Many recent discussions and reviews assess how new therapies for actinic keratoses (AKs) can effectively treat clinical and pre-clinical lesions with adequate if not good tolerability, and still there are these basic questions to ponder:

- Why do we bother to treat AKs?
- Who needs topical therapies?
- Isn’t destruction good enough?

Many of our colleagues in dermatology are still of the mindset that AKs either don’t need treatment, need destruction alone, or that topical therapies are not worth the price that many patients have to bear (not remembering that development of squamous cell carcinoma (SCC) is an entirely different price to pay). Even in 1974, an article published on the subject stated that “Actinic Keratosis is likely underdiagnosed and under-reported, partially because separating AK from SCC is a challenge and partially because it is difficult to track, since reports of AK diagnosis are not included in cancer registries.”

This was a concept well before therapies other than topical 5-FU were available.

In reality, not every patient is a surgical candidate or can come to the office every three months for treatment, let alone want to come back and be frozen over and over again. In the meantime, the potential for malignant transformation of the dysplastic keratinocytes and mutations that are already in motion continues to roll downhill. Many of the patients that are at the highest risk for developing skin cancer also demonstrate the greatest need for therapy between office visits (Table 1). Keep in mind that many of the patients in this category are in some way immunosuppressed, which predisposes them to further progression of mutations that lead to carcinogenesis.

Simultaneously, the photodamage that creates the initial cascade also creates relative immunosuppression:

**Take-Home Tips.** Medical management of AKs is a logical and increasingly important approach to patient care. Medical therapy targets visible lesions as well as preclinical lesions and other symptoms of chronic photodamage. It may be more convenient for patients and, by providing a field effect, potentially provides better long-term outcomes than destructive modalities.
in the same way that we use several minutes of phototherapy to treat psoriasis or dermatitis by stabilizing the dendritic cells, lymphocytes, and mast cells, imagine what several years of unprotected solar exposure does to the local immune system. Long-term unprotected solar exposure results in a defect in tumor surveillance, antigen processing, and wound repair. All of these consequences lead to what we see with dermatoheliosis, secondary folliculitis and dyschromia, which are the appearance of photodamage.

A prevailing impediment to adding topical management is truly understanding the disease state that is being treated. Actinic keratoses are a reflection of sun exposure from years, not days, almost like an investment in time of pathogenesis, with a consequence of skin cancer. Therefore, we can describe AKs as a “symptom” of the “disease” of photodamage with SCC as an “endpoint” of that disease, which in many ways can help place medical management into its context.

In many ways, we should treat AKs like we treat acne. We don’t just use spot treatment such as clindamycin solution. We use retinoids to treat the keratinization defect, benzoyl peroxide to treat surface area, and antibiotics to control inflammation—all of which are approaching the disease process, not just the symptoms.

With that in mind, the appearance of multiple AKs in a field should signal that the entire area is photodamaged. Therefore the goal of field therapy is not only to treat clinical lesions (what we see), but also to reveal and destroy the actinic keratoses that are not visible before the start of treatment (what is on the way). More importantly, aggressive field therapy should even attempt to restore local immune mechanisms to restore and repair the effects of photodamage. This includes counteracting reactive oxygen species, maximizing wound healing, and most importantly, restoring tumor surveillance and antigen presentation to stop “disease” progression, rather than just treating the “symptoms.”

The challenges of successful integration of field therapy are not limited to prescribers who require a change in mindset. Some patients, especially those with a history of previous topical therapy for AKs, such as 5-FU or on-label imiquimod 5%, may have experienced or be concerned about significant inflammatory responses and may be reluctant to undergo medical treatment. Inflammation and irritation associated with topical fluorouracil and imiquimod are well documented in the literature, prompting development of novel formulations and alternative dosing regimens. For example, fluorouracil is now available in concen-
trations as low as 0.05% and the latest addition to the treatment armamentarium is imiquimod 3.75% for cycle dosing. In phase 3 trials, among patients who applied up to two packets (250mg each) of imiquimod 3.75% once daily for two three-week treatment cycles, with a three-week no-treatment interval, there were few treatment discontinuations and only 27.2 percent of patients required an additional therapeutic break.11

Clinicians should be prepared to discuss with patients the reality of medical therapy for AKs. Patients should expect to experience some degree of irritation and inflammation. Even if discomfort is minimal, erythema may develop. Swelling, significant erythema, and crusting are all possible. Avoidance of sun exposure and faithful use of sunscreens during the treatment phase is essential and serves as a good preparation for a future of sun-safety practices.

Patients should also understand that there are strategies to minimize the effects of treatment. Cycle therapy is approved for imiquimod 3.75% but intermittent or pulse therapy has also been used effectively with imiquimod 5%12 and fluorouracil. Additionally, gentle skin care, bland moisturizers, and even cold compresses can be used to reduce the degree of therapy-induced irritation. In the event of significant inflammation, topical corticosteroids may be used to calm the response.

Adequate patient follow-up is essential to successful medical management of AKs with check-up appointments scheduled at appropriate intervals. Patients must be encouraged to call with any questions or concerns. Some practices have even implemented “walk-in” privileges for all medically managed AK patients so that they can receive immediate evaluation of any application site reaction.

The Issue of Substitution
Given the prescriber’s expertise in selecting a medical treatment and dosing regimen for AKs that will optimize efficacy and tolerability, it is important that patients receive the prescribed intervention. Pharmacists can play a crucial role in supporting medical therapy of AKs or, unfortunately, in inhibiting therapeutic success. The issue of inappropriate substitution is a problem across dermatology but can be particularly challenging in the management of AK. Consider a recent case from my practice.

An 89-year-old man presented with diffuse photodamage and multiples AKs on his entire face. He was prescribed imiquimod cream 3.75%, which is indicated for treatment of the full face and/or scalp. He presented to the office with severe response after daily use of medication (Figs. 1-3). The degree of inflammation had not been noted in any previous patient treated with imiquimod 3.75%, so the patient’s medication was reviewed. The pharmacist had dispensed imiquimod 5% as a generic substitution but had failed to provide any clarification to the patient. This substitution is illegal, given that the novel imiquimod 3.75% formulation, on the market for less than one year, is protected by patent and has no generic equivalent. In addition to difference in the concentration of active ingredient, the indications for imiquimod 3.75% and imiquimod 5% differ (Tables 2, 3). Treating more than eight AKs, more than 25cm² surface area, or any hyperkeratotic lesions makes use of imiquimod 5% cream off-label. The patient was being treated with imiquimod 3.75% within its label-
Management of Actinic Keratoses

Table 4. Pharmacologic treatments for AK and generic equivalents

<table>
<thead>
<tr>
<th>Brand</th>
<th>Generic</th>
<th>Non-equivalent possible substitution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imiquimod</td>
<td>Zyclara 3.75% cream</td>
<td>Non-available</td>
</tr>
<tr>
<td>Aldara 5% cream</td>
<td>Imiquimod 5% cream</td>
<td></td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>Efudex 5% Cream</td>
<td>Fluorouracil 5% Cream</td>
</tr>
<tr>
<td>Efudex 5% Solution</td>
<td>Fluorouracil 5% Solution</td>
<td></td>
</tr>
<tr>
<td>Efudex 2% solution</td>
<td>Fluorouracil 2% solution</td>
<td></td>
</tr>
<tr>
<td>Fluoroplex 1% cream</td>
<td>Fluorouracil 2% or 5% cream</td>
<td></td>
</tr>
<tr>
<td>Fluoroplex 1% solution</td>
<td>Fluorouracil 2% or 5% solution</td>
<td></td>
</tr>
<tr>
<td>Carac 0.5% cream</td>
<td>Fluorouracil 2% or 5% cream</td>
<td></td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Solaraze 3% gel</td>
<td>Voltaren 1% gel, Diclofenac 1% gel</td>
</tr>
</tbody>
</table>

Table 5. New Developments

Letter regarding update to the hepatic section of PI of oral diclofenac.

Voltaren 1% gel dosing is twoicall 2g-4g per affected area, 4 times a day (up to 16g per day) with no set length of time.

Solaraze 3% gel is 0.5g per treatment area BID, which is approx 1g per day for up to 90 days.


Dr. Bhatia has affiliations with Coria, Galderma, Graceway, Intendis, Ortho, Ortho-N eutrogena, PharmaDerm, Promius, Quinnova, and Stiefel/GSK.


