

# Skin Therapy Letter<sup>®</sup>

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Clinical Evidence. Practical Advice.

Editor-in-Chief: Dr Stuart Maddin

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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 24<sup>th</sup> 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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## New Evidence for the Treatment and Management of Actinic Keratoses

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### Background

Cutaneous concerns continue to be a significant part of family and specialty practices, as increasingly, patients are seeking medical consultation for the management of photodamage, actinic keratoses, and nonmelanoma skin cancer (NMSC), which is now a global epidemic. The 2 most prevalent forms of NMSC are basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).

- The earliest clinically recognizable manifestation of SCC is actinic keratosis (AK).
- The impact of skin malignancies is substantial. They commonly result in considerable deformities, either from the disease itself or from the results of selected therapies.
- The incidence of both AKs and SCC continues to rise.

### Actinic Keratoses

- All AKs deserve our attention and treatment.
- They represent clinical evidence that patients have sustained sufficient UV damage to the epidermis to cause visually abnormal skin changes and alteration in the DNA structure.
- The risk of progression of AK to invasive SCC has been estimated to range from 0.025% to 16% per year.<sup>1</sup>

### Diagnosis

Actinic keratoses are skin neoplasms that reflect cumulative UV damage to the epidermis.

- Present as skin-colored, lightly pigmented, or erythematous scaly papules localized on chronically sun-exposed areas.
- Are generally <1cm in diameter.
- Frequently, confirmation of diagnosis is achieved by palpation rather than visual examination alone.
- Predominantly found on skin areas receiving the highest levels of sun-exposure, such as the face, scalp, ears, neck, arms, and hands.
- Any lesion with induration or epidermal thickening should be biopsied.
- Risk factors for their development include blonde hair, blue eyes, fair complexion, an inability to tan, a history of long-term sun exposure, and immunosuppression, such as that seen in organ-transplant recipients.

## Treatment

Successful treatment of AK rests on the:

- choice of appropriate modality
- medical status of the patient
- patient's lesion count
- lesion characteristics (e.g., size, duration, and growth pattern)
- anatomic location.

Several treatment options are available for AKs, including local destruction and topical drug therapy.

## Locally Destructive Measures

Locally destructive measures are specialized, office-based, physician-administered, and are well suited to treat:

- individual lesions (i.e., cryosurgery, curettage, electrosurgery, or excision).
- extensive diffuse disease (i.e., chemical peels, dermabrasion, or laser ablation).

### *Cryosurgery*

- Considered the “gold standard” of locally destructive measures.
- Can be associated with patient discomfort.
- Can result in scar formation or dyschromia (abnormal skin color).
- Success rate is highly technique-dependent.

## Topical Drug Therapy

### *Imiquimod*

- The only topical immune response modifier approved by Health Canada and the US FDA for the topical treatment of AKs and superficial BCCs (sBCCs).
- Enhances both the innate and acquired immune responses by increasing regional antiviral, antitumor and immunoregulatory activities.
  - Stimulates cytokine production, especially interferon, which explains imiquimod's success in the treatment of AKs and sBCCs.

### *5-fluorouracil (5-FU)*

- 5-FU is one of the most commonly used topical treatments.
- It is a structural analog of the DNA precursor thymine.
- The majority of people being treated with 5-FU will have moderate-to-severe erythema.
- Works by inhibiting the enzyme thymidylate synthetase, and:
  - interferes with the DNA synthesis.
  - creates unbalanced growth and cell death.
  - has its greatest effect in more rapidly dividing cells.

### *Photodynamic Therapy*

- Based on the activation of a photosensitizer by visible light.
- Creates cytotoxic oxygen species and free radicals, which selectively destroy rapidly proliferating cells.
- 5-aminolevulinic acid (5-ALA) is:
  - a topical form of a photosensitizer.
  - absorbed to a greater extent by rapidly proliferating cells than by normal cells.
  - converted to protoporphyrin IX (PpIX), which is a potent photosensitizer within the cell. Activation of PpIX by physician-administered visible light produces singlet oxygen and free radicals, which leads to cell destruction.

## Combination Therapy

In clinical practice, physicians frequently combine physical/destructive modalities, such as liquid nitrogen cryotherapy, to deal with visible AKs and imiquimod to treat the underlying field cancerization. This combination of cryotherapy and topical immunomodifier brings together a targeted approach through the precise immune system destruction of subclinical AK lesions that likely offers enhanced AK clearance. A recent study reported<sup>2</sup>:

- imiquimod or vehicle used twice weekly was applied for 8 weeks following 3- to 5-second cryotherapy of target AKs within 50cm<sup>2</sup> fields on the face or scalp.
- at 12 weeks, more subjects treated with imiquimod achieved clearance of subclinical and total AKs.

## Head-to-Head European Study

A recent comparative study evaluated 5% imiquimod with cryotherapy and 5-FU for the treatment of patients with AKs.<sup>3</sup> This pivotal study by Stockfleth and colleagues addressed several critical components in the therapeutic management of AKs:

- clinical observation
- histologic assessment
- cosmetic outcome
- sustained clearance.

*Histologically confirmed AKs were treated as follows:*

Patients	Therapy Used	Therapy Details
26 patients	5% imiquimod	3 times/week for 4 weeks, 4 week rest period followed by the second cycle of 3 times/week for 4 weeks
24 patients	5% 5-FU	b.i.d. for 4 weeks
25 patients	Cryotherapy with liquid nitrogen	20-40 seconds for each lesion for up to two treatments

The assessment was performed after the treatments (Test of Cure [TOC] 6 weeks after cryotherapy, 4 weeks after 5-FU and 8 weeks after imiquimod therapies), and at 12 months following the end of treatment. Treatment dosages are based on levels approved by the European Medicines Agency.

Therapy Group	Clinical Clearance at TOC	Histological Clearance at TOC	Sustained Clearance at 12 Months	Excellent Cosmetic Outcome (% of patients)
Cryotherapy	68% (17 of 25)	32% (8 of 25)	4% (1 of 25)	4%
5% 5-FU	96% (23 of 24)	67% (16 of 24)	33% (8 of 24)	4%
5% imiquimod	85% (22 of 26)	73% (19 of 26)	73% (19 of 26)	81%

- TOC clearance rate is similar between 5-FU and imiquimod.
- In terms of extended efficacy, imiquimod demonstrates significantly greater sustained clearance rates at 12 months.
- The cosmetic outcome at 12 months also favors the use of imiquimod.

The differences in the results may be explained by their mode of action.

- Cryotherapy indiscriminately destroys good and bad cells.
- 5-FU interferes with DNA synthesis (again, good and bad cells are affected).
- Imiquimod selectively stimulates the immune system to act against both subclinical and clinically visible abnormal cells.
- Targeted lesion treatment using cryotherapy in combination with field therapy with imiquimod may yield optimal rates of clearance.

Previous research initiatives lacked the thorough comparative approach taken by this evidence-based study in exploring these common AK treatments. The data presented confirms that treatment with a topical immunomodifier provided superior sustained clearance and cosmetic outcomes in comparison to other commonly used therapies. Furthermore, these new study findings suggest that imiquimod can be considered by physicians as one of the first therapeutic options in the treatment of actinic keratoses.

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# The Role of Cosmeceuticals in Anti-Aging Therapy

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## Background

As baby boomers reach retirement age, they have shown greater interest in anti-aging preparations (cosmeceuticals), and their purported ability for rejuvenation. Anti-aging topicals, with their multiple claims, seemingly limitless key active ingredients, and complex formulations are leading the way in this huge growth industry, especially as this segment of the population opts for less invasive, nonsurgical alternatives to slow the effects of aging on the skin.

- The term cosmeceutical was introduced by Albert Kligman in 1984 to refer to substances that exerted both cosmetic and therapeutic benefits.<sup>1</sup>
- This term is not applied universally, e.g., sunscreen is an OTC drug in North America but a cosmeceutical in Europe.
- Efforts to address quality control and to establish industry standards and regulations have only recently begun.
- Safety is generally assessed, but claims of efficacy are largely unsubstantiated.<sup>2</sup>
  - Limited research is being done in academic dermatology.
  - The best evidence on cosmeceuticals comes from industry.
- Demonstrating the skin effect of a cosmeceutical can be difficult.
  - The vehicles used as placebos can affect skin texture.
  - It may take >3 months to see a difference.
- Any therapeutic benefits derived from cosmeceuticals can only be maintained through sustained use.
- Some types of cosmeceuticals include: hydroxy acids, moisturizers, retinoids, sunscreens, antioxidants, botanicals, exfoliants, and depigmenting agents.

## Antioxidants

- Antioxidants reduce free-radical damage, thereby preventing impairment at the cellular level.
- They inhibit inflammation that leads to collagen depletion.
- They offer protection against photodamage and skin cancer.
- Combining antioxidants may create a synergistic effect that can enhance efficacy.
- Important for formulation to maintain stability and active penetration.
- Most research data showing therapeutic benefits was based on their use as dietary supplements.
- Common antioxidants include:
  - Ascorbic acid (vitamin C)
    - Has been shown to improve fine lines and reduce both pigmentation and inflammation; however, some authors believe that cosmetic formulations should<sup>3</sup>:
      - contain L-ascorbic acid in a high enough concentration (at least 10%).
      - be stable. It is important to note that stabilizing ascorbic acid presents many formulary challenges.
      - have an acid pH of around 3.5 to optimize vitamin C absorption.
    - Newer formulations of stabilized derivatives may be more efficacious.
  - Niacinamide (vitamin B<sub>3</sub>)
    - Potent antioxidant that improves the lipid barrier component of the epidermis.
    - Studies showed significant reduction in fine lines, wrinkles, hyperpigmented spots, red blotchiness, skin sallowness, and improved skin elasticity.<sup>4</sup>
  - $\alpha$ -Tocopherol (vitamin E)
    - When taken orally, it protects membrane lipids from peroxidation.
    - Acts as a humectant and has been shown to reduce sunburn cells after UV exposure.
    - Once diminished,  $\alpha$ -tocopherol's activity can be restored by combining it with vitamin C.
  - Ubiquinone (coenzyme Q10)
    - Fat-soluble antioxidant that is a component of all cell membranes.
    - Good *in vitro* evidence that it can reduce periorbital wrinkles.<sup>5</sup>

## Botanicals

- Botanicals are the largest category of cosmeceutical additives found in the marketplace today.
- Their use is unregulated and often unsupported by science. Their purported therapeutic properties remain largely unexplored.
- Some botanicals that may benefit the skin include: aloe vera, tea tree oil, thujaplicin, ginkgo biloba, green tea, and grape seed.

## Depigmenting Agents

- Skin-lightening agents added to product formulations have become increasingly popular.
- Improvement rate depends on whether the pigment is in the dermis or epidermis; at best it takes 2-4 months.
  - Concomitant use of broad spectrum sunscreens is required.
- Common depigmenting ingredients include:
  - Ascorbic acid (vitamin C)
    - A naturally occurring antioxidant found in citrus fruits and leafy green vegetables.
    - Hydrophilic, so skin penetration is low.
  - Hydroquinone
    - The agent of choice for skin lightening.
    - The European Community countries have restricted its use in cosmetics to  $\leq 2\%$ .
    - The US FDA has proposed concentrations between 1.5% and 2% in skin lighteners.
    - There are concerns about exogenous ochronosis, permanent depigmentation, and possible carcinogenicity, especially at higher concentrations or use on larger body surface areas.
      - Based mainly on studies with animal models utilizing long-term exposure at high doses.<sup>6</sup>
  - NAG (N-acetyl glucosamine) 2% and Niacinamide 4%
    - Shown to reduce facial hyperpigmentation in 3 double-blind, vehicle-controlled clinical studies.<sup>7,8</sup>
    - Improvement was seen in 4-8 weeks and no adverse effects were reported.
- Other depigmenting agents include: kojic acid and licorice extract (glabridin).

## Exfoliants

- Exfoliants promote skin turnover by removing accumulations of dead cells and thickened outer layers.
- Side-effects include skin irritation and photosensitization.
  - Repeated use could increase penetration of dermis and epidermis by UV radiation.
  - Patients must be warned to use adequate sun protection.
- Common exfoliants used in cosmeceuticals include: salicylic acid, alpha hydroxy acids, beta hydroxy acids, lactic acid, and glycolic acid.

## Hydroxy Acids (alpha, beta, poly)

- Also referred to as fruit acids.
- Exert exfoliating and hydrating effects, although mechanisms of action are not well understood.
- Examples include:

• Citric acid	• Glycolic acid	• Malic acid	• Salicylic acid
• Gluconalactone	• Lactic acid	• Pyruvic acid	• Tartaric acid
- Potential to increase sensitivity to the sun; due to their exfoliating action rather than true photosensitivity.

## Moisturizers

- Moisturizers restore water content in the epidermis and improve barrier function.
  - Emollients provide a soothing protective film.
  - Humectants aid in absorption and retention of moisture.
- They improve the appearance and tactile properties of dry and aging skin.
- They reduce the release of inflammatory cytokines.
- They are important for the management of various skin conditions (e.g., eczema, psoriasis, pruritus, aged skin).



## Retinoids

- Natural and synthetic derivatives of vitamin A include retinol, retinyl-propionate and retinaldehyde, among others.
- Cosmeceutical claims are based mainly on data from studies on tretinoin and other classes of retinoid drugs.
- Retinoids reduce hyperpigmentation and inhibit enzymes from breaking down collagen.
- Retinol (vitamin A)
  - Is oxidized into retinaldehyde and then into retinoic acid, the biologically active form of vitamin A.
  - *In vivo* studies showed that topical retinol had only a modest retinoid-like biologic activity compared with topical retinaldehyde and retinoic acid.<sup>9</sup>
  - Randomized, controlled trials showed significant improvement in fine lines after 12 and 24 weeks of treatment.<sup>10,11</sup>
- Retinaldehyde
  - Can produce significant clinical improvement in the appearance of fine lines and deep wrinkles.<sup>9</sup>

## Sunscreens

- This is the single most important cosmeceutical.
  - Should be part of a daily skin care regimen.
  - Should provide broad spectrum coverage that includes UVA blocking agents to inhibit photoaging.
- They contain active ingredients that act as ultraviolet filters.
- Recommended application is 2mg/cm<sup>2</sup>, though this is rarely achieved in real-life practice.<sup>12</sup>
- Labeling changes proposed by the US FDA on sunscreen products are forthcoming. Health Canada is monitoring developments from the FDA's proposal and recognizes the need for international standardization.
- Photoprotection of cosmetic formulations that incorporate a sunscreen has not been adequately studied.

## Formulation Considerations

Safety, efficacy, and formulation consistency are areas that have been neglected and necessitate regulation. To evaluate the merits of claims made by the producers of cosmeceutical formulations, consider the following questions<sup>13</sup>:

- Can the active ingredient penetrate the stratum corneum?
- Are the concentrations of the active ingredients sufficient to provide the intended therapeutic benefits?
- Can their mechanism of action be explained by well-designed research supported by the scientific community?

Cosmeceuticals can play an integral part of an effective anti-aging regime. However, clinicians need to be diligent in ensuring the products they recommend are supported by rigorous studies and published in peer reviewed publications. Efforts should be made to establish methods to reliably evaluate their claims of efficacy.

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# New Seal of Approval Initiative to Assess Skin Care Product Claims

## Dermatology Review Panel

For the average consumer, choosing nonprescription skin care products can be confusing, time consuming and stressful. Personal care in Canada is a \$5 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, it will assist consumers and medical professionals to easily identify nonprescription skin care products that meet independent approval standards with regard to product claims. Second, it will encourage manufacturers to engage in more clinical research.

## The Review and Approval Process

The DRP is comprised of leading dermatologists from across Canada. The Panel provides independent dermatological assessments of the available scientific data supporting the skin care-related product claims in order 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 who want 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 criteria set out by the DRP.

The DRP Seal of Approval has received a number of submissions to date and several products have already received approval.

For more information about The Dermatology Review Panel and to learn what products have been approved, go to [www.dermatologyreviewpanel.ca](http://www.dermatologyreviewpanel.ca).

## SIGN UP FOR YOUR FREE SUBSCRIPTION

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