# What Is the Role of Field-Directed Therapy in the Treatment of Actinic Keratosis? Part 2: Commonly Used Field-Directed and Lesion-Directed Therapies

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*Actinic keratosis (AK) constitutes the initial epidermal lesion in a disease continuum that may potentially progress to invasive squamous cell carcinoma (SCC). A number of treatment options are available to clear lesions and thus reduce the risk for progression to SCC. Field-directed therapies are primarily used to clear multiple AKs and subclinical lesions. Part 1 of this review explaining the role of field-directed therapy for the treatment of AK discussed the unmet needs with current therapies and the investigational agents that are being developed to fill treatment gaps. Part 2 will mainly focus on field-directed therapies that currently are available for AK, such as resurfacing procedures, patient-administered topical therapy, and photodynamic therapy (PDT), as well as lesion-directed therapy, which is used to clear discrete lesions in relatively small numbers.*

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Proper diagnosis and treatment of actinic keratosis (AK) is essential because the lesions can potentially progress to invasive squamous cell carcinoma (SCC). Because there is no way to clinically determine which lesions will transform and invade the dermis and metastasize, most dermatologists treat all AK lesions. In addition, new AK lesions can arise de novo or develop from subclinical lesions. Although individual lesions may be treated effectively with cryotherapy and other lesion-directed approaches, these treatments are impractical for multiple lesions. Field-directed therapy primarily is used for multiple, visible, and palpable AK lesions on contiguous areas of skin; for subclinical lesions; or for an entire sun-damaged area at risk for subclinical lesions. The various approaches to field-directed therapy offer different benefits and disadvantages based on efficacy and tolerability, treatment duration, practical use, patient downtime, and discomfort, which may affect treatment adherence and thus the end result. A number of investigational topical agents will be evaluated as field-directed therapy for AK. One such agent, ingenol mebutate gel, has a short treatment period and was recently approved for the treatment of AK in the United States.

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We will address current field-directed therapies including resurfacing procedures, patient-administered topical therapy, and photodynamic therapy (PDT), as well as lesion-directed therapy for AK. Levels of evidence for treatment recommendations also are provided (Table).[1,2]

## Resurfacing Procedures

*Nonablative and Ablative Laser Resurfacing*—The $CO_2$ laser induces thermal injury to the skin with consequent subepidermal blister formation followed by the promotion of collagen synthesis and deposition in the dermis, thereby eliminating the lesions and leaving the skin with a smooth texture.[3] However, the erbium:YAG laser induces less thermal injury, which owes to its higher selectivity for cellular water and produces better cosmetic results with a similar cure rate.[4] The complete response rates associated with these lasers have been as high as 90% and the long-term recurrence rates after follow-up periods up to 42 months have ranged from 14% to 50%.[5-8] The common adverse events associated with nonablative and ablative laser resurfacing include hypopigmentation and hyperpigmentation, scarring, infections, and acne. The other disadvantages associated with these modalities, though less common with the erbium:YAG laser, include prolonged healing time and downtime as well as poor compliance during postoperative care[5-8] (level of evidence: C, III).[1]

*Dermabrasion/Microdermabrasion*—Dermabrasion is used to treat relatively large areas of photodamaged skin, such as the face, and as a second-line treatment of areas containing thick (ie, hypertrophic) lesions. This technique involves the application of a high-frequency rotating diamond fraise or a stainless steel wire brush to the skin. Several skin layers are affected depending on the duration of the application, number of passes, and other factors. The contraindications to dermabrasion include a personal and family history of abnormal scarring; prior use of isotretinoin (within 12 months of the initial examination); and a history of hepatitis, human immunodeficiency virus infection, or impetigo. Both before and after the procedure, patients must undergo prophylaxis for herpes virus infection, and some patients also may require preoperative sedation and anxiolytic therapy, regional nerve block, or cryoanesthesia. Although reepithelialization is expected to occur 7 to 10 days following dermabrasion, the erythema may persist for as long as 3 months. The adverse events associated

### Explanation of Levels of Evidence

| Evidence Level | Definition |
|---|---|
| **British Association of Dermatologists Therapy Guidelines and Audit Subcommittee**[1] | |
| Strength of recommendation | |
| A | There is good evidence to support the use of the procedure |
| B | There is fair evidence to support the use of the procedure |
| C | There is poor evidence to support the use of the procedure |
| Quality of evidence | |
| I | Evidence obtained from at least 1 properly designed RCT |
| III | Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees |
| **Guideline Subcommittee of the European Dermatology Forum**[2] | |
| Level of evidence | |
| 2b | Individual cohort study (including low-quality RCT; eg, <80% follow-up) |
| 3b | Individual case-control study |

Abbreviation: RCT, randomized controlled trial.

with this procedure include permanent hypopigmentation, occurring in as many as 20% of patients; reversible hyperpigmentation; and scarring.[9-11]

Microdermabrasion is a more conservative treatment of photoaging and AK that produces abrasion through the application of a stream of fine crystals (eg, aluminum oxide crystals) via a compressed air delivery system. After delivery of the crystals, both the particles and the cellular debris that are loosened are removed to a separate container for disposal via a vacuum suction system. Microdermabrasion can be used safely on all skin phototypes. Compared to standard dermabrasion, microdermabrasion involves a simpler technique that is associated with a lower risk for adverse events, faster recovery time, and less downtime. The usual treatment causes partial ablation of the stratum corneum, though more aggressive treatments involving more passes or a slow ablation rate can affect the papillary dermis. The common vacuum-dependent adverse events include petechiae, purpura, and skin wounding, which usually resolve in 1 to 3 days. The preprocedural assessments, contraindications, and prophylactic measures are similar to dermabrasion. In addition, the eyes must be protected and contact lenses must be removed before the procedure is started. Reports of a potential association with pulmonary complications such as fibrosis and interstitial pneumonia due to inhalation of aluminum oxide crystals have not been confirmed[12,13] (level of evidence: C, III).[1]

*Deep and Medium-Depth Chemical Peels*—Chemical peels cause ablation of the skin through topically applied caustic agents, which lead to necrosis of different skin layers depending on the strength and concentration of the agent, the duration of the application, and the thickness of the skin. The efficacy rate of chemical peels is 75% and the recurrence rate is as high as 35%.[2] The most common agent used is trichloroacetic acid; in a 35% concentration, trichloroacetic acid can reach the papillary dermis (medium depth), and at 50% or more, it can reach the reticular dermis (deep peel) where it leads to the production of new collagen, increasing the risk for scar formation.[14,15] The phenol peel is a deep peel that damages endothelial cells and keratinocytes, leading to ischemia and further necrosis of the epidermis.[16-19] As many as 85% (39/46) of patients with AK or Bowen disease on the face and scalp demonstrated a complete response to the phenol peel, and the associated recurrence rate was low after 1-year follow-up.[20] Phenol can be systemically absorbed, leading to cardiac, hepatic, and renal toxic effects, and to respiratory depression, depending on the duration and extent of the application.[21] The common associated adverse events include postprocedural infection and pigmentary alterations, particularly in patients with Fitzpatrick skin types III or IV (level of evidence: C, III).[1]

## Patient-Administered Topical Therapy

*5-Fluorouracil*—5-Fluorouracil (5-FU) is an antimetabolite that inhibits DNA synthesis. It is available as a cream or solution in a 5% concentration, solution in a 2% concentration, cream or solution in a 1% concentration, or as a micronized cream in a 0.5% concentration. The 2007 British Association of Dermatologists Therapy Guidelines and Audit Subcommittee concluded that 5-FU cream used twice daily for 6 weeks is effective for up to 12 months in the clearance of most lesions (level of evidence: A, I) (Table)[1]; however, a recurrence rate of 55% has been reported.[2] The prolonged course of therapy required with 5-FU and its irritation profile may lead to less than optimal compliance, which can adversely affect lesion clearance. Less aggressive regimens, such as pulse therapy, designed to reduce the erosions and discomfort of 5-FU applications, may be effective but have not been fully evaluated (level of evidence: B, III, and 3b)(Table).[1,2] To reduce inflammation until complete healing occurs, the application of 5-FU can be used after 15 minutes with a low-potency corticosteroid cream.[22]

*Imiquimod*—Imiquimod is an imidazoquinolinamine nonspecific immunomodulatory agent, specifically a toll-like receptor agonist, that stimulates local immunity.[23] In a study by Torres et al[23] of patients with AK lesions on the scalp, imiquimod cream 5% applied 3 times a week for 4 weeks modulated the expression of a large number of genes involved in innate and adaptive immune responses and genes associated with activation of macrophages, dendritic cells, cytotoxic T cells, and natural killer cells. The authors concluded that "topical application of imiquimod stimulates cells . . . that lead to . . . subsequent apoptotic and immune cell-mediated destruction of lesions."[23] Therefore, immunosurveillance following treatment with imiquimod ("immune memory") may minimize the recurrence of AK lesions.[22] The safety and efficacy of imiquimod have not been evaluated in immunocompromised patients.[24]

Imiquimod is available as a cream in the following concentrations: 3.75% and 5%. The 2007 British Association of Dermatologists Therapy Guidelines and Audit Subcommittee concluded that imiquimod cream 5% is effective over a 16-week course of treatment (level of evidence: B, I)(Table).[1] The 2006 Guideline Subcommittee of the European Dermatology Forum noted that the associated complete remission rate is 84%, and the recurrence rate is 10% within 1 year of treatment and 20% within

2 years (level of evidence: 2b)(Table).[1,2] However, in 3 vehicle-controlled studies involving a total of 1214 patients who received imiquimod cream 5% applied to AK lesions on the face or balding scalp 3 times a week for 16 weeks[25,26] or 2 times a week for 16 weeks,[27] the complete response rates ranged from 45.1% to 57.1% in the active treatment groups. The prolonged course of therapy required for treatment with imiquimod and its irritation profile may lead to less than optimal compliance, which can adversely affect lesion clearance. A shorter 4-week treatment regimen with an optional second 4-week course in patients with residual AK lesions on the head, excluding the eyelids, nostrils, vermilion border of the lips, and inside the ears, was as effective as the 16-week course of treatment.[28]

The results of studies that compared imiquimod with 5-FU were mixed. Tanghetti and Werschler[29] found that 5-FU cream 5% administered twice daily for 2 to 4 weeks was significantly more effective than imiquimod cream 5% applied twice weekly for 16 weeks to the face or scalp ($P<.05$). Krawtchenko et al[30] observed a significantly higher initial clinical clearance rate with 5-FU ointment 5% administered twice daily for 4 weeks than with 1 or 2 courses of imiquimod cream 5% applied 3 times per week for 4 weeks ($P=.03$); however, the histologic clearance rate and sustained clearance of the total treatment field at 1 year were significantly higher with imiquimod ($P=.03$). In a study by Price,[31] the combination of 5-FU 5% and imiquimod 5% creams administered for 1 week each month during a 3-month period proved to be more rapid and convenient than the administration of each agent separately.

In a split-face, placebo-controlled, double-blind study, 20 patients who had a minimum of 6 symmetrically distributed AK lesions applied imiquimod cream 5% once a week for 6 months on a 20-cm$^2$ area on one side of the face and a matching placebo cream on the other side.[32] Among 15 assessable patients, 46.7% (7/15) demonstrated marked improvement with imiquimod at 6 months compared with 6.7% (1/15) on the placebo side. All patients showed some improvement on the imiquimod-treated side, whereas 6 patients had no improvement and 7 patients had slight worsening on the placebo-treated side. The investigators' assessment score for imiquimod increased 2.20 points on average, whereas the average score for the placebo side decreased 0.27 points ($P=.0002$).[32] The less-frequent application schedule used in this study should be assessed for a longer period and also compared with the currently approved twice weekly dosing regimen.

*Diclofenac*—Diclofenac is available as diclofenac gel 3% in hyaluronate sodium 2.5%. Diclofenac inhibits the synthesis of prostaglandin; elevated levels have been associated with photodamage and AK. However, the exact mechanism of action of diclofenac in AK remains unclear. The 2007 British Association of Dermatologists Therapy Guidelines and Audit Subcommittee noted that diclofenac gel 3% is moderately efficacious in mild AK, but the follow-up data concerning its duration of benefits were insufficient (level of evidence: B, I)(Table).[1] The 2006 Guideline Subcommittee of the European Dermatology Forum stated that several randomized, double-blind, vehicle-controlled studies have shown that diclofenac significantly reduced the number and extent of AK lesions ($P<.001$) when applied twice daily for 60 to 90 days (level of evidence: 2b)(Table).[2] Smith et al[33] conducted a split-face comparison of 5-FU cream 5% and diclofenac gel 3% in the treatment of AK lesions on the face and scalp. Each treatment effectively cleared the lesions, but inflammation was milder and patient satisfaction was greater with diclofenac gel 3% despite the longer treatment period of 90 days for diclofenac gel 3% versus 28 days for 5-FU cream 5%.[33] The prolonged course of therapy required with diclofenac gel 3% may lead to less than optimal compliance, which can adversely affect lesion clearance.

*Photodynamic Therapy*—Photodynamic therapy may be particularly effective in the treatment of AK.[1] Treatment begins with the topical application of 5-aminolevulinic acid (ALA) or methylaminolevulinic acid (MAL), which are both photosensitizing agents. After topical application, ALA and MAL are converted to protoporphyrin IX, which generates reactive oxygen species in dysplastic keratinocytes on exposure to light of the proper wavelength: blue light 14 to 18 hours after application of ALA, and red light 3 hours after application of MAL. Reactive oxygen species production destroys the dysplastic keratinocytes that comprise AK lesions. The illumination process can cause pain, which sometimes is severe. Photodynamic therapy primarily is used for nonhyperkeratotic (eg, minimally to moderately thick) lesions on the face and scalp and may be particularly helpful in cases of multiple or confluent AK lesions or those demonstrating a poor response to standard therapies (level of evidence: B, I)(Table).[1] Photodynamic therapy usually is well tolerated, typically produces excellent cosmetic results, and possibly clears more than 90% of lesions.[1]

*Daylight PDT*—Activation of protoporphyrin IX by daylight, rather than red light after application of MAL, could allow for at-home treatment of AK lesions. Wiegell et al[34] compared the effects of MAL-PDT illuminated by light from a red light–emitting diode following a 3-hour incubation period

with that of MAL-PDT illuminated by daylight for 2.5 hours following a half-hour incubation period for the treatment of AK lesions on the face and scalp. Continuous activation of protoporphyrin IX with daylight PDT proved as effective as conventional MAL-PDT and was associated with similar post-treatment erythema and crusting but significantly less pain during the illumination period ($P<.0001$). The authors concluded that daylight PDT could provide a more rapid, cost-effective, and convenient treatment of AK.[34]

## Lesion-Directed Therapy

Lesion-directed therapy primarily is reserved for single AK lesions that must be completely cleared, are clinically suspicious or likely to progress to SCC, or must be examined via biopsy (eg, curettage or surgical excision only).

Lesion-directed approaches include cryotherapy, surgical excision (full-thickness or shave excision), electrodesiccation, and curettage. The most common choice is cryotherapy with liquid nitrogen applied directly to individual lesions with a cotton-tipped applicator or spray.[35] Although it sometimes is painful and can cause scarring, cryotherapy provides rapid inexpensive results and readily is reimbursed as an in-office procedure. However, clinical response rates widely vary among cryotherapy trials.[30,36-40] One study of AK treatment with cryotherapy involved biopsy control and found that the histologic clearance rate of 32% (8/25) was considerably lower than the initial clinical clearance rate of 68% (17/25).[30] The authors also found that the histologic clearance rate was higher with topical therapy for AK lesions on the head, neck, or décolletage. After 1 year, only 4% (1/25) of patients who underwent cryotherapy sustained clinical clearance of the total treatment field and demonstrated excellent cosmetic results. Interestingly, 72% (18/25) had a recurrence of the treated lesion at 1-year follow-up after a prolonged 20- to 40-second application of liquid nitrogen.[30] These low-efficacy rates do not support the widespread use of cryotherapy as a mainstay therapy. The duration of application of liquid nitrogen can be highly variable, which leads to differing study results. For example, in a study by Thai et al[39] that evaluated 421 AK lesions in 90 patients, when the freezing time exceeded 20 seconds, the clinical response rate was 83%, but when the freezing time was 5 seconds or less, the rate was 39%.

Biopsy or surgical excision should be performed when a lesion appears suspicious or malignant because distinguishing an AK lesion from SCC may be difficult without histopathologic examination.[41] Full-thickness surgical excision rarely is used as a first-line treatment of AK lesions,[42-46] and it is only performed after invasive SCC has been histopathologically documented with a partial-thickness tangential shave biopsy, shave excision, or full-thickness punch biopsy.[1,2,44] Shave excision for AK lesions often is performed by dermatologists, whereas full-thickness excision commonly is used by plastic surgeons,[45] general surgeons, and general practitioners.[42] This difference may be attributed to variations in the clinical recognition of AK, the anticipation of the best clinical outcome with either procedure, and systematic differences and expectations in the types of patients consulting each specialty, though financial and reimbursement factors also should be considered.[46,47] In addition, full-thickness surgical excision is associated with greater morbidity than shave excision. Individual lesions also can be treated with "spot therapy" involving modalities also used for field-directed therapy including PDT, laser resurfacing therapy, and topical agents.

## Combined Lesion-Directed and Field-Directed Therapy

In patients with many AK lesions, field-directed therapy can be used together with lesion-directed ablation because field therapy is the only modality capable of clearing multiple foci and subclinical lesions on sun-damaged areas.[22] For example, topical therapy for multiple or subclinical lesions can be combined with cryotherapy or curettage for hyperkeratotic lesions that may not adequately respond to field-directed therapy.[48] The potential benefits include better overall clearance with limited local skin responses and better cosmetic results.

Tan et al[49] found that imiquimod therapy administered to the face or scalp after cryotherapy increased the clearance of subclinical and total AK lesions more than vehicle alone after a 3-month follow-up, though the difference between imiquimod and vehicle was not statistically significant. Clearance of subclinical AK lesions occurred in 58% (18/31) of patients given imiquimod versus 34% (11/32) of patients given vehicle ($P=.06$), and complete clearance occurred in 23% (7/31) and 9% (3/32), respectively ($P=.21$).[49] Jorizzo et al[50] found that 5-FU administered prior to cryotherapy for residual AK lesions on the face was associated with a significantly lower mean lesion count than vehicle alone at 6-month follow-up (67% vs 45.6%, respectively; $P=.01$) and with a higher complete clearance rate (30% vs 7.7%; $P<.001$).

## Pharmacoeconomic Issues

Few studies have focused on the relationship between the cost and effectiveness of AK treatments.[51] A meta-analysis by Gupta[52] showed that the treatment

of 6 or more AK lesions was more cost-effective with 5-FU cream 0.5% than with the 1% and 5% concentrations. Muston et al[53] found that the cost-effectiveness of MAL-PDT was comparable to 5-FU and imiquimod. Caekelbergh et al[54] used a medical decision tree to simulate all possible outcomes leading to a medical decision. The cost-effectiveness ratio was calculated according to the total cost per year and the effects expressed as the percentage of patients obtaining a clinical response and an excellent cosmetic result after 1 year.[54] The AK data were extracted from a large, multicenter, phase 3, randomized, controlled clinical trial that compared MAL-PDT with cryotherapy and placebo on face or scalp lesions[36]; MAL-PDT was more expensive than cryotherapy, but the cost per full responder over 1 year was comparable with that of cryotherapy. Wilson[55] also used a decision tree model to compare MAL-PDT with imiquimod and found that imiquimod was a more cost-effective treatment of AK.

Gold[56] performed a pharmacoeconomic analysis of imiquimod, diclofenac, 5-FU, and ALA-PDT in combination with cryotherapy in the treatment of AK. The analysis assumed standard costs of procedures and office visits based on April 2007 Medicare reimbursement data and 2 courses or sessions of each treatment followed by cryotherapy until 100% clearance was demonstrated. The total cost of each combination was $725.17 for ALA-PDT, $845.07 for diclofenac, $942.13 for 5-FU, and $1473.39 for imiquimod. Imiquimod is more expensive because the application period is longer and also because the cost per dosage unit is higher.[56]

## Conclusion

The treatment of AK is important because the lesions can potentially progress to invasive SCC, which can recur and metastasize. Dermatologists have access to a wide range of effective options for treating AK. Lesion-directed therapies focus on discrete lesions in relatively small numbers, particularly lesions with clinical features that indicate an increased risk for progression to SCC. Field-directed therapies are mainly used for multiple and subclinical lesions, particularly in sun-damaged skin. Topical therapy applied to a field of AK lesions can treat both clinically nonvisible lesions and clinically distinct lesions. Combined lesion-directed and field-directed approaches may offer greater efficacy with few local adverse events than either approach alone, but additional research is necessary to confirm this conclusion and to determine the optimal combinations and regimens. Field-directed therapy is still associated with a number of unmet needs. In particular, topically applied approaches to field-directed therapy can be improved by shortening the duration of treatment, decreasing the severity and duration of local skin responses, improving tolerability, enhancing compliance, increasing patient satisfaction, reducing the risk for recurrence, and lowering associated costs. Investigational agents may address some of these unmet needs.

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