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Imiquimod for non-genital cutaneous warts

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Imiquimod is indicated for the treatment of genital warts in adults. Off-label use of imiquimod for non-genital warts has increased in the last decade, and according to US ambulatory care data, imiquimod is now the most commonly used medication for warts, despite a lack of good evidence to support its use.¹ DPIC has received a number of queries regarding the use of imiquimod for treating non-genital warts in various populations, such as children and the immunocompromised.

Cutaneous warts

Warts are benign tumours caused by infection with human papilloma viruses (HPV), of which there are over 100 types.^{2,3} Warts are mucosal (oropharyngeal and genital) or cutaneous. Cutaneous warts can be further described by their appearance and location, e.g. common warts, flat warts, and filiform warts; unguinal and periungual warts, and plantar warts.^{2,3} The focus of this article will be on imiquimod for cutaneous warts.

The immune response of the host to HPV is important for resistance to and resolution of infection, with or without treatment. Cutaneous warts often resolve spontaneously in immunocompetent patients, So why do we treat warts?^{2,3} Spontaneous resolution may take months to years, in the interim warts can grow and spread, cause pain and emotional distress due to their appearance.

Numerous treatments have been suggested for cutaneous warts (see Table), but none are consistently effective. A recent Cochrane review concluded that the evidence for many therapies is poor, and even for topical salicylic acid, for which evidence of benefit exists, the cure rate is only 50-60%.

Table: Treatments for cutaneous warts²⁻⁶

Mechanism	Examples
Ablative therapies*	Salicylic, lactic and other acids; cantharadin; silver nitrate; laser therapy and photodynamic therapy; hyfrecation; curettage
Antimitotic and antiviral therapy	5-fluorouracil, bleomycin, topical cidofovir, podophyllin/podophyllotoxin
Stimulate host immune responses against the virus	Oral cimetidine; topical and oral zinc; intralesional candida antigen; <i>Trichophyton</i> antigen; intralesional interferon; contact sensitizers: dinitrochlorobenzene, diphencyprone, and squaric acid diethyl ester
Miscellaneous	Duct tape*, retinoids

*It is proposed that ablative therapies and even therapies such as duct tape might expose the immune system to HPV antigen, causing a host immune reaction.

Imiquimod - no direct antiviral activity

Imiquimod is a Toll-like receptor 7 analogue that induces production of inflammatory cytokines including interferon-alpha, tumour necrosis factor alpha, and interleukin-12, and also enhances antigen presentation to T-cells. The overall effect is an enhanced immune response to viral infection.⁷

Imiquimod is available as a cream in 2.5%, 3.75% and 5% strengths, and is indicated for superficial basal cell carcinoma (5%), actinic keratosis (3.75% and 5%), and external genital warts and condyloma accuminata (2.5%, 3.75% or 5%).⁸

Off-label use for cutaneous warts

Common warts

Several case reports and case series have been published.⁹⁻¹³ In the earliest case series (n=50), imiquimod 5% applied daily for 5 days per week resulted in complete clearance in 30% of patients, and >50% reduction in wart size in 26%.⁹ There was worsening or no change in 22%, and the other 22% were lost to follow-up or withdrew from the study (2 withdrew due to local side effects). In another case series (n=10), 90% of patients were successfully treated with imiquimod applied daily, under occlusion, for 4 weeks.¹⁰

In one open-label study of imiquimod 5% twice daily, 13 patients had warts other than plantar warts. The reduction in the volume of the warts in these patients ranged from 42% to 100% (6 patients had complete clearing of the warts).¹¹ However, in an unpublished controlled trial conducted by the manufacturer and briefly described in the Cochrane Review, the cure rate for imiquimod was only 9.5% to 10%, compared to 4.9% for the control.³

Plantar warts

There have been a number of published case reports and one open-label trial.^{11,14-18} In the open label trial, 24 patients had plantar warts resistant to other treatments. Imiquimod 5% twice daily resulted in a median reduction in wart volume of 59% (complete clearing in 4 patients, >75% clearing in 5, with no response in 4 patients).¹¹ Successful treatment of plantar warts with imiquimod sometimes required use of occlusion, or treatment with other modalities such as salicylic acid, cryotherapy, or dinitrochlorobenzene. In an unpublished controlled trial of imiquimod 5% conducted by the manufacturer, using the vehicle as the control, complete clearance of plantar warts was achieved in 10% to 12.8% of patients, compared to 2.9% in the control group.³

Flat warts

Flat warts tend to appear on the neck and face where pigmentation and scarring may be a concern. A number of case reports and one case series (n=15) of imiquimod for flat warts were found.^{19,20} In the case series, imiquimod 5% applied nightly for up to 12 weeks resulted in complete response in 40%, excellent response (>75% clearing) in 33%, but poor response in 27%.²⁰ No patients had pigmentation disorders or scarring. For some patients, the reduction in wart size allowed the use of ablation to complete wart removal. The onset of response was at 1 week for many patients, with a mean time for clinical response of 10.5 weeks.

Ungual and periungual warts

Warts growing under and around nail beds can be difficult to treat due to difficulty accessing the wart, and pain caused by treatment. In one case series (n=15), imiquimod 5% applied 5 nights per week under occlusion (following pre-treatment with salicylic acid) resulted in complete resolution of recalcitrant unguinal and periungual warts in 80% of patients within 1-6 weeks. Two patients also had clearing of other untreated warts. The remaining 20% of patients were non-responders.²¹

Special populations: immunocompromised patients and children

Topical imiquimod has been used successfully to treat cutaneous warts in immunocompromised patients (HIV positive patients, immunosuppressive therapy),²²⁻²⁷ However, in one series of organ transplant patients the clearance rates were relatively low.²⁶

Imiquimod 5% has also been used in children as young as 5 years of age with good success and safety.^{9,21,28}

Safety

In all of the case reports, case series and trials we reviewed, side effects were mainly mild and local, such as erythema, burning, itching, erosion, and scabbing. In one series involving children, imiquimod was applied sparingly with a toothpick twice daily, with no redness or itching observed. Systemic side effects (fever, lymphadenopathy, muscle aches) were rarely reported^{9,19} This may be due to the limited transdermal absorption of imiquimod (estimated to be <1%)⁸.

Limitations

The main limitation to stronger recommendations for the use of imiquimod is the lack of evidence from controlled trials. All of the published evidence for using imiquimod for cutaneous warts is case reports, case series, or uncontrolled trials. Imiquimod has not been directly compared to other treatments such as topical salicylic acid, preventing firm conclusions about its place in therapy from being made.

Many of the patients in the case reports and uncontrolled trials had warts that were recalcitrant to other treatments. Various regimens that may add ancillary measures (occlusion, pre-treatment or co-treatment with keratolytics and other therapies) were reported. The optimal dose and duration of therapy are unknown. The lower strength imiquimod creams may be better tolerated, but they have not been studied for cutaneous warts.²⁹

Imiquimod has some theoretical advantages over other therapies in that it is easy to apply, well-tolerated and cosmetically acceptable, may also clear distant lesions. However, the cost of imiquimod is a disadvantage.

Conclusions

Topical imiquimod appears to be a useful agent for non-genital cutaneous warts, with reasonable efficacy and good safety. However, despite its growing popularity, the use of imiquimod for non-genital cutaneous warts remains off-label, and the lack of well-designed controlled trials and comparative studies prevents firm conclusions about its place in therapy from being made.

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