Pharmacist Edition

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Clinical Evidence. Practical Advice.

Editor-in-Chief: Dr Stuart Maddin

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EDITOR-IN-CHIEF

Dr. Stuart Maddin, Chairman of SkinCareGuide, is one of North America's leading dermatologists, and is the author of numerous dermatologic journal articles, monographs and textbooks. In addition to providing consultative input to a number of pharmaceutical and biotech companies, he is the director of the clinical trials unit at the Department of Dermatology and Skin Science, University of British Columbia. Dr. Maddin has also acted in an advisory capacity to a number of drug regulatory agencies, such as the Health Protection Branch (Ottawa), the AAD-FDA Liaison Committee, and WHO (Geneva). He is the founder of the Dermatology Update symposia, now in its 24th year. As well, he is Past President of the Canadian Dermatology Association and served as Secretary-General of the International Committee of Dermatology — International League of Dermatological Societies.

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External Genital Warts

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Background

Human papillomavirus (HPV) is a very common sexually transmitted disease that is associated with a number of benign, premalignant, and frankly malignant lesions of the anogenital tract. In Canada, its prevalence varies depending on a number of risk factors, but appears to be highest in people between 15-25 years of age. [Varela A, et al. *Skin Therapy Lett – US FP Ed* 1(2): 1-3 (2006 Winter).] With a relatively new immunomodulator for treatment and the recent approval of a vaccine, the options for managing this condition have improved significantly.

Condyloma Acuminatum (anogenital warts) is a common form of HPV infection. The majority of these are due to infection with HPV 6 or 11, and are clinically benign. Genital warts are usually asymptomatic, but can cause pruritus, bleeding, or mild burning. The warts present as:

- small, wart-like papules
- discrete, sessile, smooth-topped papules or nodules
- large exophytic masses.

Lesion color can range from flesh colored to pink to reddish brown, and are often multifocal. Lesion distribution generally corresponds with the areas of highest friction during sexual activity.

Pathogenesis

The HPV virus is inoculated directly into the epidermal layers of the skin through epithelial defects, especially with maceration. Increased epidermal growth produced by the HPV infection leads to the formation of warts. Genital infections are primarily contracted through sexual contact. These infections can then be transmitted to newborns via passage through the infected birth canal. [Kaye JN, et al. *J Gen Virol* 77(Pt 6):1139-43 (1996 Jun).]

Diagnosis of Genital Warts

- Primarily made by visual inspection.
- A biopsy may be useful if
  - Diagnosis is uncertain.
  - Lesions do not respond to standard therapy.

Diagnosis of Genital Warts (cont.)

- The disease worsens during therapy.
- The patient is immunocompromised.
- The warts are pigmented, indurated, fixed, bleeding, or ulcerated.[Centers for Disease Control. Genital Warts Treatment Guidelines 2006. URL: http://www.cdc.gov/std/treatment/2006/genital-warts.htm.]

Management

For the majority of patients, treatment can induce wart-free periods. If left untreated, warts may resolve on their own, remain unchanged, or increase in size or number. Treatment can reduce, but does not eliminate, HPV infection. No definitive evidence suggests that any of the available treatments are superior to any other and no single treatment is ideal for all patients or all warts. Most patients require a course of therapy rather than a single treatment, and improvement will generally be seen within 3 months when administered by a health care professional. [Centers for Disease Control. Genital Warts Treatment Guidelines 2006. URL: http://www.cdc.gov/std/treatment/2006/genital-warts.htm.]

Before beginning any treatment for genital warts, it is essential to screen patients for other sexually transmitted diseases. Most treatment modalities address the symptom of the disease (warts) vs. the cause of the disease itself. However, imiquimod goes further by inciting an immunologic response, thereby providing an attack on the obvious warts, as well as the virus that resides in normal looking skin around the warts, i.e., in both clinical and subclinical HPV.

Four Treatment Modalities

- Antiproliferative agents
- Destruction/excision therapies
- Immunomodulatory therapy (imiquimod)
- Combination therapy.

Antiproliferative Therapies

- Podophyllin resin 10%-25%
  - It is administered by a health professional.
  - To minimize irritation, a petroleum-based product can be applied to adjacent tissue.
  - Multiple applications may be needed.
  - Should not be used in pregnant women.
- Podophylox 0.5% solution or gel
  - Self-administered by patient.
  - Does not contain the mutagenic substances that podophyllin resin has.
  - Could be used in combination with destructive therapy.

Destruction/Excision Therapies

- Local cryotherapy is the most common destructive mode.
  - It is safe during pregnancy.
- Application of topical trichloracetic acid
- Electrocautery
- Ablative laser treatment
- Excision by scissor, curette, or scalpel.
- Administered by a health professional.
- All of these options have a risk of scarring.

Immunomodulatory Therapy

- Approved by Health Canada in 1999.
- Self-administered by patient, which improves patient compliance.
- Enhances the cytotoxic immune response, which is usually seen as an inflammatory response.
- Applied directly to the affected skin 3 times per week for up to 16 weeks. Initially the frequency of applications can be reduced if the patient is overly concerned by the degree of inflammation.
- Acts to reduce the viral load, thereby reducing recurrence rates to very low levels.
- A significant advantage is the ability to affect subclinical lesions.
- Is more effective in women than in men, possibly because warts are more commonly found on mucosal skin.

Combination Therapy

- Monotherapy can often be inadequate for treating anogenital warts.
- Combination therapy can provide a better result.

Four Treatment Modalities (cont.)

- Treatment with imiquimod followed by excision of residual lesions may provide long-term clearance of anogenital warts in those patients for whom monotherapy was insufficient.[Carrasco D, et al. *J Am Acad Dermatol* 47(4 Suppl):S212-6 (2002 Oct).] The patient and physician must decide when monotherapy has been given sufficient time. In many instances, combination therapy is used as initial treatment.

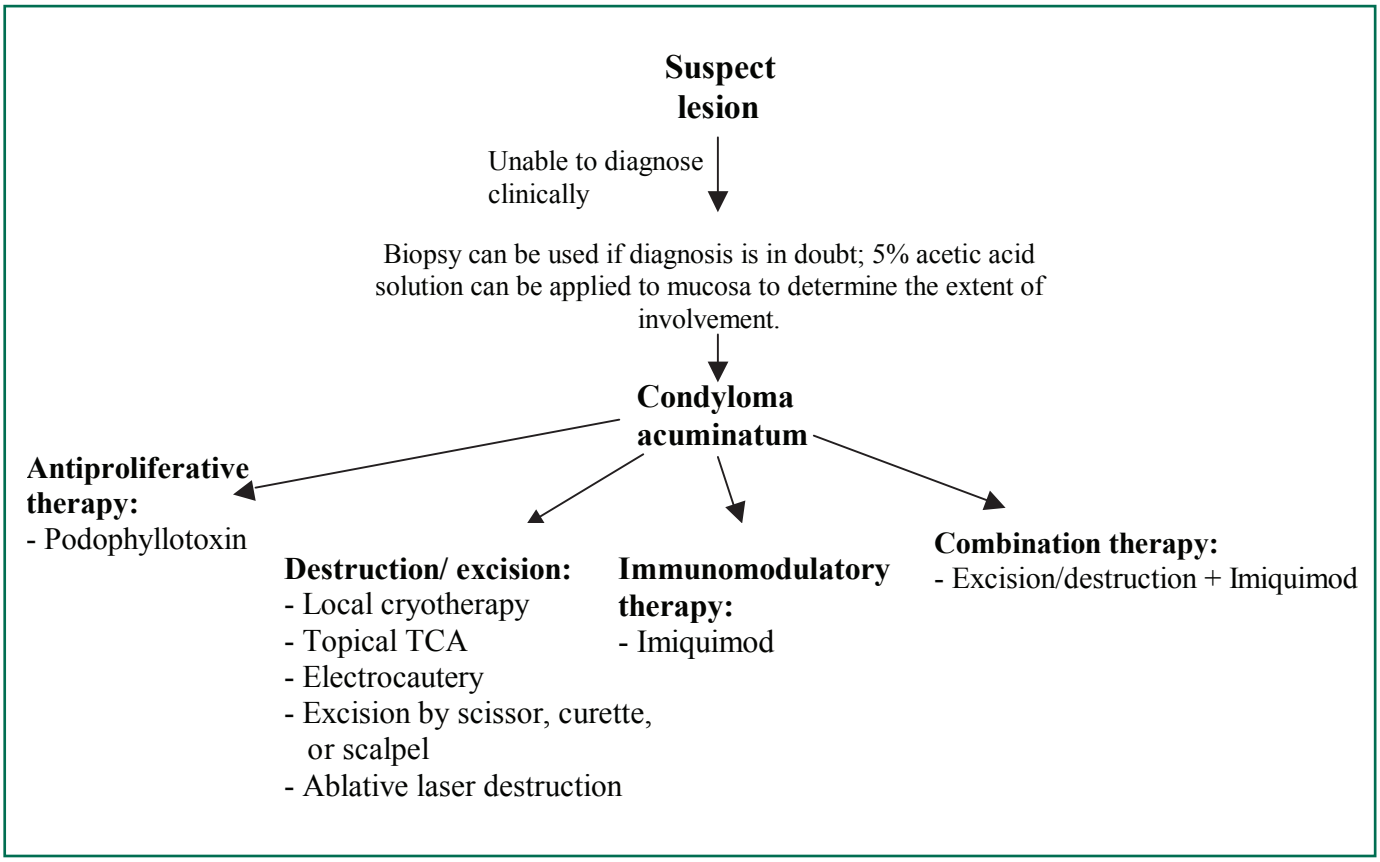

Figure 1: Algorithm for treatment of suspect lesions. [Adapted from Varela A, et al. *Skin Therapy Lett – US FP Ed* 1(2):1-3 (2007 Winter).] TCA= trichloracetic acid.

Prevention

Prophylaxis

A quadrivalent HPV (types 6, 11, 16, 18) recombinant vaccine is now available and is indicated in girls and women aged 9-26 years for the prevention of the following diseases caused by HPV types 6, 11, 16, and 18, including genital warts, cervical cancer and other neoplasias of the cervix, vagina and vulva. It should be administered intramuscularly as three separate 0.5ml doses. Studies with this vaccine are now ongoing in males. There is no evidence for effectiveness in treating those who already have genital warts. Not only does the vaccination largely prevent incident external genital warts, but it also protects against genital tract HPV-associated neoplasia.

Behaviour Modification

- Avoid sexual contact if infected.
- Barrier contraception may be of benefit.
- Regular cervical pap smears are recommended for all women, but especially important in those with exposure to genital warts.

Patient Counseling

- Irritation and inflammation causing pain and discomfort are seen with all of the treatment modalities, whether self-administered or given by a health care professional.
- Imiquimod can cause redness and swelling.
    - The most common issue reported by patients.
    - Because this medication is designed to trigger the patient's immune response, an inflammatory reaction can be expected.
        - Inflammation is desirable and the patient needs to understand this to ensure that treatment is not interrupted.
        - Resist efforts to suppress the redness using topical corticosteroids.
        - Inflammatory response is variable.
        - Some patients may need to apply the cream less often than is standard.
        - It is reasonable to titrate the frequency of applications to best suit the patient.
        - If the reaction is very brisk, the applications can be discontinued and restarted after the inflammation has decreased.
- Genital warts are caused by a viral infection, and the pathogens are found in the skin around the warts themselves so imiquimod should be applied on the surrounding skin, as well as on the warts.
    - Apply medication at least 1cm around the obvious area of involvement.
    - Only a thin layer needs to be applied to the genital region.
    - The sachet can be used more than once. It is recommended that a pinprick be made in the packet and the cream squeezed out. It may be that only ½ a sachet is used if the area is not extensive.

Conclusion

HPV infections can be asymptomatic and can spontaneously clear on their own. However if treatment is required, there are a number of antiproliferative, destructive, and immunomodulatory modalities available. Combination therapies have been shown to be advantageous in terms of enhanced efficacy. In general, time to response can be expected within 3 months of therapy. Patients should be evaluated throughout the course of therapy for treatment response and side-effects, and treatment should be changed if substantial improvement is not seen within that time frame. Cryotherapy combined with imiquimod is very commonly used, because it helps debulk or reduce the size of the warts, as well as enhance the patient's own immune response in the treated area. A quadrivalent HPV recombinant vaccine is now available for girls and women 9-26 years of age. While not affecting current infections, future generations may be spared considerable burden from external genital warts due to the development, approval, and release of HPV polyvalent vaccines.

New Developments in Hormonal Therapy for Acne

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Introduction

Oral contraceptives (OCs) have been used for many years by dermatologists as a treatment option for women with acne. The onset of acne is triggered by the production of androgens. Oral contraceptives inhibit ovulation, thereby resulting in the prevention of androgen production. The lower serum androgen levels reduce sebum secretion, which consequentially exerts an antiacne effect. OCs that are indicated for use in acne are effective across the spectrum of disease severity:

- in mild acne as an adjunct to topical therapy for female patients desiring contraception
- in moderate acne as a form of systemic therapy
- in severe acne
  - as a primary form of therapy (e.g., ethinyl estradiol/ cyproterone acetate)
  - as one of two preferred forms of contraception for women treated with systemic isotretinoin.

These preparations have evolved to include less estrogen and incorporate progestins with less intrinsic androgenicity in order to reduce the potential risk of thromboembolic events, hepatic tumors, hypertension, altered glucose metabolism, and rare androgenic side-effects such as acne, hirsutism, and weight gain.

OCs for the Treatment of Acne

In Canada, four hormonal preparations are presently approved by Health Canada for the treatment of acne.

- All contain estrogen and progestins
  - with minimal androgenicity
    - ethinyl estradiol/ norgestimate
    - ethinyl estradiol/ levonorgestrel
  - with anti-androgenic potential
    - ethinyl estradiol/ drospirenone
    - ethinyl estradiol/ cyproterone acetate
- All have demonstrated efficacy in the treatment of acne and long-term safety profiles.

Ethinyl Estradiol 0.030mg/ Drospirenone 3mg (Yasmin®)

Drospirenone (DRSP) is a novel progestogen derived from spironolactone, which is an antiandrogen.

- DRSP 3mg combined with 0.030mg ethinyl estradiol
- Recently approved in Canada for the treatment of moderate acne.
- Competitively binds to androgen receptors.
- Inhibits 5α-reductase activity, which results in the down regulation of sebum production.
- Reduces androgen biosynthesis.
- For antimineralocorticoid activity, the dose equivalence for DRSP 3mg is spironolactone 25mg.
- Efficacy for treating acne vulgaris was evaluated in a randomized controlled trial with ethinyl estradiol 0.035mg/ cyproterone acetate 2mg as the active comparator.[van Vloten WA, et al. *Cutis* 69(4 Suppl):2-15 (2002 Apr).]
  - 125 subjects aged 16-35 years with mild-to-moderate facial acne treated for 9 cycles
  - Median reduction in total facial acne lesions:
    - 62% for ethinyl estradiol 0.030mg/ drospirenone 3mg
    - 59% for ethinyl estradiol 0.035mg/ cyproterone acetate 2mg
  - Both formulations were effective for treatment of acne and well tolerated
    - Adverse events were mild-to-moderate in intensity and typical of those associated with OCs.

Ethinyl Estradiol/ Norgestimate (Ortho Tri-Cyclen®)

- Ethinyl estradiol 0.035mg with norgestimate in increasing doses, 0.180mg/ 0.215mg/ 0.250mg
- Norgestimate has low intrinsic androgenicity with low binding affinity for androgen receptors. It is strongly selective and avidly bound to progesterone receptor sites. This combination estrogen and progestin preparation produces a synergistic effect which enhances regulation of hormonal levels.
- Shown to be efficacious in moderate facial acne in two randomized placebo-controlled trials involving 324 subjects over 6 cycles.[Lucky AW, et al. *J Am Acad Dermatol* 37(5 Pt 1):746-54 (1997 Nov); Redmond GP, et al. *Obstet Gynecol* 89(4): 615-22 (1997 Apr).]
  - Inflammatory lesions were reduced by 56%, noninflammatory lesions by 41%, and 32% achieved excellent improvement using investigator global assessment scores.[Redmond GP, et al. *Obstet Gynecol* 89(4): 615-22 (1997 Apr).]

Ethinyl Estradiol/ Levonorgestrel (Alesse®)

- Ethinyl estradiol 0.020mg and levonorgestrel 100µg
- Shown to be efficacious for moderate facial acne in two randomized placebo-controlled trials.[Leyden J, et al. *J Am Acad Dermatol* 47(3):399-409 (2002 Sep); Thiboutot D, et al. *Fertil Steril* 76(3):461-8 (2001 Sep).]
  - A compilation of both studies showed 721 women treated for 6 cycles.
  - Significant improvements seen:
    - Reduction in acne counts:
      - 32%–47% inflammatory
      - 13%–25% noninflammatory
      - 23%–40% total lesions.
    - Investigator global assessment scores were rated as clear to almost clear in 48%-58% of subjects.

Ethinyl Estradiol/ Cyproterone Acetate (Diane-35®)

The combination of ethinyl estradiol 0.035mg and cyproterone acetate 2mg has been available as a hormonal treatment for acne in Canada since 1998.

- Cyproterone acetate is an analogue of hydroxyprogesterone and has progestational activity.
- It also acts as a potent antiandrogen:
  - by inhibiting gonadotropin secretion.
  - by competitive inhibition of testosterone and dihydrotestosterone (DHT) binding to the androgen receptor.

Efficacious in mild-to-moderate facial acne based on smaller trials with variable study designs and parameters, which produced data that could not be combined for metanalysis.[Tan J. *J Cutan Med Surg* 8(Suppl 4):11-5 (2004 Dec).]

European Study Comparing Efficacy and Safety of OCs

- A European multinational, prospective, observational new-user cohort study evaluated the safety of DRSP-containing OCs and other OCs. [Dinger JC, et al. *Contraception* 75(5):344-54 (2007 May).]
- 58,674 women were observed for 142,475 women-years.
- Serious adverse and fatal events were rare.
- Regression analysis of adverse cardiovascular events:
  - Hazard ratios for DRSP-containing OCs vs. levonorgestrel-containing and other OCs
    - 1.0 vs. 0.8 (upper 95% confidence intervals [CI], 1.8 and 1.3) for venous thromboembolism
    - 0.3 vs. 0.3 (upper 95% CI, 1.2 and 1.5) for arterial thromboembolism.

The risks of adverse cardiovascular and other serious events in users of DRSP-containing OCs in this study were found to be similar to those associated with other OCs.

Conclusion

The proven therapeutic benefits of OCs extend a valuable alternative to physicians for the treatment of acne. The accumulating evidence on the efficacy and safety of recently available drospirenone-containing hormonal preparations provides dermatologists with a new option for the treatment of acne and other hyperandrogenic disorders.

New Seal of Approval Relieves Consumer Doubt About Skin Care Product Claims

For the average consumer, choosing nonprescription skin care products can be confusing, time consuming and stressful. Personal care in Canada is a $5.0 billion industry that offers thousands of competing products, many of which make skin care-related claims. Advertisers inundate us with messages about what their products can do for us, but how can we be sure that the products we buy will actually live up to their claims?

Phrases such as "Dermatologist Tested" or "Dermatologist Approved" offer reassurance that a nonprescription skin care product has been reviewed by a professional and is likely to provide the desired results. But, in reality, there is no standard for what these phrases mean; they can, in fact, simply indicate that several dermatologists have tried a product at the manufacturer's request.

For these reasons, several organizations have created seals of approval for products; for example, the Canadian Dermatology Association (CDA) created a seal of approval for sunscreens, much like the American and Canadian Dental Associations have done for dental products like toothpaste. Products that carry a "Seal of Approval" can take some of the guesswork out of selecting products.

In response to this consumer confusion, a new professional review process for over-the-counter skin care products has been formed. In July 2007, the Dermatology Review Panel (DRP) was established to provide professional reviews of skin care product claims. The overall purpose of the DRP is two-fold. First, the DRP will assist consumers and medical professionals to easily identify nonprescription skin care products that meet independent approval standards with regard to product claims. Second, the DRP will encourage manufacturers to engage in more clinical research.

The Review and Approval Process

The DRP reviewers are comprised of 15 leading dermatologists from across Canada. The review panel provides independent dermatological assessments of the available scientific data supporting the skin care-related product claims to ensure that they meet the criteria set out by the DRP.

Manufacturers are invited to submit skin care products to the DRP for review. The DRP accepts applications for Canadian over-the-counter skin care products and other consumer products that make skin care-related claims. Each product's scientific data is reviewed by a minimum of three reviewers, who are chosen from the panel depending on their expertise in a relevant product area. The reviewers independently assess each submission to verify that there is enough scientific data to support the product's claims. Evaluations are tabulated and a final decision is rendered by the Board of Governors, which is comprised of three additional nationally recognized dermatologists.

The Dermatology Review Panel Seal of Approval is only granted to products that meet the criteria set out by the DRP. The DRP seal is easy to recognize and can be prominently displayed on approved products; its visual impact is meant to encourage Canadians wanting to make educated choices about their skin care products.

Using the Seal

Manufacturers can display the Seal of Approval on a product's packaging, advertisements, and any other promotional vehicles within Canada. Prominently placing the seal on products and promotional materials can help consumers and medical professionals easily identify products that have been reviewed by professionals and meet the critera set out by the DRP.

DRP Review Process

Step One - A manufacturer submits a product application form and supporting data to DRP.

Step Two - The product goes through a standardized review process by three reviewers. Results are tabulated and a decision is rendered by the Board of Governors.

Step Three - Upon approval, the manufacturer receives permission to use the Seal of Approval on the approved product's packaging, advertisements and any other promotional vehicles within Canada.

The DRP Seal of Approval has received a number of submissions to date and the review process is presently underway with these products.

For more information about The Dermatology Review Panel and to learn what products have been approved, go to www.dermatologyreviewpanel.ca.

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