OBJECTIVES
After completion of this continuing education lesson, pharmacists will be able to:
1. discuss the definition of atopic dermatitis as well as associated epidemiology and effects on patient quality of life.
2. assess the role of topical anti-inflammatories in the treatment of atopic dermatitis
3. discuss the mechanism of action of topical calcineurin inhibitors
4. compare and contrast the role in therapy of topical calcineurin inhibitors versus topical corticosteroids
5. empower patients to make informed decisions about topical anti-inflammatory treatment in light of warnings issued by the U.S. Food and Drug Administration concerning safety of topical calcineurin inhibitors
6. recommend appropriate treatment of atopic dermatitis

INSTRUCTIONS
1. After carefully reading this lesson, study each question and select the one answer you believe to be correct. Circle the appropriate letter on the attached reply card.
2. To pass this lesson, a grade of 70% (14 out of 20) is required. If you pass, your CEU(s) will be recorded with the relevant provincial authority(ies). (Note: some provinces require individual pharmacists to notify them.)

ANSWERING OPTIONS
A. For immediate results, answer online at www.pharmacygateway.ca.
B. Mail or fax the printed answer card to (416) 764-3937. Your reply card will be marked and you will be advised of your results within six to eight weeks in a letter from Rogers Publishing.

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A FREE CONTINUING EDUCATION LESSON

Topical anti-inflammatory treatment for management of atopic dermatitis: Demystifying the role of topical calcineurin inhibitor therapy

By Tom Smiley, BSc Phm, Pharm D

Tom Smiley is a pharmacist consultant with Pharmavision Health Consulting, as well as a community pharmacist in Brantford, Ontario. In addition to his clinical experience helping patients afflicted with dermatological conditions over the past 25 years, and his own personal experience with the condition, Tom has developed and presented many CE lessons and workshops for pharmacists in the topic area, as well as patient brochures and web postings.

The author, expert reviewers and Pharmacy Practice magazine have each declared that there is no real or potential conflict of interest with the sponsor of this lesson.

UNDERSTANDING TOPICAL ANTI-INFLAMMATORY ISSUES IN ATOPIC DERMATITIS
Some confusion may exist among health professionals about the role of topical calcineurin inhibitors due to their relatively recent availability as topical anti-inflammatory therapy in the treatment of atopic dermatitis.

What is Atopic Dermatitis?
Atopic dermatitis (AD) is a chronic, relapsing, highly pruritic, inflammatory skin disease that is associated with significant costs and reduced quality of life for patients and their families. AD is clinically diagnosed by physicians in patients with an itchy skin condition that presents with three or more of the following additional characteristics:
- past involvement of skin creases, such as the bends of elbows or behind the knees, fronts of ankles, and areas around the neck or eyes.
- Personal, or immediate family history (if child is under four years), of asthma or hay fever (allergic rhinitis)
- tendency to generally dry skin over the past year
- onset of condition before the age of two
- visible flexural dermatitis (including dermatitis affecting the cheeks or forehead and outer aspects of limbs in...
children under four years).

The terms eczema and dermatitis are often interchangeable with differential diagnoses, including seborrheic dermatitis, allergic and irritant contact dermatitis; however it is most often used to describe AD.3

**Epidemiology of Atopic Dermatitis**

AD is a very common childhood problem, affecting 14-22% of children in Canada.4 It develops before age one in approximately 80% of cases, and by age five in 90% of those affected.3 The prevalence of AD has increased dramatically (two- to threefold) over the past 30 years, especially in industrialized populations such as Canada.5 Asthma develops in approximately 30% of children affected with AD and allergic rhinitis in about 35%.2 The reason for the increase in cases of AD is not clear, but it is thought to be related to both environmental and genetic factors.

The intensity of symptoms associated with AD generally decreases with age, and the condition is relatively rare after the age of 40.6 The few adults who do present with the condition generally have more severe and persistent symptoms. Most childhood cases (approximately 84%) are mild in nature; approximately 14% are moderate in severity, and only 2% are considered severe.6

**Triggers of Atopic Dermatitis**

People who suffer from AD have personal “triggers” that will exacerbate their symptoms. Allergen triggers may include:3
- foods (most common are milk, eggs, peanuts, soy, wheat, shellfish, fish). Food most commonly triggers reactions in infants under the age of one. Foods as allergens are often overemphasized.
- airborne allergens (most common are house dust mites; others include pollen, mould, animal dander, and cockroach allergens)
- microorganisms (bacteria such as *Staphylococcus aureus* and Streptococci or fungi/yeasts such as *Pityrosporum ovale* and *P. orbiculare*, *Trichophyton species* or other yeast species such as *Candida or Malassezia*)
- chemical irritants (laundry detergents, bleaches, soaps and household cleaning chemicals)
- wool fabrics - also synthetic fibers such as nylon and polyester, as they may impede normal perspiring mechanisms
- acidic foods - although not primary allergens, foods that are acidic (e.g., tomatoes, oranges, grapesfruits and strawberries) can exacerbate AD

Identification and avoidance of personal triggers is a first step in management of AD.

**Pathogenesis**

Understanding the pathogenesis of AD helps one to appreciate the mechanism of action of agents indicated for treatment. AD is an inflammatory skin disease with a strong inheritable component.3 Eosinophils are associated with the production of proinflammatory products in the skin.3 Many concepts exist around the exact cellular mechanisms associated with the pathogenesis of AD. Several additional cell types associated with inflammation (e.g., T lymphocytes, Langerhans cells,
**Focus on Topical Anti-Inflammatory Treatment of Atopic Dermatitis**

Management of AD with topical anti-inflammatories is considered the “cornerstone of pharmacological treatment.”

### The Role of Topical Anti-Inflammatories in the Treatment of Atopic Dermatitis

The International Consensus Conference on Atopic Dermatitis II lists the therapeutic objectives for AD as follows:

- reduce signs and symptoms
- prevent or reduce recurrences
- provide long-term management by preventing exacerbation
- modify the course of the disease

A risk versus benefit must also be included in any analysis or comparison of the value of available treatments.

Management of AD including the role of topical anti-inflammatories is presented in Figure 1.

Patients should monitor their condition on a daily basis while using topical medication. Health professionals should follow-up within 7-10 days after start of treatment in acute conditions and after 2-3 weeks when the condition is chronic. Here are some suggested monitoring parameters for management of AD.

### Acute Condition

- inflammation - decrease by 50% within 7-10 days
- surface area involvement - no progression
- itching/scratching - control to tolerable level within 7-10 days
- disruption of sleep or daily activities - restore normal pattern within 2-3 weeks
- stress, anxiety, depression - restore normal pattern within 2-3 weeks

### Chronic Condition

- changes in inflammation, scaling, dryness, itch, scratching - control by 4-8 weeks
- severity progression - none
- recurrence of episodes - lengthen time between episodes throughout treatment
- lichenification - no progression

### Negative Endpoints

- allergic reactions - none. If allergy occurs, discontinue therapy.
- severe dryness, irritation - minimal, and should disappear, diminish, or be controlled with continued treatment. Otherwise, refer to physician.

If the endpoints are achieved, therapy should be tapered in response to resolution. If the endpoints are not achieved, the patient should be referred to a physician for further assessment.

### Comparison of Available Topical Anti-Inflammatories

In assessing the role of new therapies it is important to compare them with current standards of treatment. In the case of calcineurin inhibitors, topical corticosteroids were the standard of treatment when they entered the market.

### Topical Corticosteroids

Although there are few well-conducted randomized controlled trials available to assess the effectiveness of topical corticosteroids (see Table 1), they have traditionally been deemed the pharmacological therapy of choice for AD. This is a result of successful use of these products dating back to 1952. The trials outlined in Table 1, although all statistically significant in terms of results, were of limited duration (maximum 4 weeks).

Therefore, long-term adverse effect assessment from topical corticosteroid clinical trials is lacking.

A systematic review comparing topical corticosteroids to each other (no control) found 11 double-blind randomized controlled trials showing significant improvements in AD in 41-97% of patients after 2-6 weeks of treatment. Unfortunately there is little good information forthcoming from well-conducted trials on long-term side effects, or effects on the natural history of AD.

Topical corticosteroids are available in various potencies and dosage forms such as creams, ointments, gels and lotions. An overview of currently available topical corticosteroids and their relative potencies is presented in Table 2. Many factors must be taken into consideration when making a topical corticosteroid recommendation for an individual. Following are some general principles.

- **Highest potency agents** (see Table 2) should be reserved for conditions that are resistant to less potent agents, as they have a high potential for serious local and systemic side effects. These agents are suitable for short-term exacerbations (e.g., no more than 2-4 weeks) of severe eczema. Potent topical corticosteroids should not be used on large areas, thin skin areas, or skin folds or in young children or infants. Use on the face and folds must be avoided.

- **Mid-potency preparations** (see Table 2) are appropriate for intermittent long-term use or chronic use where...

**TABLE 1: Randomized Placebo-Controlled Trials Available for Evaluation of Topical Corticosteroid Treatment**

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of Patients</th>
<th>Age (yrs)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednicarbate oint. 0.25% twice daily for 4 weeks</td>
<td>51</td>
<td>18-60</td>
<td>Dermatitis ↓ in 87% of treated patients, 8% of controls. Pruritus significantly ↓ by treatment (patient assessment)</td>
</tr>
<tr>
<td>Hydrocortisone valerate cream, 0.2% 3 times daily for 2 weeks</td>
<td>20</td>
<td>2-75</td>
<td>Excellent results, or eczema clear in 75% of treated patients, 20% of controls</td>
</tr>
<tr>
<td>Clobetasol propionate cream 0.05% twice daily for 4 weeks</td>
<td>81</td>
<td>≥12</td>
<td>Good or excellent results, or eczema clear in 82% of treated patients, 29% of controls</td>
</tr>
</tbody>
</table>

**Notes:**

- ↓ Decrease
- ↑ Increase
Topical anti-inflammatory treatment for management of atopic dermatitis: Demystifying the role of topical calcineurin inhibitor therapy

Skin areas are thick (e.g., hand eczema). These preparations should be avoided on areas of thin skin, with extreme caution if used on face or intertriginous (skin folds) areas such as the folds of the groin, creases of the neck, and under the armpits.

- **Lowest potency agents** (see Table 2) are preferred for skin areas that are thinner (e.g., face, eyelids, skin flexures, scrotum), in the elderly, young children, or infants, or if use of the topical agent is required long-term. These are appropriate for maintenance therapy after initial control of the rash is obtained.

- **Creams** are best suited for treatment of sub-acute, wet lesions, as they are less occlusive than ointments and more cosmetically acceptable.

- **Ointments** are more greasy and occlusive and may be more appropriate in dry, scaly, or hyperkeratinized skin areas as often seen in AD. Ointments of the same topical medication in the same strength are more potent in an ointment dosage form compared with cream or lotion. Ointments may cause itch due to their occlusive effect.

- **Lotions** are the least occlusive agents and are preferred for acute weeping lesions in the axilla, foot, groin, and hairy areas.

- **Gels** are non-occlusive and non-greasy. They dry quickly and do not leave residue. They are particularly suited for use on hairy areas and the face.

- **Occlusive therapy** may be used to increase the absorption and effectiveness of topical corticosteroids, especially those less potent. Often a doctor will instruct the patient to use a polyethylene film (plastic household wrap) and apply it over prescribed cream or ointment overnight. Occlusive therapy increases risk for atrophic striae, folliculitis and bacterial or fungal infections. Children are especially at risk for pituitary and adrenal suppression after prolonged use of this method over large areas of skin. If body temperature is elevated, occlusive therapy with topical corticosteroids should not be employed.

- **Using short bursts of potent topical corticosteroids** compared to longer-term use of weaker corticosteroids has demonstrated no differences in the management or side effects of children with mild to moderate AD.

- **Phenol, menthol and/or camphor** may be added to topical corticosteroids in small quantities (e.g., 0.25%) for additional itch control.

Overall, it is very difficult to pinpoint

### TABLE 2: Estimated Potencies and Dosage Forms of Currently Available Topical Corticosteroid Preparations (adapted from reference 18)

<table>
<thead>
<tr>
<th>Medication</th>
<th>Available dosage forms</th>
<th>Potency level*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High Potency</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>betamethasone dipropionate glycol 0.05%</td>
<td>cream, oint, lotion</td>
<td>1</td>
</tr>
<tr>
<td>clobetasol propionate 0.05%</td>
<td>cream, oint, scalp lotion</td>
<td>1</td>
</tr>
<tr>
<td>desoximetasone 0.25%</td>
<td>cream, oint</td>
<td>2</td>
</tr>
<tr>
<td>desoximetasone 0.05%</td>
<td>gel</td>
<td>2</td>
</tr>
<tr>
<td>fluocinonide 0.05%</td>
<td>cream, oint, gel</td>
<td>2</td>
</tr>
<tr>
<td>halcinonide 0.1%</td>
<td>cream, oint, solution</td>
<td>2</td>
</tr>
<tr>
<td>halobetasol propionate 0.05%</td>
<td>cream, oint</td>
<td>2</td>
</tr>
<tr>
<td>betamethasone valerate 0.1%</td>
<td>oint</td>
<td>3</td>
</tr>
<tr>
<td>mometasone furoate 0.1%</td>
<td>oint</td>
<td>3</td>
</tr>
<tr>
<td><strong>Mid-Potency</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>amcinonide 0.1%</td>
<td>cream, oint, lotion</td>
<td>4</td>
</tr>
<tr>
<td>beclomethasone dipropionate 0.025%</td>
<td>cream, lotion</td>
<td>4</td>
</tr>
<tr>
<td>clobetasone butyrate 0.05%</td>
<td>cream, oint</td>
<td>4</td>
</tr>
<tr>
<td>desoximetasone 0.05%</td>
<td>cream</td>
<td>4</td>
</tr>
<tr>
<td>diflucortolone valerate 0.1%</td>
<td>cream, oily cream, oint</td>
<td>4</td>
</tr>
<tr>
<td>fluocinolone acetonide 0.025%</td>
<td>oint</td>
<td>4</td>
</tr>
<tr>
<td>hydrocortisone valerate 0.2%</td>
<td>oint</td>
<td>4</td>
</tr>
<tr>
<td>mometasone furoate 0.1%</td>
<td>cream, lotion</td>
<td>4</td>
</tr>
<tr>
<td>triamcinolone acetonide 0.1%</td>
<td>cream, oint</td>
<td>4</td>
</tr>
<tr>
<td><strong>Lowest Potency</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>betamethasone valerate 0.05%, 0.1%</td>
<td>cream</td>
<td>5</td>
</tr>
<tr>
<td>fluocinolone acetonide 0.01%</td>
<td>solution, shampoo, topical oil</td>
<td>5</td>
</tr>
<tr>
<td>fluocinolone acetonide 0.025%</td>
<td>cream</td>
<td>5</td>
</tr>
<tr>
<td>hydrocortisone valerate 0.2%</td>
<td>cream</td>
<td>5</td>
</tr>
<tr>
<td>prednicarbate 0.1%</td>
<td>cream, lotion</td>
<td>5</td>
</tr>
<tr>
<td>triamcinolone acetonide 0.025%</td>
<td>cream</td>
<td>5</td>
</tr>
<tr>
<td>betamethasone valerate 0.05%, 0.1%</td>
<td>lotion</td>
<td>6</td>
</tr>
<tr>
<td>desonide 0.05%</td>
<td>cream, oint, lotion</td>
<td>6</td>
</tr>
<tr>
<td>hydrocortisone 1%/urea 10%</td>
<td>cream, lotion</td>
<td>6</td>
</tr>
<tr>
<td>hydrocortisone 0.5%, 1%</td>
<td>cream, oint, lotion, scalp lotion</td>
<td>7</td>
</tr>
<tr>
<td>hydrocortisone 2.5%</td>
<td>cream, lotion, scalp lotion</td>
<td>7</td>
</tr>
</tbody>
</table>

*Potency level 1 is most potent and is rarely indicated in children. Potencies may vary depending on drug’s characteristics and concentrations as well as on base in which it is used, site of application, skin condition, use of occlusion, and individual patient characteristics."
Potential Adverse Effects Associated with Topical Corticosteroids

Common adverse effects of topical corticosteroids include:

- Atrophic changes
  - Steroid atrophy
  - Telangiectasia
  - Striae
  - Purpura
  - Stellate pseudoscars
  - Ulceration
  - Easy bruising

- Infections
  - Masked, microbial infections (tinea incognito)
  - Aggravation of cutaneous candidiasis, herpes or demodex
  - Reactivation of Kaposi sarcoma
  - Granuloma gluteale infantum

- Ocular changes
  - Ocular hypertension
  - Glaucoma, cataract

- Pharmacologic effects
  - Steroid rebound, steroid addiction, tachyphylaxis

- Miscellaneous
  - Steroid acne
  - Perioral dermatitis
  - Steroid rosacea
  - Hirsutism
  - Hyperpigmentation
  - Hypopigmentation
  - Photosensitization
  - Rebound flare (psoriasis)

Evidence about the potential for topical corticosteroids to cause systemic adverse effects is unfortunately lacking, and any investigation into this issue has been inconclusive. The Guidelines of Care for Atopic Dermatitis published by the American Academy of Dermatology Association in 2004 suggests that the effects of topical corticosteroids on suppression of the hypothalamic-pituitary-adrenal axis (HPA) in pediatric patients is associated with percutaneous absorption in those with more severe disease and in those younger than 2 years of age. With respect to potential effects of topical corticosteroid application on linear growth rate in children and bone density in adults, the expert panel agrees that background factors related to these potential adverse effects should be considered when considering treatment or which agent to employ. Generally, if topical corticosteroids are to be used, the lower-potency dosage forms should be utilized for treatment of AD in children. Long-term continuous treatment around the age of puberty should be avoided, as the epiphyses could potentially close prematurely at this age. Any patient using the highest-potency preparations for 2 weeks or more is susceptible to percutaneous absorption and systemic toxicity.

The following principles have been recommended for the use of topical corticosteroids:

- Steroids should not be prescribed unless the diagnosis is reasonably certain. Corticosteroids are suppressive to all types of inflammations.
- When topical corticosteroids are used, any co-existing infection should be treated promptly.
- Use the topical corticosteroid that is just sufficiently potent to control the skin condition in order to avoid significant local and systemic side effects.
- Of note, unlike other topical corticosteroids, topical hydrocortisone has not been associated with HPA suppression.
- Avoid use of potent topical corticosteroids on the face, flexures and scrotum; also avoid strong steroids in infants and young children whenever possible.
- In some situations, a potent topical steroid can be used initially to gain rapid control.

Efficacy of Calcineurin Inhibitors

Many more randomized placebo-controlled trials exist for topical calcineurin inhibitors compared with topical corticosteroids.

Summary of Clinical Evidence for Efficacy of Topical Tacrolimus and Topical Pimecrolimus

As illustrated in the evidence outlined in Table 3 (randomized, placebo-controlled trials), both tacrolimus and pimecrolimus offer significant benefit in the treatment of AD compared to vehicle alone. Furthermore, tacrolimus ointment 0.1% has been shown as effective as hydrocortisone butyrate 0.1% ointment (mid-potency steroid) in adults, and both tacrolimus 0.03% and 0.1% were more effective than hydrocortisone acetate 1% ointment (low potency steroid) in children with AD. Pimecrolimus was effective in 2 trials in reducing the number of flares requiring topical corticosteroid intervention compared to vehicle (i.e., steroid-sparing effect). Although not a blinded trial, a study of 56 patients with AD were treated for one year with either tacrolimus 0.1% ointment or usual treatment (most...
Topical anti-inflammatory treatment for management of atopic dermatitis: Demystifying the role of topical calcineurin inhibitor therapy

After completion of treatment there was a significant increase in collagen synthesis in the tacrolimus group accompanied by an increase in skin thickness. This study suggests that long-term therapy with tacrolimus ointment reverses corticosteroid-induced skin atrophy.

Finally, in a randomized-controlled study of 1,065 adults and children comparing the efficacy of tacrolimus ointment and pimecrolimus cream suggests that over a 6-week treatment period tacrolimus ointment is significantly more effective and has a faster onset of action than pimecrolimus cream, with similar safety profiles. Longer term, open-label non-comparative studies of tacrolimus ointment support the randomized placebo-controlled trial results. In a study where 95.5% of 8,000 patients had moderate to severe AD (3,964 adults and 3,959 children), there was a 52% reduction in body surface area affected after one month of treatment and a 91% reduction after 18 months. In another open-label comparative study of 316 adults using tacrolimus ointment 0.1%, marked or excellent improvement or clearance of disease was reported in 54%, 81% and 86% of patients at 1 week, 6 months and 12 months respectively. Finally, in a study where 300 patients using tacrolimus 0.1% ointment were followed for more than 3 years and up to 4 years, efficacy was evident after one week of treatment and maintained for the full treatment period.

Current Product Monograph Indications for Tacrolimus and Pimecrolimus

Tacrolimus ointment 0.03% and 0.1%...
burning is usually temporary and of short duration. In clinical trials involving tacrolimus up to 36% of pediatric patients using 0.03% ointment and up to 47% of adults using 0.1% ointment experienced a localized burning sensation when applied.12

SAFETY PROFILE OF CALCINEURIN INHIBITORS—EVALUATING THE EVIDENCE

On February 15, 2005, the Pediatric Advisory Committee of the Food and Drug Administration (FDA) recommended a “black box” warning for tacrolimus ointment and pimecrolimus cream due to concerns for potential safety risks (i.e., skin cancer and lymphoma). On March 10, 2005, the FDA issued a Public Health Advisory informing health-care providers of these concerns.47 The advisory commented that the concern is based on animal studies, case reports in a small number of patients, and the mechanism of action of the drugs.48 Since it may take human studies of 10 years or longer to determine if use of calcineurin inhibitors is linked to cancer, the FDA advises that the agent be used only as labeled, for patients who have failed treatment with other therapies.

Following are the recommendations as cited directly from the FDA Public Health Advisory:47

• Use Elidel and Protopic only as second-line agents for short-term and intermittent treatment of atopic dermatitis (eczema) in patients unresponsive to, or intolerant of other treatments.

• Avoid use of Elidel and Protopic in children younger than 2 years of age. The effect of Elidel and Protopic on developing immune system in infants and children is not known. In clinical studies, infants and children younger than 2 years treated with Elidel had a higher rate of upper respiratory infections than did those treated with placebo cream.

• Use Elidel and Protopic only for short periods of time, not continuously. The long-term safety of Elidel and Protopic are unknown.

• Children and adults with a weakened or compromised immune system should not use Elidel or Protopic.

• Use the minimum amount of Elidel or Protopic needed to control the patient’s symptoms. In animals,
increasing the dose resulted in higher rates of cancer.

On January 19, 2006, the FDA announced that the black box warning will be added to the labeling of the topical calcineurin products, and a medication guide will be distributed upon dispensing of a prescription. At time of publication, Health Canada was still deciding on its course of action in this regard. Many groups and associations in North America, including the Canadian Dermatological Association have raised issue with this “black box” warning. Evidence on which the decision of the FDA to release this Public Health Advisory was made is claimed to be weak. For example, the animal data showing dose-dependent carcinogenicity showed lymphoma formation only in mice where tacrolimus and pimecrolimus exposures were 26-47 times the maximum recommended equivalent dose for humans. Lymphomas identified in studies or reported by users of the products is lower in number than what one would expect 61 cases in the general population. The Canadian Dermatological Association has issued a position statement on topical calcineurin inhibitors as well as a Topical Calcineurin Inhibitors Fact Sheet which summarizes the evidence as follows:\textsuperscript{49,50}

- To ensure safety of calcineurin inhibitors, clinical studies have been done on 38,000 people including 14,000 children under the age of 17. Two cases of non-lymphoma cancer were discovered. Scientists usually expect to find three lymphomas among such a large group.
- In North America there are nearly seven million patients safely using these medications. There have been 25 cases of malignancy reported, four of them in children 2-16 years old. There were 13 lymphomas (in general population one would expect 61 cases in this number of people).

The Canadian Dermatology position statement states the following:\textsuperscript{49}

- There is no evidence of an increased rate of lymphoma when compared to the general population.
- The clinical and histological patterns of the observed lymphomas are not consistent with typical immunosuppression-related lymphomas.
- There is minimal absorption of topical calcineurin inhibitors, with non-detectable or negligible blood levels, making long-term intense immunosuppression unlikely.
- There is no evidence of interference with effectiveness of immunization.

Similar positions have been taken by the American Academy of Dermatology, and The American College of Allergy, Asthma and Immunology.\textsuperscript{49} A Consensus Statement on the Safety Profile of Topical Calcineurin Inhibitors resulting from the gathering of experts around the world appeared in the journal Dermatology.\textsuperscript{51} The consensus states: “We are deeply troubled by the FDA’s actions because there is no evidence that topical use of pimecrolimus and tacrolimus causes malignancies.”\textsuperscript{49} A position paper of the European Dermatology Forum entitled Review of the Potential Photo-Carcinogenicity of Topical Calcineurin Inhibitors, concluded that available data suggest long-term application of topical calcineurin inhibitors is safe, and there is no evidence of increased skin cancer risk and it is ethical to treat patients with these agents when indicated.\textsuperscript{52}

The reason for the position taken by these various associations is understandable. AD can severely affect quality of life, and there are patient populations not able to use topical corticosteroids, or in whom these agents are not effective. Many could, and do, benefit from topical calcineurin inhibitor therapy. The American Academy of Dermatology cites concern that the warnings will confuse and unnecessarily worry patients and health professionals.\textsuperscript{53} Patients who would benefit greatly from the therapy may needlessly suffer with their condition.

As health professionals, it is important that patients make treatment decisions based on balanced evidence. A discussion of topical calcineurin inhibitors with patients should include a discussion of the evidence presented above.

- Based on available evidence it appears highly unlikely that topical calcineurin inhibitors are associated with increased risk for malignancy.
- It is acknowledged that enough time has not elapsed since launch of these products to fully evaluate long-term effects.
- Potential risks and benefits of topical corticosteroids and topical calcineurin inhibitors should be discussed with patients and/or their advocates in light of the patient’s current circumstances.

**SUMMARY: PHARMACISTS HELPING PATIENTS UNDERSTAND AND MANAGE ATOPIC DERMATITIS**

Pharmacists should play a very important role in helping patients understand management of AD as well as benefits and risks of therapy. Following are a variety of topics that should be included in a discussion about AD:

- Information about the causes and usual progression of the condition (i.e., in many cases a disease of childhood that progressively improves into adulthood).
- Triggers, their role in exacerbation of the disease, and helping patients identify their triggers.
- Importance of trigger avoidance in managing disease.
- Importance of skin hydration with emollients in managing AD.
- Importance of reporting any type of infection to physician.
- A balanced discussion of benefits and risks associated with currently available topical anti-inflammatory agents.
- Appropriate application of topical therapy.
- Monitoring of the condition on a daily basis with referral back to physician when appropriate.

**REFERENCES**


1. Would a doctor be able to use the information concerning MF stated above to confirm a diagnosis of atopic dermatitis?
   a. No, because there is no mention of dry skin over the past year.
   b. No, because he doesn’t mention rash on the fronts of ankles.
   c. Yes, because he is itchy and has had the condition from an early age and has a family history of hay fever and asthma.
   d. Yes, because he is itchy and has had the condition since one month old, has visible flexural dermatitis and has a family history of hay fever and asthma.

2. Is it odd that MF developed atopic dermatitis at one month of age?
   a. Yes, 80% of cases develop between age one and two.
   b. Yes, 80% of cases develop after age two.
   c. No, 80% of cases develop before age one.
   d. No, 95% of cases develop before six months of age.

3. Which statement(s) is/are TRUE with respect to progression of atopic dermatitis?
   a. AD usually gets worse as a person ages.
   b. AD symptoms usually resolve as one becomes an adult.
   c. Adults with AD symptoms are likely to have symptoms that are more severe and persistent than younger people.
   d. b and c

4. Which situation would be LEAST likely to be a trigger of MF’s eczema symptoms?
   a. Pollen in the air
   b. Cotton shirts
   c. Eating tomatoes as a snack food
   d. Eating eggs

5. Which suggestion is best for MF to use chronically regardless of symptom flares?
   a. A product containing glycerin to prevent the skin from drying
   b. A mild topical corticosteroid to keep inflammation in check
   c. Wear nylon or polyester to prevent topical allergy
   d. Keep windows open as much as possible to allow circulation of air

6. You recommend MF visit a doctor for assessment. Which prescription is appropriate for a doctor to write for MF?
   a. Topical corticosteroid for 2 weeks
   b. Topical corticosteroid for 3 months
   c. Calcineurin inhibitor for 2 weeks
   d. a or c would be appropriate

7. If MF’s physician asked you for a recommendation of a mid-potency topical corticosteroid, which would be the most appropriate?
   a. Clobetasone butyrate 0.05% cream
   b. Clobetasol propionate 0.05% ointment
   c. Desonide 0.05% cream
   d. Fluocinonide 0.05% cream

8. Which dosage form would be most appropriate on areas where MF has dry and scaly skin as is common in AD?
   a. Cream
   b. Ointment
   c. Lotion

9. Which agents would be most appropriate for use in skin flexures?
   a. Mometasone furoate 0.1% ointment
   b. Desoximetasone 0.25% cream
   c. Tacrolimus 0.03% ointment
   d. b or c would be appropriate

10. LL would like to know how tacrolimus works. What is the most appropriate response?
   a. Tacrolimus ointment prevents the formation of inflammatory factors in the body that can cause atopic dermatitis.
   b. Tacrolimus ointment physically protects the skin from contact allergens that could make AD worse.
   c. Tacrolimus ointment soothes eczema with a camphor-like effect to help prevent itching.
   d. a and b

11. What evidence is available to compare calcineurin inhibitors with low potency topical corticosteroid therapy in children?
   a. Unfortunately there have been no randomized controlled trials comparing topical corticosteroid therapy with topical calcineurin inhibitors.
   b. Tacrolimus ointment 0.03% and 0.1% ointment was shown to be as effective as hydrocortisone acetate 1% ointment in children with AD.
   c. Tacrolimus ointment 0.03% and 0.1% ointment was shown to be more effective than hydrocortisone acetate 1% ointment in children with AD.
   d. Pimecrolimus 0.03% cream was shown to be more effective than hydrocortisone butyrate 1% cream in children

12. Which statement about pimecrolimus 0.1% cream is TRUE?
   a. Pimecrolimus cream was shown to be more effective in a randomized controlled trial than tacrolimus 0.03% ointment for treatment of AD in children.
   b. Pimecrolimus 0.1% cream has been shown in randomized controlled trial to reduce the number of AD flares requiring topical corticosteroid intervention.
   c. Pimecrolimus 0.1% cream is indicated for use in children aged 2 years or older with moderate to severe AD.
   d. Pimecrolimus cream has been associated with more local and systemic adverse events than tacrolimus 0.1% ointment.

13. What would be indicated for treatment of LL’s daughter according to the product monographs?
   a. Tacrolimus 0.03% only
   b. Pimecrolimus 0.1% only
   c. Tacrolimus 0.03% ointment or Pimecrolimus 0.1% cream
   d. Tacrolimus 0.03% or 0.1% ointment or Pimecrolimus 0.1% cream
14. What should you tell LL is the most common side effect associated with tacrolimus or pimecrolimus topical dosage forms?
   a. Initial worsening of itch
   b. Temporary local mild burning sensation when applied
   c. Increased sensitivity to cold
   d. Hyperpigmentation of skin

15. LL is concerned about the warnings associated with use of tacrolimus ointment and pimecrolimus cream that she read about in a paper. Which statement about safety of these medications is TRUE?
   a. In experimental studies mice developed lymphomas at a dose twice the equivalent of that used in humans.
   b. Malignancies have been reported in only 0.1% more of patients using topical calcineurin inhibitors compared to the general public.
   c. The clinical and histological patterns of observed lymphomas in patients using topical calcineurin inhibitors are not consistent with those normally found in immunosuppressed patients.
   d. The effectiveness of immunizations is decreased in people using topical calcineurin inhibitors.

16. What do the Canadian Dermatology Association and others NOT cite as reasons for concern over black box warnings such as those directed by the FDA in the United States?
   a. Patients who could benefit from the medication may not use it out of confusion and worry.
   b. Topical calcineurin inhibitors are generally more effective than topical corticosteroids and should normally be tried first.
   c. Available data suggest that topical calcineurin inhibitors are safe.
   d. All of the above.

17. How do the black box warnings issued by the FDA of the United States conflict with the International Consensus Conference on Atopic Dermatitis II?
   a. The black box warnings recommend using calcineurin inhibitors only for short periods, and not continuously.
   b. The black box warnings state that calcineurin inhibitors should be used only after patients have tried other treatments.
   c. The black box warnings state that topical corticosteroids are safe for long-term maintenance therapy.
   d. a and b

18. What side effects may be associated with topical corticosteroids but not in topical calcineurin inhibitors?
   a. Long-term continuous use of topical corticosteroids may increase risk for premature closure of the epiphyses during puberty.
   b. Long-term continuous use of topical corticosteroids may cause epidermal thinning.
   c. Long-term topical corticosteroid used at high dose may cause hypothalamic-pituitary-adrenal axis suppression in pediatric patients.
   d. All of the above.

19. LL's mother asks if she could use a stronger topical corticosteroid but just use it intermittently. Which statement is CORRECT regarding use of short bursts of potent topical corticosteroids compared to long-term use of weaker ones?
   a. Short bursts of potent topical corticosteroids have been shown to be more effective with similar adverse effect profile.
   b. Short bursts of potent topical corticosteroids have been shown to be more effective with increased adverse effect profile.
   c. Short bursts of potent topical corticosteroids have been shown to be no more effective than longer-term weaker agents and with similar adverse effect profile.
   d. Short bursts of potent topical corticosteroids have been shown to be no more effective than longer-term weaker agents and have a worse adverse effect profile.

20. What is the most important reason for not being able to pinpoint the exact efficacy of topical corticosteroids in treatment of AD?
   a. There are so many of them.
   b. There are too few clinical studies available.
   c. There are many different potencies.
   d. There are many different stages of eczema.
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