Family Practice Edition

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Clinical Evidence. Practical Advice.

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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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Dr. Janet McKay graduated from medical school at the University of Western Ontario in 1988, followed by a residency in Family Medicine and Emergency Medicine. She received her CCFP in 1990 and CCFP-EM in 1991. She became a Fellow of the College of Family Physicians of Canada in 2004. She has been in private family practice for the past 15 years, and is presently in solo practice in London, Ontario.

Take our new Dermatologic Diagnostic Challenge on Page 8!

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 (2007 winter).] The introduction of a relatively new immunomodulator, and the approval of a vaccine significantly improves treatment options in managing this condition.

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, verrucous papules
- discrete, sessile, smooth-topped papules or nodules
- large exophytic masses.

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

Risk Factors

- The number of sexual partners over a lifetime
- The sexual promiscuity of the sexual partners
- Correlations between oral contraceptives and smoking have been reported.[Trottier H, et al. *Vaccine* 24 Suppl 1:S1-15 (2006 Mar).] However, the literature has not consistently supported such findings.

Pathogenesis

The virus is inoculated directly into the epidermal layers of the skin through epithelial defects, especially with maceration. 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

- Primarily made by visual inspection.
- For hard to detect lesions, particularly on the cervix, a 5% acetic acid solution can be applied to the suspected area. After a few minutes, the condylomata should appear as white patches on the mucosa. These changes are not diagnostic for HPV.
- A biopsy may be useful if :
  - diagnosis is uncertain.
  - lesions do not respond to standard therapy.
  - the disease worsens during therapy.
  - the patient is immunocompromised.
  - the warts are pigmented, indurated, fixed, bleeding, or ulcerated.[CDC. Genital Warts Treatment Guidelines 2006. URL: http://www.cdc.gov/std/treatment/2006/genital-warts.htm.]

Differential Diagnoses

- Molluscum contagiosum
- Benign penile pearly papules
- Hymenal remnants
- Bowenoid papulosis
- Seborrheic keratosis
- Syphilitic condyloma lata
- Skin tags
- Squamous cell carcinoma
- Verrucous carcinoma (Giant condyloma of Buschke-Lowenstein)
- Vulvar dysplasia
- Linear epidermal nevus
- Lichen nitidus
- Angiokeratomas
- Milium
- Fordyce spots

Treatment

In 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. The choice of treatment should be guided by the preference of the patient, the available resources, and the health provider's experience. No single treatment is ideal for all patients or all warts. The majority of patients require a course of therapy rather than a single treatment, and improvement will generally be seen within 3 months. [CDC. Genital Warts Treatment Guidelines 2006. URL: http://www.cdc.gov/std/treatment/2006/genital-warts.htm.] Before beginning any treatment, it is essential to screen patients for other sexually-transmitted diseases.

Most treatment modalities treat the symptom of the disease (warts) versus the disease itself. However, imiquimod, goes further by inciting an immunologic response, thereby providing a field effect in clinical and subclinical HPV.

There are three treatment modalities:

- Antiproliferative agents
- Destruction/excision therapies
- Immunomodulatory therapy
- Combination therapies

Antiproliferative Therapies

- Podophyllin resin 10%-25%
  - provider-administered
- Podophylox 0.5% solution or gel
  - can be applied by the patient
  - does not contain the mutagenic substances found in podophyllin resin.

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
- All of these options have a risk of scarring.

Immunomodulatory Therapy

- Imiquimod
- Approved by Health Canada in 1999.
- Topical cream – administered by patient.
- Self-administration 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 over 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.

Treatment (continued)

Combination Therapy

- Often monotherapy can be inadequate for treating anogenital warts. Combination therapy can provide a better result.
- 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).]

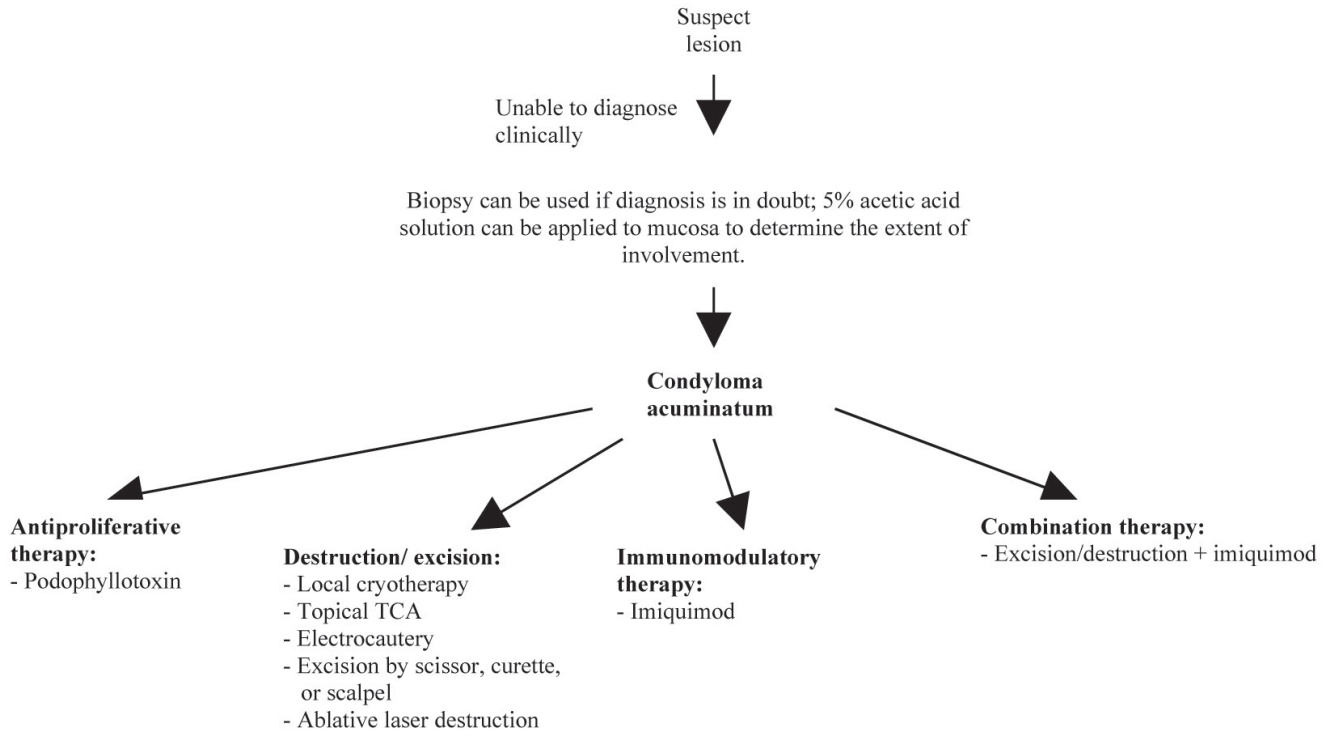

Figure 1: Algorithm for treatment of suspect lesions. [Adapted from Varela A, et al. *Skin Therapy Lett – US FP Ed* 1(2):1-3 (2007 Winter).] TCA= trichloroacetic acid

Prophylaxis

A quadrivalent HPV recombinant vaccine is now available in Canada, and is indicated in girls and women aged 9-26 years for the prevention of diseases caused by HPV types 6, 11, 16, and 18, which include genital warts, cervical cancer and other neoplasias of the cervix, vagina and vulva. It should be administered IM as three separate 0.5ml doses. Studies with this vaccine are now ongoing in males. Another bivalent HPV vaccine (for HPV types 16 and 18) is currently under review with Health Canada. There is no evidence for effectiveness in treating those who already have genital warts.

Conclusion

Most HPV infections are asymptomatic and can spontaneously clear on their own. However if treatment is required, there are a number of antiproliferative, destructive, immunomodulatory modalities available. Combination therapies have been shown to be advantageous. In general, the response time 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 appears to be very commonly used. A quadrivalent HPV recombinant vaccine is now available for girls and women 9-26 years of age, and a bivalent vaccine is under review with Health Canada. While not of benefit to those already infected, future generations may be spared considerable burden from external genital warts due to the development, approval, and release of HPV polyvalent vaccines. Not only does the vaccination largely prevent incident external genital warts, but it also protects against genital tract HPV-associated neoplasia.

Topical Treatment for Acne: A Case Study

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Case History

A 22-year-old woman who had developed a problem with her complexion over the past year presented to the clinic. She had recently been prescribed a topical retinoid, however, she believed she was allergic to it. She wore make-up to conceal her problem and was very embarrassed by her appearance. Her job requires her to be in contact with the public, and she confessed to being very impatient with the rate of treatment response.

Further questioning revealed that her periods were regular and she was not taking oral contraceptives (OCPs). She had a history of eczema and adverse reactions to some topical products. The patient was not taking any medications that could aggravate acne (e.g., lithium, phenytoin). She confirmed that her make-up was oil-free and non-comedogenic.

Clinical Assessment

The patient was asked to remove her make-up. Closer examination revealed the presence of inflamed papules with some comedones that were located mainly on the cheeks and forehead; there were many whiteheads and no blackheads; and the background skin appeared normal. (See Figure 1.)

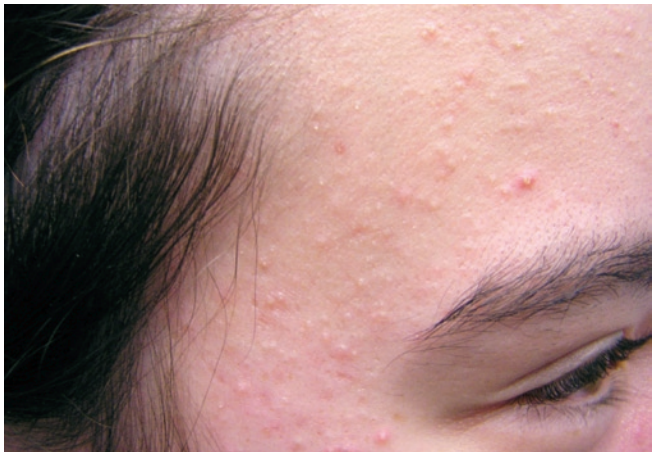

Figure 1: Examination revealed the presence of inflamed papules with some comedones, many whiteheads, no blackheads and normal appearing background skin.

It is unlikely that the patient has a retinoid allergy. Her reaction began within 48 hours of using a retinoid product, producing skin redness, scaling, and sensitivity, but no swelling of the eyelids. Moreover, she had no previous exposure to retinoids. The evidence indicated that it was an irritant rather than an allergic reaction.

Diagnostic Features

Acne
- Non-inflammatory lesions (comedones)
- Inflammatory lesions (papules & pustules)
- Scarring (examine using tangential light)
- May have significant psychological impact.

Rosacea
- Fair complexion
- Flushing, telangiectasias
- Background redness, which eventually becomes permanent
- Papules and pustules in the central face
- Absence of comedones

Perioral Dermatitis
- Most prevalent in young women and adolescents.
- Scaling, erythema, and papulopustular lesions – may have small vesicles.
- Papules are small and avoid the vermillion border.
- Usually situated around the mouth, chin, and nasolabial folds.

Treatment Options

Topical	Systemic	Light/ Laser
• Retinoids • Benzoyl peroxide (BP) • Antibiotics • Combination therapies	• Antibiotics • Hormonal OCP +/- Aldactone • Isotretinoin	• Blue light • Aminolevulinic Acid + light • Laser, e.g., smoothbeam diode laser

Treatment Options (continued)

It was difficult for the patient to accept retinoid treatment as an option because of her recent experience. Moreover, she wanted to avoid systemic therapy, at least initially, and could not afford the light or laser treatments.

Recommendation

With this patient profile, a topical antibiotic-BP combination was recommended.

Practical Tips for Application of Combination Therapy

- Apply a small amount (pea sized) to the face in the evening.
- Apply to dry skin that has not been washed recently.
- If the product is irritating, short contact application can be used, such as washing off after 2-3 minutes.
- Warn of potential for bleaching clothes.
- It is reasonable to expect about a 25% improvement after 1 month.
- Acne may flare in the first few weeks, so the patient needs to be warned.
- This is not photosensitizing.

Discussion

In general, laboratory assessments are not necessary if the patient's periods are regular. She is not taking an OCP so this could be a future avenue of treatment if she is unresponsive to topicals.

It is reasonable for the patient to be prescribed a combined product such as BP plus an antibiotic, to be applied once daily in the evening to decrease inflammation and reduce the number of lesions. In conjunction, a once-daily application of a topical retinoid may need to be introduced later, probably using short contact initially, i.e., leave on for a few minutes and then wash off the product.

Acne patients should return for a 2-month follow-up visit to check for compliance and proper application of topical preparations. The first sign of improvement is a reduced number of new lesions and this frequently occurs, but it may not be enough to be noticed by the patient. If, after another 2 months, further improvement is not seen, adding a systemic drug may be necessary. If scarring is seen, then a more aggressive treatment may be warranted. A multifaceted approach is required in assessing and successfully treating acne due to the range of causes, symptoms, and available treatment options. Since patient compliance is a concern, a great deal of attention must be given to the methods available to minimize the chance of irritation. In the opinion of the author, this may be the single most important factor influencing the success of topical therapy in acne.

Benzoyl Peroxide

- Considered to be the most frequently used topical treatment for acne.
- Acts as a potent antibacterial and converts to benzoic acid on the skin.
- Is safe and effective, especially for inflammatory acne.
  - Lowers *Propionibacterium acnes (P. acnes)* by 98%.
  - Lowers free fatty acids by 50%.
  - Reduces the size and number of comedones.
  - Strengths of 2.5% and 5% can be as effective as 10%, depending on the formulation.
- Is as effective as topical antibiotics against papules/pustules.
- Is effective against comedones, but less so than the retinoids.
- Precautions include dryness, warm sensation, tingling, stinging and bleaching of colored fabrics.

Topical Antibiotics

Topical antibiotics, e.g., clindamycin and erythromycin, reduce *P. acnes* on the skin and in hair follicles.

- Very effective, but concerns about antibiotic resistance make their use as a single agent less acceptable.
- Anti-inflammatory; reduces *P. acnes.*
- Lacks comedolytic effects, therefore has limited use as a single treatment; more useful in a combined treatment regimen.

Combination Therapy

Acne is caused by multiple pathogenic factors; combination therapy can increase the chances of treatment success.

- BP/clindamycin
- BP/erythromycin
- Has synergistic effects.
- Can produce less irritation.
- BP appears to inhibit antibiotic resistance to topical clindamycin and erythromycin.

Retinoids

- Effective for mild-to-moderate acne.
- Include tretinoin, tazarotene, adapalene.
- Exhibit comedolytic, anticomedogenic, antiinflammatory, and antibacterial properties.
- Have been shown to prevent the formation of comedones.
- It is essential to advise patients of the importance of sunscreen protection.

Topical Calcineurin Inhibitors—Efficacy and Safety in Atopic Dermatitis

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Atopic Dermatitis

Atopic Dermatitis (AD) is a chronic or chronic-relapsing inflammatory skin disease associated with hyperreactivity to environmental triggers; it can affect up to 20% of children [Williams H, et al. *J Allergy Clin Immunol* 103(1 Pt 1):125-38 (1999 Jan).]. Symptoms include flexural (facial and extensor in children) erythema, excoriations, lichenification, and xerosis.

- Part of the atopic triad (AD, hay fever, asthma).
- Itch is often so intense that patients cannot sleep or concentrate.
- Patients commonly scratch to the point of bleeding and may have secondary infection.
- Significantly impacts the sufferer as well as his or her family. It is a 'life-altering' disease.

Treatments include:

- Avoidance of triggers
- Emollients
- Topical corticosteroids
- Topical calcineurin inhibitors (TCIs)
- Antimicrobials for infection
- Oral antihistamines for pruritus
- Systemic corticosteroids, systemic immunosuppressants and phototherapy for severe disease

Mechanism of Action of TCIs

- Blocks T-cell activation and suppress release of pro-inflammatory cytokines.
- Binds to FK-506 binding protein-12, forming a complex that inhibits calcineurin, thereby preventing activation of the nuclear factor of activated T cells (NFAT), which in turn blocks gene transcription for interleukin-2.
- Tacrolimus reduces Langerhans cell activation of T cells, and cytokine production in eosinophils, mast cells, and basophils.

[Alomar A, et al. *Br J Dermatol* 151(Suppl 70):3-27 (2004 Dec).]

Approved Indication of TCIs

- The US FDA approved tacrolimus ointment for moderate-to-severe AD (0.03% for 2+ years, 0.1% for 16+ years) in December 2000, and pimecrolimus 1% cream for mild-to-moderate AD for 2+ years in December 2001.
- Both medications are indicated for short-term and intermittent long-term treatment in patients for whom conventional therapies are contraindicated, not tolerated, or not sufficiently effective.

Black Box Warning for TCIs

- A Black Box warning, issued in January 2006, resulted from the FDA's concern that the TCIs were aggressively and inappropriately marketed as first-line agents for AD and that physicians were using them off-label in children <2 years. In 2004, 13% of all pimecrolimus and 7% of all tacrolimus were administered to children <age 2.[Qureshi A, et al. *Arch Dermatol* 142(5):633-7 (2006 May).] The long-term effect of TCIs on the developing immune system in infants and children is unknown.
- Rare cases of malignancy, including skin cancer and lymphoma, have been reported, although a causal relationship has not been established.
- Long-term safety is not established.
- Avoid long-term continuous use in any age group.
- Limit application to areas affected with AD.
- Only the 0.03% tacrolimus concentration is indicated for 2- to15-year-old children.

[FDA Public Health Advisory issued January 19, 2006. http://www.fda.gov/bbs/topics/news/2006/NEW01299.html.]

- Following the FDA's action, Health Canada issued a "dear doctor" letter to outline these concerns to Canadian healthcare professionals.

Efficacy

- Three studies (n=589) showed that 41% of subjects were clear/almost clear after 6 weeks of pimecrolimus (vs. 20% on vehicle).[Eichenfield LF, et al. *J Am Acad Dermatol* 46(4):495-504 (2002 Apr); Ho VC, et al.

Efficacy (continued)

J Pediatr 142(2):155-62 (2003 Feb).]

- Three weeks of betamethasone valerate 0.1% cream was superior to pimecrolimus (50% vs. 11%, respectively, clear/almost clear).[Luger T, et al. *Br J Dermatol* 144(4):788-94 (2001 Apr).]
- Three studies (n=655) showed 90+% improvement after 12 weeks of tacrolimus 0.1% in 37% and tacrolimus 0.03% in 28% of adults, and 41% and 36% of children (0.1% and 0.03%, respectively) vs. 7% on vehicle.[Hanifin JM, et al. *J Am Acad Dermatol* 44(1 Suppl):S28-38 (2001 Jan); Paller A, et al. *J Am Acad Dermatol* 44(1 Suppl): S47-57 (2001 Jan).]
- Tacrolimus 0.1% has similar efficacy to hydrocortisone butyrate (midpotent steroid).[Reitamo S, et al. *J Allergy Clin Immunol* 109(3):547-55 (2002 Mar).]
- Tacrolimus 0.03% and 0.1% are more effective than 1% hydrocortisone ointment.[Reitamo S, et al. *J Allergy Clin Immunol* 109(3):539-46 (2002 Mar).]
- Tacrolimus 0.1% is more efficacious than pimecrolimus 1% in adults (54.1% vs. 34.9% respective reduction in EASI score, p<0.0001) and children (67.2% vs. 56.4% respective reduction, p=0.04) with moderate-to-very severe AD.[Paller AS, et al. *J Am Acad Dermatol* 52(5):810-22 (2005 May).]
- Tacrolimus 0.03% ointment and pimecrolimus 1% have similar efficacy in children with mild AD (52.1% vs. 42.7% respective reduction in EASI score, p=0.07).[Paller A, et al. *J Am Acad Dermatol* 44(1 Suppl):S47-57 (2001 Jan).]
- Treatment with 0.1% tacrolimus ointment over 6 months was shown to be significantly more efficacious than a corticosteroid ointment regimen in adults with moderate-to-severe AD.[Reitamo S, et al. *Br J Dermatol* 152(6):1282-9 (2005 Jun).

Safety of Calcineurin Inhibitors

- Skin burning and pruritus may occur at the start of treatment; typically resolve within the first 2 weeks.
- Low blood levels seen in a small minority of patients (not in the range typically associated with immunosuppression).
- High blood levels rarely seen in patients with compromised epidermal barriers, e.g., Netherton syndrome. [Allen A, et al. *Arch Dermatol* 137(6):747-50 (2001 Jun).]
- Do not cause atrophy, striae, or pigmentation changes (in contrast to topical steroids).
- No increase in systemic infections, and no increased risk of malignancy in clinical studies.[FDA Pediatric Advisory Committee. February 15, 2005, Briefing Information. http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4089b2.htm.]
- The American Academy of Dermatology (AAD) task force found that "there is no causal proof that TCIs cause lymphoma or nonmelanoma skin cancer."[Berger TG, et al. *J Am Acad Dermatol* 54(5):818-23 (2006 May).]
- Animal studies showed an increase in lymphoma at doses far exceeding those achieved with topical use. The applicability of animal studies to humans is poor due to differences in biology, concomitant exposures, and innate protective mechanisms.[Berger TG, et al. *J Am Acad Dermatol* 54(5):818-23 (2006 May).]
- The blood concentrations detected in a few patients with AD, including young children with extensive disease, have been insufficient to cause sustained immunosuppression leading to the development of lymphomas.[Bieber T, et al. *Dermatology* 211(2):77-8 (2005).]
- There have been rare spontaneous reports of lymphomas in the >7.5 million patients treated with TCIs, but their histology and clinical presentation are not in keeping with lymphomas occurring in the setting of immunosuppressive therapy.[Ormerod AD. *Br J Dermatol* 153(4):701-5 (2005 Oct).]
- An odds ratio analysis (with a 95% Confidence Interval [CI]) of 293,253 patients with A.D. showed no increased risk of lymphoma in patients treated with TCIs. [Arellano FM, et al. *J Invest Dermatol* 127(4):808-16 (2007 Apr).]
- DNA repair in keratinocytes is inhibited *in vitro* by TCIs, suggesting a theoretical risk that they might affect local skin carcinogenesis. Clinical evidence is however lacking.[Berger TG, et al. *J Am Acad Dermatol* 54(5):818-23 (2006 May).]
- The AAD task force recommends use in patients at high risk for developing skin cancer (e.g., patients on immunosuppressants, or with xeroderma pigmentosum or nevoid basal cell carcinoma syndrome) only after failure of reasonable alternatives. Broad-spectrum sunscreen should be applied to exposed skin.
- The TCI task force of the American College of Allergy, Asthma, and Immunology and the American Academy of Allergy, Asthma, and Immunology concluded that the risk/benefit ratio of TCIs was similar to those of most conventional therapies for chronic relapsing AD. Use in children <2 years of age who require more than emollients might be necessary since most topical steroids and other immunomodulators have not been studied or approved in this age group.[Fonacier L, et al. *J Allergy Clin Immunol* 115(6):1249-53 (2005 Jun).]

Conclusions

TCIs have an important place in the therapeutic armamentarium for AD. They are approved as second line agents for individuals >2 years of age, and have a good safety profile when used short-term or intermittently long-term. Studies so far have not shown an increase in malignancy in humans, but long-term vigilance is required to ensure that this remains the case.

Dermatologic Diagnostic Challenge

Question: An 83 year-old Caucasian male presents with a slowly enlarging plaque on his leg. He has a history of actinic keratoses on his face for which he receives periodic liquid nitrogen cryotherapy.

What is your diagnosis?

a. Squamous cell carcinoma
b. Wart
c. Amelanotic melanoma
d. Seborrheic keratosis
e. Keratoacanthoma
f. Basal cell carcinoma

Go online to www.SkinTherapyLetter.ca/cases to view an image and learn the answer.

Case study submitted by Benjamin Barankin, MD FRCPC

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RosaceaGuide.ca	SkinCancerGuide.ca	Sweating.ca	UnwantedFacialHair.ca

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