients withdrew for reasons related to treatment: one patient in each imiquimod group for local skin reactions, four patients in the 1% imiquimod cream group and two patients in the vehicle group for lack of a therapeutic effect, and three patients in the 1% imiquimod cream group and six patients in the vehicle group for clinically significant increases in wart area. An additional 55 patients (24 in the 5% imiquimod cream group, 11 patients in the 1% imiquimod cream group, and 20 patients in the vehicle group) did not complete treatment because they were lost to follow-up, were noncompliant, or had an intercurrent illness, among other reasons.

In the intent-to-treat analysis, the rates of clearance of the baseline warts among treatment groups were 52% (49 of 94) in the 5% imiquimod cream group, 14% (13 of 90) in the 1% imiquimod cream group, and 3% (3 of 95) in the vehicle group (Table 2). The clearance rate obtained with 5% imiquimod cream was significantly higher than that obtained with the vehicle and the 1% imiquimod cream ($P < 0.0001$). The clearance rates for female patients were higher than those for male patients in all treatment groups (Table 2). A Kaplan-Meier analysis of the estimated proportion of female and male patients treated with 5% imiquimod cream with complete clearance of warts over the 16-week treatment period (Fig. 1) was in close agreement with the analysis of the subset used for efficacy evaluation.

TABLE 2. Proportion of patients from whom warts were completely cleared, by treatment group

Analysis and patient group	% (no. of patients whose warts cleared/ total no. of patients)			Pairwise comparison (P value)[a]		
	5% Imiquimod cream group	1% Imiquimod cream group	Vehicle group	5% cream group vs vehicle group	5% cream group vs 1% cream group	1% cream group vs vehicle group
Intent-to-treat analysis group						
All patients	52 (49/94)	14 (13/90)	3 (3/95)	<0.0001	<0.0001	0.008
Males	42 (22/52)	4 (2/49)	0 (0/53)	<0.0001	<0.0001	0.228
Females	64 (27/42)	27 (11/41)	7 (3/42)	<0.0001	<0.0009	0.020
Analysis of subset evaluable for efficacy						
All patients	71 (49/69)	16 (13/79)	4 (3/75)	<0.0001	<0.0001	0.016
Males	59 (22/37)	5 (2/40)	0 (0/42)	<0.0001	<0.0001	0.235
Females	84 (27/32)	28 (11/39)	9 (3/33)	<0.0001	<0.0001	0.071

[a] Fisher's exact test.

The subset evaluable for efficacy consisted of 223 patients (69 in the 5% imiquimod cream group, 79 in the 1% imiquimod cream group, and 75 in the vehicle group). Complete clearance of baseline warts was noted for 49 of 69 (71%) patients in the 5% imiquimod cream group, 13 of 79 (16%) patients in the 1% imiquimod cream group, and 3 of 75 (4%) patients in the vehicle group (Table 2). The clearance rates obtained with 5% imiquimod cream were significantly higher than those obtained with both vehicle and 1% imiquimod cream ($P < 0.0001$). In addition to complete responses, many patients had partial responses. By the last evaluation during the treatment period, 64 of 69 (93%) patients in the 5% imiquimod cream group, 32 of 79 (41%) patients in the 1% imiquimod cream group, and 17 of 75 (23%) patients in the vehicle group had at least a 50% reduction in wart area; the difference among the groups was significant ($P < 0.0001$).

Patients were allowed to take rest periods of 1 to 7 days at any point in therapy when local skin reactions made continued application of the cream difficult. Rest periods were taken by 50% of all patients in the 5% imiquimod cream group. During the study, the mean number of rest days per patient was 11 for all patients, 14 for female patients, and 9 for male patients. The majority of the rest periods lasted 1 to 4 days. Female patients tended to take more 5- to 7-day rest periods than male patients. Comparing the clearance rates (intent-to-treat analysis) for all patients, the clearance rates were independent of how many rest days were taken and the lengths of the rest periods.

The median times to the complete clearance of baseline warts were 9 weeks for the 5% imiquimod cream group, 7 weeks for the 1% imiquimod cream group, and 12 weeks for the vehicle group. For the imiquimod cream treatment groups, the median time to clearance of baseline warts was shorter for female patients than for male patients (8 versus 10 weeks for the 5% imiquimod cream group and 6 versus 11 weeks for the 1% imiquimod cream group).

New warts (not present at treatment initiation) developed in 27 of 92 (29%) patients in the 5% imiquimod cream group, 44 of 86 (51%) patients in the 1% imiquimod cream group, and 58 of 92 (63%) patients in the vehicle group ($P < 0.0001$). By the end of treatment, new warts had cleared totally from 11 of 27 (41%) patients in the 5% imiquimod cream group, 4 of 44 (9%) patients in the 1% imiquimod cream group, and 15 of 58 (26%) patients in the vehicle group ($P = 0.006$).

The recurrence of baseline warts in patients who completed the follow-up occurred in 9 of 48 (19%) patients in the 5% imiquimod cream group, 2 of 12 (17%) patients in the 1% imiquimod cream group, and none of the patients in the vehicle group. Of the 11 patients who experienced a recurrence during the follow-up period, three of these recurrences were noted at week 4, four were noted at week 6, two were noted at week 8, one was noted at week 10, and one was noted at week 12 of follow-up.

The most common local skin reactions in all treatment groups were erythema, excoriation or flaking, and erosion (Ta-

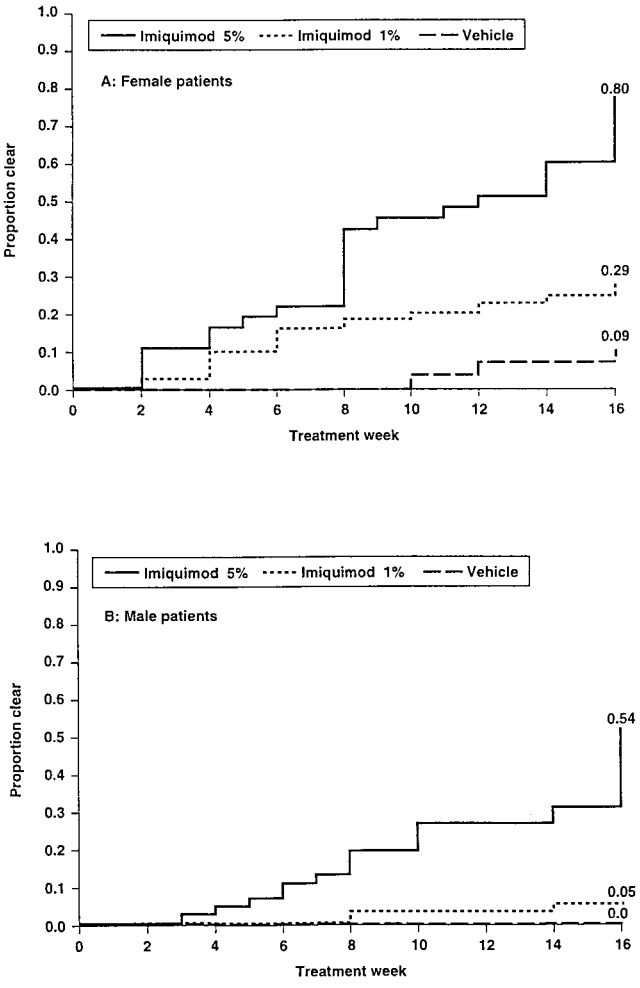

FIG. 1. Kaplan-Meier estimate of the proportion of female (A) and male (B) patients treated with 5% imiquimod cream, 1% imiquimod cream, or vehicle with complete clearance of warts over the 16-week treatment period.

TABLE 3. Frequency of most severe wart-site reactions assessed by the investigators[a]

Treatment and severity of reaction	No. (%) of patients with the following reaction:							
	Erythema	Excoriation or flaking	Erosion	Edema	Scabbing	Induration	Ulceration	Vesicles
5% Imiquimod cream group (n = 92)								
None	16 (17.4)	53 (57.6)	48 (52.2)	56 (60.9)	61 (66.3)	70 (76.1)	80 (87.0)	85 (92.4)
Mild	15 (16.3)	20 (21.7)	15 (16.3)	19 (20.7)	14 (15.2)	17 (18.5)	3 (3.3)	4 (4.3)
Moderate	40 (43.5)	16 (17.4)	26 (28.3)	13 (14.1)	12 (13.0)	5 (5.4)	8 (8.7)	3 (3.3)
Severe	21 (22.8)	3 (3.3)	3 (3.3)	4 (4.3)	5 (5.4)	0 (0.0)	1 (1.1)	0 (0.0)
Vehicle group (n = 92)								
None	58 (63.0)	78 (84.8)	87 (94.6)	89 (96.7)	87 (94.6)	89 (96.7)	92 (100)	92 (100)
Mild	26 (28.3)	10 (10.9)	4 (4.3)	2 (2.2)	5 (5.4)	3 (3.3)	0 (0.0)	0 (0.0)
Moderate	8 (8.7)	3 (3.3)	1 (1.1)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Severe	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a] Excludes patients who did not return to the clinic for any visits following the initiation visit.

ble 3). For the 5% imiquimod cream group, erythema was reported as mild for 16.3% of the patients, moderate for 43.5% of the patients, and severe for 22.8% of the patients. For the 1% imiquimod cream group, 34.9% of the patients reported mild erythema, 16.3% reported moderate erythema, and 9.3% reported severe erythema. None of the vehicle-treated patients had severe erythema; only 8.7% had moderate erythema, 28.3% had mild erythema, and 63.0% had no erythema. In the 5% imiquimod cream group there was a relationship between the complete clearance of warts and erythema at the wart site (assessed by using the highest level of erythema noted by either the investigator or the patient). For patients who experienced mild or greater erythema the warts were more likely to clear completely; however, not all individuals whose warts cleared developed an erythematous reaction. Among the female patients treated with 5% imiquimod cream, the complete response rate was 17% (1 of 6) for those who never experienced erythema at the treatment site, while the complete response rates were 63% (5 of 8), 56% (5 of 9), and 89% (16 of 18) for those who experienced mild, moderate, or severe erythema at the treatment site, respectively (P = 0.008; Fisher's exact test). Similarly, among the male patients treated with 5% imiquimod cream, the warts of none (0 of 8) of those who experienced no erythema at the treatment site cleared completely, while the warts of 43% (3 of 7), 48% (10 of 21), and 60% (9 of 15) of those who experienced mild, moderate, or severe erythema, respectively, cleared completely (P = 0.034; Fisher's exact test).

The most commonly reported wart-site reactions reported by patients were pain, itching, and burning at the application sites (Table 4). In the 5% imiquimod cream group, pain was reported at least once by 34.8% of the patients, itching was reported by 32.6% of the patients, and burning was reported by 16.3% of the patients. The reported systemic reactions and laboratory abnormalities reported by patients in the 5% imiquimod cream group were not significantly different from those reported by patients in the vehicle group. Headache and upper respiratory tract infections were the most common systemic adverse reactions among patients in all groups. No patients discontinued therapy because of systemic adverse reactions. One patient (1%) in each of the imiquimod cream groups discontinued therapy because of local skin reactions.

DISCUSSION

The extent to which patients develop visible warts is perhaps influenced by the host immune response to the virus (17, 32). Although HPV infections occur in a large proportion of the population, only a minority of individuals have visible symptoms, and even smaller numbers have severe or frequently recurrent disease (16, 21). The clinical observation that HPV infections are very common in chronically immunosuppressed patients strongly suggests an immune basis for the natural control of these infections (12, 23).

In this study, imiquimod, an immune-response modifier, had clinically significant efficacy in the treatment of genital warts. Complete response rates with 5% imiquimod cream were comparable to those achieved with other modalities (33, 34). In well-controlled trials, complete response rates ranged from 36 to 62% for intralesional IFN (8, 9, 28, 36) and from 45 to 58% for podofilox (5, 10, 19, 37). The 19% recurrence rate with 5% imiquimod cream also compares favorably with those reported for IFN (21 to 33%) (8, 9, 28) and podofilox (33 to 91%) (5, 10, 19).

The observed difference in response to imiquimod between male and female patients in this study may be due to the type of skin on which warts were located. The majority (90%) of male patients had warts on the penile shaft, which is predominantly covered by fully keratinized skin. Most (88%) female patients had warts on the vulva, which is primarily covered by moist, partially keratinized skin. Drug penetration may be greater through partially keratinized skin (which has a thin stratum corneum) than through fully keratinized skin (which

TABLE 4. Most frequent adverse events

Adverse event	No. (%) of patients with at least one reported adverse event			P value[b]
	5% Imiquimod cream group (n = 92[a])	1% Imiquimod cream group (n = 86[a])	Vehicle group (n = 92[a])	
Most common application-site reactions				
Itching	30 (32.6)	20 (23.3)	17 (18.5)	0.084
Pain	32 (34.8)	11 (12.8)	2 (2.2)	<0.0001
Burning	15 (16.3)	12 (14.0)	1 (1.1)	0.0003
Tenderness	11 (12.0)	11 (12.8)	2 (2.2)	0.0120
Other symptoms				
Headache	27 (29.3)	26 (30.2)	30 (32.6)	0.892
Upper respiratory tract infection	13 (14.1)	23 (26.7)	25 (27.2)	0.053

[a] Excludes patients who did not return to the clinic following the initial visit.
[b] Fisher's exact test.

has a thicker stratum corneum), which could explain the difference in response rates between male and female patients. This is also suggested by the observation that 1% imiquimod cream versus vehicle approached a significantly complete response in female but not male subjects (Table 2).

Although local reactions were more common in the 5% imiquimod cream group than in either the 1% imiquimod cream or vehicle group, fewer than 40% of the patients in the 5% imiquimod cream group had edema, scabbing, induration, ulceration, or vesicles; 83% had erythema; 43% experienced excoriation or flaking; and 48% had erosions. These findings compare favorably with those for patients treated with podofilox. Of the patients treated with podophyllotoxin, 64% experienced inflammation, 63% experienced erosion, 59% experienced burning, and 46% experienced pain (10). By the very nature of ablative therapy (e.g., trichloroacetic acid therapy, cryotherapy, or electrosurgery), local pain, burning, and wounding are nearly universal.

The local reactions noted with imiquimod are most likely due to cytokine-induced inflammation and/or an immune response. Local reactions, which were predominantly of mild and moderate severity, required the discontinuation of treatment in only two patients. In preclinical trials, the cumulative rate of irritation produced by 5% imiquimod cream was less than that produced by Vaseline Intensive Care Lotion (35), indicating that imiquimod is not inherently irritating to normal skin. In this clinical study, there was a significant correlation between the clearance of warts and erythema at the wart site for both male and female patients. An inflammatory response was not required to achieve clearance of the warts; however, patients with such a response were more likely to have wart clearance.

The mechanism by which imiquimod produces wart regression is probably dependent on the local induction of IFN-α and other cytokines. In the guinea pig model of genital herpes, imiquimod reduced acute and latent neural infection and acute and recurrent herpetic disease by inducing cytokines and enhancing cell-mediated immunity (3, 13–15, 26). Imiquimod may stimulate a wart-specific, cell-mediated immune response analogous to the enhancement of herpes simplex virus-specific, cell-mediated immunity reported in the guinea pig model of genital herpes (14).

A clear distinction between viral immunity and tumor immunity has been shown in the cottontail rabbit papillomavirus (32). Viral immunity apparently is mediated by a virus-specific antibody, while tumor immunity or regression results from wart-specific, cell-mediated immunity. Through its induction of IFN, imiquimod could enhance antigen presentation by increasing the expression of the major histocompatibility complex class I antigen, thus favoring the development of TH-1 helper T-cell response and a cell-mediated immune response (27).

Imiquimod stimulates other cytokines, including TNF-α, IL-1, IL-6, and IL-8 (13–17), an action that may contribute to both wart regression and local inflammatory reactions. TNF-α may alter T-cell infiltration of the epidermis by inducing expression of intracellular adhesion molecule-1 on keratinocytes (11). IL-6 can increase natural killer cell cytotoxicity and stimulate acute-phase protein synthesis and B-cell growth (24). Patients with epidermodysplasia verruciformis, a genetic disorder in which affected individuals are susceptible to extensive warts, are thought to have a defect in natural killer cell activity (22). Interestingly, warts clear from patients with epidermodysplasia verruciformis while they are receiving IFN (1).

Once infected, the major determinant of the clinical outcome of HPV infection may be the host immune response (17). Patient application of the immune-response modifier imiquimod results in significant wart clearance, an apparently low recurrence rate, acceptable local reactions, and no significant systemic adverse reactions. Imiquimod represents the first topical immune-response modifier to be shown to have significant activity against a human cutaneous viral infection. Prior to imiquimod, all topical treatments for external genital warts were either caustic, cytotoxic, or antimitotic. The traditional rationale for believing that the immune response was important in the control of HPV expression was based on observations from the immunocompromised population, in which extensive warts are often a problem. The efficacy of imiquimod represents a positive indication of the importance of the immune system in controlling these infections.

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