Skin Therapy Letter ©

Volume 3 • Number 2 • 1997

EDITOR: STUART MADDIN

Imiquimod

Imiquimod cream 5% (Aldara®; 3M Pharmaceuticals) was approved by the FDA February, 1997 for the treatment of external genital and perianal warts/condyloma acuminata in adults. Anogenital warts are very common, sexually transmitted, virally induced tumors that although benign themselves, have been associated with the development of squamous cell carcinoma, particularly cervical carcinoma.[1]

Imiquimod is an immune response modifier. Studies have shown that it has potent immunomodulatory effects and stimulates human peripheral mononuclear cells to release interferon alpha, sub-types α1,α2, α5, α6, and α8. It also induces monocytes and macrophages to produce other cytokines including interleukins 1, 6, 8 and tumor necrosis factor α.[2] The clinical relevance of these findings is not fully understood.

Imiquimod's advantages

- Low recurrence rate.
- Self-application.
- Limited systemic effects and only mild (rarely moderate) local inflammation.

Previously available treatments (e.g. *cryotherapy*, *laser vaporization*, *electrocautery* and *excision*) for anogenital warts are often painful and expensive. Local therapy with *podophyllin*, or *podophyllotoxin* or *trichloracetic* acids, requires multiple applications, is slow acting and often causes problems associated with local inflammation.[1] *5-Fluorouracil*, although sometimes used for external anogenital warts, is not yet approved for this indication, has neither antiviral nor immunomodulatory effects, earlier formulations were irritating and intralesional injections are painful.[3,4] Unfortunately, recurrence often follows cessation of treatment following the use of these therapies.[1]

Recent reports suggest that multiple injections of *interferon alpha* produce clearance rates of 36 – 62% and are well tolerated locally; however, such treatments are time-consuming, expensive and are associated with systemic side effects.[5,6]

Efficacy

In early multicenter, double-blind, dose-ranging, vehicle controlled clinical trials, imiquimod 5% has proven effective in treating anogenital warts. In 311 patients, imiquimod 5% three times weekly completely cleared warts in 50% of patients, compared to 11% clearance in patients treated with the vehicle ($p < 0.0001$, intent-to-treat analysis). In a subsequent trial, daily application of the 5% cream completely cleared the warts of 52% of patients compared to 3% clearance of warts in patients using the vehicle alone ($p < 0.0001$, intent-to-treat analysis). In these two trials, following cessation of treatment, wart recurrence rates were 13% and 19% respectively.[7]

Combination treatment, using this new topical immunomodulator, imiquimod, and ablative destructive therapy, is currently under study.[8] Although results are not available, it seems logical to combine imiquimod with an ablative therapy so that imiquimod could induce an immune response which has the potential to affect the virus, eliminate residual lesions, and possibly reduce recurrence rates.

Side Effects

The trials discussed above revealed that erythema and increased skin irritation was the most common reaction and was severe in 4% of both male and female patients

treated three times weekly.[9] Other adverse events reported by more than 1% of patients include fatigue, fever, influenza like symptoms, headache, diarrhea, myalgia and fungal infections.[9]

Safety During Pregnancy & Lactation

There are no adequate and well controlled studies in pregnancy and it is not known whether topically applied imiquimod is excreted in breast milk.

Pharmacokinetics

Percutaneous absorption was minimal (less than 0.9%) following a single dose, topical application of 5 mg of imiquimod to the skin of six healthy volunteers.

Dosage and Administration of Imiquimod

Prior to retiring, a thin layer of the cream is applied to the wart area, rubbed in until cream is no longer visible, left on the skin overnight and then in the morning washed off with mild soap and water. Hands should be washed before and after being used to apply the cream. The anogenital warts should be treated three times per week. For those patients who respond, clearance of warts requires on average 8 weeks for female patients and 12 weeks for male patients.

Patient Information

- Local skin reactions are common but are usually mild to moderate in severity. Severe skin reactions should be reported to the physician promptly.
- Do not occlude the treatment area. Uncircumcised males treating warts under the foreskin should clean the area daily.
- The cream is for external use. Avoid contact with the eyes. Avoid sexual (genital, anal, oral) contact while the cream is on the skin.
- Imiquimod cream may weaken condoms and vaginal diaphragms and should not be used concurrently.

Clinical Assessment

Imiquimod has not yet been compared to any other treatment for anogenital warts. Podophyllin, the most frequently used topical treatment, is not a standardised preparation[10], has an unknown shelf life[10], contains potentially carcinogenic mutagens and has no known antiviral/immunomodulatory activity. Imiquimod has no mutagenic activity, is immunomodulatory/antiviral and would appear to be the drug of choice[3] for multiple warts when cryotherapy is inappropriate and cost is not a problem.

Imiquimod's place in therapy:

- Imiquimod provides a new and practical treatment option to previously available treatments.[10]
- First line therapy[3, 8] for patients who do not demand immediate removal of warts – it takes as long as eight weeks and sometimes longer to achieve clearance of warts.
- Alternative therapy for persons who have failed another first line treatment and who have experienced recurrences of genital warts.
- A potential component of combination therapy for patients with large/multiple warts.[8] The immune response engendered by imiquimod may affect the virus, eliminate residual lesions, and possibly reduce recurrence rates.
- Applying imiquimod three times per week costs the patient approximately US $100 per month for the cream.

> Preliminary clinical data suggests that this new treatment approach utilizing imiquimod to treat external genital and perianal warts/condyloma can be justified on phamacoeconomic grounds.
>
> *Dr. Stephen Tyring, Galveston, Texas.*

This review was prepared by Rodger Hall, Vancouver.

References

1. Edwards L, Ferenczy A, Eron L. Self-administered 5% imiquimod cream for external anogenital warts. *Arch Dermatol.* In press.
2. Megyeri K, Au WC, Rosztoczy I *et al*. Stimulation of interferon and cytokine gene expression by imiquimod and stimulation by Sendai virus utilize similar signal transduction pathways. *Molecular and Cellular Biology* 1995; 15: 2207-2218.
3. Tyring SK. Personal communication. August 1997.
4. Krebs Hans-B. Treatment of genital condylomata with topical 5-fluorouracil. *Dermatol Clin* 1991; 9: 333-341.
5. Eron SJ, Judson F, Tucker S *et al*. Interferon therapy for condyloma acuminata. *N Eng J Med* 1986; 315: 1059-1064
6. Friedman-Kein AE, Eron LJ, Conant M *et al*. Natural interferon alfa for treatment of condyloma acuminata. *JAMA.* 1988; 259: 533-538.
7. Edwards L, Beutner K, Tyring S *et al*. Comparison of results from two vehicle controlled clinical trials evaluating topical imiquimod for the treatment of genital/perianal warts. Clinical Dermatology 2000, Vancouver, British Columbia, May 28-31, 1996.
8. Sauder DN. Personal communication. August 1997.
9. Physician Packet Insert.
10. Beutner KR. Personal communication. October, 1997.

Antimicrobial Prophylaxis Prior to Dermatologic Surgery

With many more dermatologists now actively involved in carrying out surgical and cosmetically related procedures, it is time to focus on some of the difficult questions surrounding prophylaxis in dermatologic surgery. Antibiotic prophylaxis aims to prevent wound infections and provide adequate antibiotic cover for patients with prostheses or at risk for endocarditis. Most recommendations are based on studies in general surgery patients, where the range of procedures and spread of risk factors may not accurately predict the risks for patients undergoing outpatient cutaneous surgery.

Haas and Grekin, San Francisco, feel that in dermatologic surgery units, the overall incidence of infection of clean-contaminated wounds is probably much lower than the 10% figure quoted for general surgery.[1] Their unit has an annual infection rate of less than 1% and they feel that prophylaxis is not usually required for this type of procedure.[1] Exceptions which may require prophylaxis are patients undergoing dermatologic surgical procedures involving areas that are considered contaminated, such as nose and mouth, genital and peri-anal areas and the axilla.[1] The type and length of procedure, contamination level and overall patient health are additional risk factors that need to be considered and may at times trigger the use of antibiotic prophylaxis.[1]

Routine dermatologic surgery in high-risk patients

There are no uniformly agreed upon recommendations, most are loosely based on American Heart Association (AHA) guidelines.[2] "High-risk" patients, as defined by the AHA, are those with prosthetic heart valves, congenital cardiac malformations, rheumatic valve disease, hypertrophic cardiomyopathy, or mitral valve prolapse with valvular regurgitation. ***It is probably advisable to seek guidance from an appropriate infectious disease consultant prior to carrying out surgery on unusually "high-risk" patients.***

- The commonly held belief that antimicrobial prophylaxis, given before procedures that can cause transient bacteremia, can prevent endocarditis in patients with valvular heart disease, prosthetic heart valves or other cardiac abnormalities *has never been established by controlled clinical trials.*[3] However, antibiotic doses pre- and post-operatively have been recommended for patients with high-risk cardiac lesions who are undergoing surgical manipulation of eroded skin, manipulation of infected skin, and for those with a distant skin infection.[1]
- Antibiotic doses pre- and post-operatively have also been recommended for patients with an *orthopedic prosthesis or ventriculoatrial or peritoneal shunts*, who are undergoing surgical manipulation of eroded skin, or manipulation of infected, or abscessed skin, and for those with a distant skin infection.[1]
- "High-risk" patients undergoing prolonged procedures (i.e Moh's), or any surgical procedure on eroded or infected skin require prophylaxis which covers coagulase positive staphylococci and streptococci. Give one pre-operative dose of antibiotic one hour before the procedure.[1, 4, 5] The most commonly used antibiotics are dicloxacillin, amoxicillin or a first generation cephalosporin[5] (e.g. Keflex® 1 gm PO, one hour pre-op. followed by 500 mg six hours later [1,2]). Erythromycin is an effective alternative in patients allergic to penicillin or its derivatives.[5]

Other precautions prior to skin resurfacing[6]

- Identify what prescription and non-prescription products are being used by the patient.
- *Peel first, laser second!* This avoids getting peeling solution on denuded skin.
- For patients with type III and higher skin types, consider starting treatment with daily use of tretinoin and sunscreens six weeks before the procedure.

Patients NOT usually requiring prophylaxis

- *Minor procedures (biopsies, small excisions, ED/C, etc.) on intact skin.*[1,4,5]
- High-risk patients undergoing surgery of intact skin in a low-risk skin region are not considered to need antibiotic prophylaxis for minor procedures when the excision can be closed quickly.[1]
- *The organisms that reside on noninfected skin are not commonly associated with endocarditis, and*

bacteremia following procedures performed through scrubbed skin is not likely. For these reasons we do not recommend prophylaxis under these circumstances. Dajani, Bolger, Taubert.[7]

- Patients with *indwelling cardiac pacemakers*, *genitourinary prostheses* or *breast implants* do not usually require any extra precautions.[1]
- Patients undergoing *hemodialysis*, or those with an *indwelling catheter* do not need antibiotic prophylaxis routinely, except when excising eroded or contaminated skin directly above the graft.[1]
- When more than one month has elaped following an *arterial graft*, routine antibiotic prophylaxis is not required.[1]

Herpes infections and other special concerns

Prior to undertaking an "abrasive" procedure (medium-depth chemical peel, laser resurfacing, dermabrasion) it is essential to determine whether or not the patient has a history of facial herpes. If this is the case, initiate prophylactic use of acyclovir,[1,2] or one of the newer analogues, famciclovir or valaciclovir.

Complications resulting from viral infections

Complications such as prolonged healing times, and without appropriate wound care atrophic or hypertrophic scarring, occur predictably in patients with a known history of recurrent labial herpes. These complications may be seen in greater than 50% of untreated patients, 6-9% of patients receiving standard prophylactic regimens, and in less than 5% of patients receiving high dose (e.g. acyclovir 800 mg TID) prophylactic regimens.[5] Herpes simplex virus infections have been reported in up to 2% of patients undergoing cutaneous laser resurfacing without prophylaxis. Herpetic infections are more uncommon in patients on a prophylactic regimen.[5]

> *Bear in mind that 80% of the population has antibodies to the virus – that's why some practitioners give the drugs to all patients regardless of their clinical history.*[8]
>
> Dr. Stephen Tyring,
> University of Texas Medical Branch at Galveston

Herpes simplex infections after skin resurfacing appears primarily on denuded skin and antiviral prophylaxis should be continued until re-epithelialization is complete.[5,6]

> *Appropriate prophylactic use of systemic and topical antibiotics is important if we are to safeguard patients undergoing dermatological procedures and maximise the post-operative cosmetic result.*
>
> Dr. Stuart Maddin, Editor

References

1. Haas AF, Grekin RC. Antibiotic prophylaxis in dermatologic surgery. *J Am Acad Dermatol* 1995; 32: 155-176.
2. Dajani AS, Taubert KA, Wilson W *et al*. Prevention of bacterial endocarditis. Recommendations by the American Heart Association. JAMA 1997; 277: 1794-1801.
3. Antimicrobial prophylaxis in surgery. *The Medical Letter* 1997, 39: 97-102.
4. Haas AF. Personal communication, November 1997.
5. Stratigos AJ, Dover JS. Personal communication, November 1997.
6. Zloty D. Personal communication, March 1997.
7. Dajani AS, Bolger AF, Taubert KA. [letter]. *JAMA* 1997; 278: 1233
8. Tyring S. Personal communication, November 1997.

Antiviral dosage regimen recommended prior to dermatologic surgical procedures

Antiviral Drug	Previous Herpes Infections	
	History of Herpes	Generalized Explosive Infection Following Procedure
Acyclovir	400 mg PO 3 times daily[4,5,6]	800 mg PO 5 times daily[4,5,6]
Famciclovir	250 mg PO twice daily[5,8]	500 mg PO 3 times daily[4,5,6]
Valciclovir	250 mg[8] – 500 mg[4,5,6] PO twice daily	1 gm PO 3 times daily[5]
Treatment Duration	Starting one day before treatment and continuing for four[4,6] to 14[5] days post-treatment. The needed duration of therapy is yet to be well defined.	10 – 14 days.[5] IV treatment should be considered in severe cases. *Seek guidance from an appropriate infectious disease consultant prior to carrying out surgery*

Name/Tradename/Company	Drug Warning
Ivermectin Mectizan® *Merck*	An apparently highly significant statistical association between the use of ivermectin in the elderly, and increased risk of death. Barkwell R, Shields S. Deaths associated with ivermectin treatment of scabies. *Lancet* 1997; 349: 1144-1145.

This antiparasitic drug has been widely used and effective against tropical filarial diseases such as strongyloidiasis and onchocerciasis. In some parts of the world it is being trialed or used in the treatment of scabies. During an outbreak of scabies in a Canadian long-term care facility, 47 residents with an mean age of 73 years, were treated with a single oral dose of ivermectin, 150-200 mcg/kg of body weight. Treatment was effective within five days, but over the next six months, 15 of the 47 treated patients died, compared with five of an age-matched and sex-matched cohort. In the treated patients, although final causes of death varied, a sudden change in behaviour with lethargy, anorexia and listlessness preceded death. The authors suggest that in the face of what appears to be a highly significant statistical association between the use of ivermectin in the elderly, and increased risk of death, ivermectin should not be used for treating scabies in this age group. Confounding factors such as underlying medical condition and the effect of earlier treatments with other drugs such as *lindane* and *psychoactive drugs* need further study before this adverse effect of ivermectin is established, but this report should serve as an early warning signal. Barkwell R, Shields S. Deaths associated with ivermectin treatment of scabies. *Lancet* 1997; 349: 1144-1145.

Name/Tradename/Company	Drug Warning
Latex devices	The FDA has ruled that all latex devices must have warning labels. Fax-Stat, Facts & Comparisons, 17/10/97

Caution:
This Product contains natural rubber latex which may cause allergic reactions

All medical devices containing latex must bear this warning. Less than 1% of the general public are allergic to latex but the percentage is higher among healthcare workers and patients who have undergone multiple surgeries.

WE'RE ON THE NET! http://www.derm.ubc.ca

Now practitioners all over the world can browse through up-to-the minute dermatological information in *Skin Therapy Letter* on the **World Wide Web**. By calling Derm Web at the University of British Columbia, you'll be able to:

- *Scan the list of articles in the current issue*
- *Read the full-text of feature articles*
- *Access hypertext links to other dermatology resources on the Web*
- *Learn how to subscribe to your own copy of the* Letter

We'd also like to hear from you.
Please send us your comments via our E-mail address so that we can continue to make *Skin Therapy Letter* the informative and practical clinical tool it is intended to be.

http://www.derm.ubc.ca

Update on Drugs

Class	Name/Company	Approval Dates and Comments
Anti-androgen	**Cyproterone** 2 mg & **ethinyl estradiol** 35 mcg Diane-35® *Berlex Canada*	Approved in Canada September 19, 1997 for the treatment of acne.
Antifungal	**Oxiconazole nitrate 1% cream** Oxistat® *Glaxo Wellcome*	Approved by the FDA August 18, 1997 for the treatment of tinea (pityriasis) versicolor. Directions for pediatric use have also been added to its labeling.
	Terbinafine solution 1% Lamasil® *Novartis*	Approved by the FDA October 17, 1997 for the topical treatment of tinea (pityriasis) versicolor due to *Malassezia furfur* (formerly *Pityrosporum ovale*), and tinea pedis (athlete's foot), tinea cruris (jock itch), or tinea corporis (ringworm), due to *Trichophyton rubrum*, *Trichophyton mentagrophytes*, or *Epidermophyton floccosum*.
	Itraconazole Sporanox® *Janssen Ortho*	New, shorter dosage regimen approved in Canada August 8, 1997 for the treatment of tinea corporis/tinea cruris (200 mg daily for seven consecutive days) and tinea pedis (200 mg twice daily for seven consecutive days).
Antirosacea	**Metronidazole cream** Noritate® *Dermik*	Approved by the FDA September 26, 1997 for the topical treatment of inflammatory lesions and erythema of rosacea.
Antiviral	**Famciclovir** Famvir® *SmithKline Beecham*	Approved by the FDA September 17, 1997 for the suppression of recurrent episodes of genital herpes in immunocompetent adults.
	Lamivudine and **Zidovudine** Combivir® *Glaxo Wellcome*	Approved by the FDA September 26, 1997 for the treatment of HIV infection.
	Valacyclovir Valtrex® *Glaxo Wellcome*	Approved by the FDA September, 26 for the suppression of recurrent episodes of genital herpes in immunocompetent adults.
Corticosteroid	**Hydrocortisone butyrate** Locoid® *Inveresk research*	Approved by the FDA September 8, 1997 for the relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses.

Skin Therapy Letter® (ISSN 1201-5989)
Published six times yearly by International Skin Therapy Newsletter Inc., 835 West Tenth Avenue, Vancouver, British Columbia, Canada V5Z 4E8. Tel: (604) 874-6112. Fax: (604) 873-9919.
Annual subscription: Canadian $85 individual; $155 institutional (GST included). US $60 individual; $110 institutional. Outside North America: US$80 individual; $130 institutional. Quotes on multiple subscriptions and student rates supplied upon request.

Printed in Canada