Therapies for Actinic Keratosis With a Focus on Cosmetic Outcomes

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PRACTICE **POINTS**

- In addition to their risk for progression to malignancy, actinic keratoses (AKs) can have negative impacts on cosmetic appearance and quality of life.
- A variety of topical medications, procedural modalities, and light-based therapies are available for treatment of AKs, which offer varying degrees of efficacy for clearance of lesions and cosmetic outcomes. Based on the current data, imiquimod and photodynamic therapy are the treatments most likely to provide an excellent cosmetic outcome.

Actinic keratosis (AK) is a commonly encountered premalignant epidermal lesion that has a predilection to manifest on highly visible areas such as the face, head, and hands. Lesions may be cosmetically unappealing and have been reported to reduce patients' quality of life (QOL), but appropriate treatment can resolve these issues. In this article, we review the efficacy of the most commonly utilized treatments for AKs including topical medications, procedural modalities, and light-based therapies, and we discuss the relevant cosmetic considerations and outcomes.

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Actinic keratosis (AK), also referred to as solar keratosis or senile keratosis, is an intraepidermal proliferation of dysplastic keratinocytes that develops in response to chronic exposure to UV radiation. Actinic keratoses are among the most commonly encountered lesions seen by dermatologists, and it has been estimated that 60% of predisposed individuals older than 40 years have at least one AK.[1,2] Prevalence is notably higher in light-skinned individuals and increases with age, presumably from higher cumulative sun exposure and decreased effectiveness of the immune system.[1,3] It remains a point of contention as to whether or not AKs actually represent squamous cell carcinoma (SCC) in situ, but the potential for progression to invasive disease has been well demonstrated, as the majority of SCCs develop from preexisting AKs.[4-6] The risk for progression to invasive disease for an individual AK has been estimated to range from 0.025% to 16% per year, with an average of approximately 8% in immunocompetent patients.[7]

The clinical morphology of AK can vary widely, but the most common presentation is an erythematous scaly macule, papule, or plaque on sun-exposed skin. The skin surrounding AKs typically shows evidence of solar damage with deep wrinkling, mottled pigmentation, scattered telangiectases, purpura, or xerosis (Figure). A variety of clinical variants with unique presentations exist, including atrophic, hypertrophic, acantholytic, lichenoid, bowenoid, and pigmented subtypes. Because more than 80% of AKs occur on highly visible areas such as the head, neck, back of the hands, and forearms, AKs can have an obvious detrimental effect on cosmetic appearance. Studies also have shown a strong

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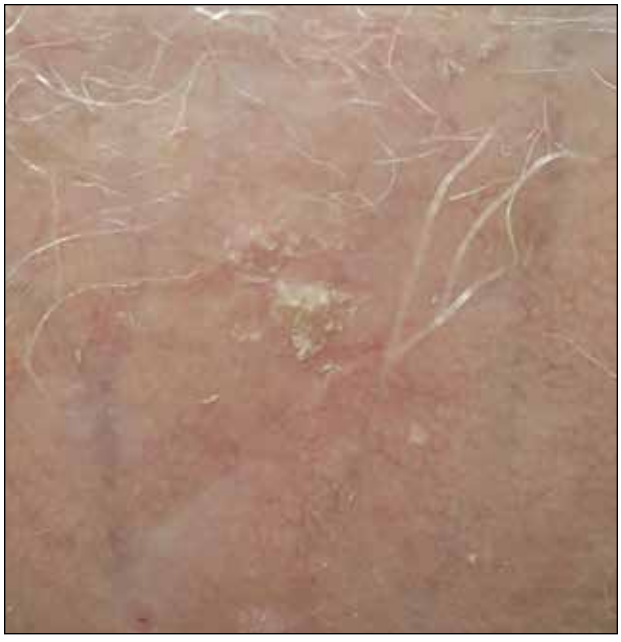

Patient with numerous actinic keratoses, scattered plaques suspicious for squamous cell carcinoma, and numerous scars from prior squamous cell carcinoma treatments.

association between AKs and decreased overall quality of life (QOL).[3,8,9]

Because of the risk for AK progression to invasive cancer along with its negative impact on cosmesis and QOL, clinicians generally opt to treat AKs. Numerous different treatment options exist, including topical medications, procedural modalities, and light-based therapies. Here, we review the efficacy of the most commonly utilized treatments and discuss the relevant cosmetic considerations and outcomes.

Topical Treatments

5-Fluorouracil—5-Fluorouracil (5-FU) is a US Food and Drug Administration (FDA)–approved, topically applied pyrimidine analogue that inhibits thymidylate synthase. The resulting suppression of DNA and RNA synthesis induces cell death with a preference for mitotically active cells.[10] 5-Fluorouracil has been used for more than 50 years as a treatment of AK and its efficacy is well established. A systematic review of 5 randomized controlled studies of topical 5-FU reported an average of 49% of 423 patients achieving complete lesion clearance with 5-FU cream 5% applied once or twice daily for up to 7 weeks.[11] Some notable drawbacks of 5-FU, however, are application-site erythema, blistering, pruritus, necrosis, erosion, and pain. These effects often lead to premature cessation of therapy, but newer formulations of 5-FU cream 0.5% have shown good efficacy with better tolerability.[12] A randomized, double-blind, multicenter, parallel-group study of 177 patients using 5-FU cream 0.5% once daily for either 1, 2, or 4 weeks demonstrated significant ($P<.001$) efficacy over vehicle gel in all treatment arms.[13] The most effective therapy was 4 weeks of treatment, which achieved a mean 91.7% reduction in lesion count as assessed 1 month after cessation of therapy. The primary adverse effect (AE) reported in this trial was mild to moderate facial irritation, which generally resolved within 18 to 21 days after treatment cessation.[13] Overall, 5-FU is a highly effective therapy for treating AKs that also can improve signs of photoaging, but patients should be aware of cosmetically unappealing effects that generally occur throughout therapy and during the immediate posttreatment period.[14]

Chemical Peels—Chemical peels traditionally employ acidic compounds to strip away outer layers of skin to variable depths depending on the concentration of the agent being applied. For treatment of AK, trichloroacetic acid (TCA) is a commonly employed cauterant that has shown efficacy comparable to topical 5-FU as well as ablative CO_2 laser resurfacing.[15] Trichloroacetic acid peels also are a convenient therapy, as good results can be achieved after a single treatment session. A split-face study of 15 patients treated with either a single application of 35% TCA and Jessner solution or twice-daily application of 5-FU cream 5% for 3 weeks demonstrated a reduction in 75% of visible AKs in both treatment arms over a 1-year follow-up period.[16] Although 80% of patients self-reported considerable cosmetic improvement with both therapies, patient preference was reported to be in favor of the TCA peel, given its quick results and relatively mild side effects as compared to 5-FU. Treatment with chemical peels will result in temporary erythema and mild desquamation that usually resolves within 2 weeks; however, there are cases in which erythema has been reported to persist for several months.[16] Adverse effects such as permanent scarring or pigmentation changes rarely are seen with TCA concentrations less than 45%.[17] Caution should be used in patients with a history of herpes simplex virus, keloids, postinflammatory hyperpigmentation, radiation exposure, immunosuppression, and those unable or unwilling to use sunscreen and avoid sun exposure in the immediate posttreatment period.

Diclofenac Sodium—Diclofenac sodium (DFS) is an FDA-approved topical, nonsteroidal, anti-inflammatory drug whose mechanism of action in the treatment of AK is thought to involve inhibition of the cyclooxygenase 2 enzyme.[18] The resulting

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reduction of prostaglandins is believed to inhibit tumor angiogenesis, induce apoptosis, and inhibit cell differentiation.[19-22] In a multicenter, double-blind, placebo-controlled study of 195 patients, application of DFS 3% in hyaluronan gel 2.5% twice daily for 60 days showed significant ($P<.05$) efficacy over placebo in achieving complete resolution of target lesions during a 30-day follow-up period (31% vs 10%). Furthermore, qualitative patient assessment of complete global improvement also was significantly ($P<.05$) higher in the active treatment group as compared to placebo (31% vs 10%).[23] Additional studies of DFS 3% in hyaluronan gel 2.5% applied twice daily for 90 days have shown even higher rates of success, with complete resolution of target lesions in 40% to 58% of cases.[24,25] This therapy also has been reported to substantially improve QOL following treatment completion.[26] The most frequently cited AEs include pruritus, rash, dry skin, erythema, and application-site reactions. Overall, DFS is a well-tolerated therapy with efficacy comparable to that of 5-FU but with a lower incidence of AEs and higher patient satisfaction as determined in 2 head-to-head studies.[27,28]

Imiquimod—Imiquimod (IMQ) is an FDA-approved topical agent that functions as an immune response modifier via agonism of toll-like receptor 7.[18] The resulting cytokine production and release enhances the innate and acquired immune responses leading to anticancer activity.[29] The efficacy of IMQ for treatment of AK has been demonstrated in numerous well-designed clinical trials. A meta-analysis of 5 randomized, double-blind trials including 1293 patients treated with IMQ cream 5% 2 to 3 times per week for 12 to 16 weeks reported complete clearance of AKs in 50% of patients treated with IMQ as compared to 5% of patients treated with vehicle.[30] The most frequently reported AEs with this therapy include erythema, scabbing, flaking, and erosion. These effects generally resolve following cessation of treatment, and therapy is considered to be well tolerated; however, there are case reports of IMQ triggering or exacerbating existing inflammatory conditions.[31] Imiquimod cream also is approved at 2.5% and 3.75% concentrations, which have demonstrated significant ($P<.001$) efficacy over placebo and a reduced incidence of AEs; complete clearance rates have been reported as 30.6% and 35.6%, respectively.[32] Notably, a study comparing 75 patients randomized to either IMQ cream 5% 3 times per week for 4 weeks, 1 or 2 courses of cryosurgery, or 5-FU ointment 5% twice daily for 4 weeks reported that IMQ achieved significantly ($P<.01$) superior sustained clearance rates during a 12-month follow-up period over cryosurgery and 5-FU (73% vs 4% vs 33%).[33] Additionally, cosmetic outcomes as determined by both participants and investigators were reported as excellent at 12 months posttreatment in more than 80% of participants treated with IMQ. These excellent, long-lasting cosmetic outcomes also were determined to be significantly ($P<.0001$) superior to the cosmetic outcomes of 5-FU and cryotherapy, which both reported excellent outcomes in less than 10% of cases.[33]

Ingenol Mebutate—Ingenol mebutate (IM) is a macrocyclic diterpene ester derived from the *Euphorbia peplus* plant that is FDA approved for the treatment of AK.[1] Ingenol mebutate's mechanism of action is thought to involve induction of cell death via disruption of the plasma membrane and mitochondria in addition to production of an inflammatory response, which produces tumor-specific antibodies and a large influx of neutrophils.[34,35] The overall evidence for the efficacy of IM is strong. A combined analysis of 4 multicenter, randomized, double-blind studies of 1005 participants reported that IM gel 0.015% applied once daily for 3 days to the face or scalp was significantly superior ($P<.001$) to placebo in achieving complete clearance as assessed 54 days after completion of therapy (42.2% vs 3.7%) and that IM gel 0.05% applied once daily for 2 days to the trunk or extremities also was significantly superior ($P<.001$) to placebo in achieving complete clearance as determined 55 days after completion of therapy (34.1% vs 4.7%).[36] A follow-up report to this study indicated that IM also appears to achieve long-lasting effects with an overall 87% decrease in total AKs at 12 months follow-up in both trial groups.[37] Additionally, it has been recently reported that treatment with IM in these trials was associated with significantly higher overall treatment satisfaction ($P<.001$) and improved QOL ($P<.001$) as compared to vehicle.[38] Cosmetic outcomes of IM therapy have been assessed in a trial analyzing the efficacy of IM gel 0.025% for 3 days or IM gel 0.05% for 2 or 3 days on nonfacial AKs. This study reported significantly ($P<.0001$) higher patient satisfaction with the cosmetic outcome at 8 weeks after therapy as compared to vehicle.[34] Studies performed in mice have demonstrated that IM is able to promote collagen matrix turnover and impose dermal elasticity, which may contribute to these good cosmetic outcomes.[39] The most common AEs of IM therapy are erythema, crusting, and flaking; these effects generally occur 3 to 8 days after starting treatment. These effects, however, generally are short lived and resolve within 2 weeks of treatment cessation when IM is applied to the face or scalp or 4 weeks when applied to the trunk or extremities.[40] Overall, IM is a useful therapeutic option given its relatively short

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treatment course as compared to other topically applied agents, as well as its lasting efficacy, mild AEs, and good cosmetic outcomes.

Procedural Modalities

Surgical Procedures—Surgical approaches for the treatment of AK include excision, curettage with or without electrodesiccation, and dermabrasion. In the past, these modalities were used with greater frequency, but the advent of effective topical medications with lower risks of AEs has largely reduced their use.[41] Excision may still be indicated in cases where SCC is suspected, and curettage can be used for treatment of thicker hypertrophic AKs.[42] Although these approaches have not been evaluated in clinical trials, they are generally effective but require the use of local anesthetics and come with substantial risk for infection, permanent scarring, and hypopigmentation. Dermabrasion employs the use of a motorized device equipped with an abrasive material to physically remove superficial layers of the skin. Studies are limited, but this method has been reported as an effective treatment in a retrospective review of 23 participants in which 96% remained free of AKs at 1 year, 83% at 2 years, 64% at 4 years, and 54% at 5 years posttherapy.[43] Notably, one split-face study of 40 participants treated with dermabrasion followed by 25% TCA on one side and either Jessner solution and 35% TCA or dermabrasion alone on the other side reported that the combination of dermabrasion with 25% TCA consistently produced excellent cosmetic results with nearly complete eradication of AKs.[44] In general, however, cosmetic outcomes with dermabrasion are variable, as the technique is highly operator dependent and treatment is associated with notable discomfort as well as risk for scarring and permanent pigmentation alteration.

Cryotherapy—Cryotherapy remains one of the most commonly utilized treatments of AK and involves the delivery of liquid nitrogen via a spray device or a cotton tip applicator to rapidly freeze cells, thus causing cellular destruction via ice crystal formation and protein denaturation.[45] Efficacy with this technique has been reported to be as high as 98.8% at 12 months follow-up, but more recent studies cite lower rates of success.[46] A prospective multicenter study of 90 participants with 421 AKs on the face or scalp treated with a single freeze-thaw cycle of liquid nitrogen reported an overall complete response rate of 67.2% at 3 months posttherapy. Additionally, higher complete response rates were associated with longer freeze times, and cosmetic outcomes were reported as good to excellent in 94% of complete response lesions.[47] Similar results were reported in an open-label, prospective, randomized, controlled clinical trial of 200 participants with 543 AKs, which compared a single freeze-thaw cycle with liquid nitrogen to a single session of CO_2 laser ablation in the treatment of isolated AKs of the face and scalp.[48] At 3 months posttherapy, complete clearance was observed in 71.6% of participants treated with cryotherapy and in 65.3% of participants treated with laser ablation ($P=.532$). At 12 months posttherapy, participants who originally showed complete response at 3 months were assessed for relapse. Complete clearance was preserved in 72.6% of participants treated with cryotherapy versus 21.9% of participants treated with laser ablation ($P<.0001$), and cosmetic outcomes were reported by participants as good or excellent at 3 months follow-up in more than 93% of participants for both treatment arms.[48] Possible AEs of cryotherapy include pain during treatment, blister formation with possible hemorrhage, infection, scarring, and permanent pigmentary changes.[47,48] Notably, the risk for hypopigmentation increases with longer freezing times, thus requiring clinicians to consider the balance between improved efficacy and reduced cosmetic outcomes.[47]

Light-Based Therapies

Laser Therapy—Ablative laser resurfacing with either the CO_2 or erbium-doped:YAG (Er:YAG) laser utilizes light of specific wavelengths to selectively induce thermolysis and destruction of the epidermal layer. Both lasers have been studied as treatments of AK, but there is a lack of large, well-designed studies. In one small study of 14 participants treated with 1 to 2 passes of the CO_2 laser, complete clearance was reported in all cases without any recurrences during a follow-up period of 6 to 24 months. Additionally, all participants in this study reported satisfaction with the cosmetic outcome.[49] The CO_2 laser also has demonstrated efficacy comparable to that of the TCA peel and 5-FU therapy in a prospective randomized trial of 34 patients with facial or scalp AKs who received either CO_2 laser with 2 passes, 30% TCA peel, or 5-FU cream 5% twice daily for 3 weeks.[15] Reduction in mean AK counts at 3 months posttherapy was significantly ($P<.03$) higher in all treatment arms as compared to the control group (92% for CO_2 laser, 89% for TCA peel, and 83% for 5-FU cream). No significant ($P=.31$) difference in outcomes was noted among the different treatment arms.[15] Similar results were reported for the Er:YAG laser in a small prospective study of 5 participants treated with 2 to 3 passes with the Er:YAG laser in which reduction in mean AK counts was reported as ranging from 86% to 96% at 3 months posttherapy.[50] The Er:YAG laser in combination with the

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CO_2 laser has shown notable long-term efficacy in achieving higher lesion clearance rates and sustained complete clearance rates over treatment with topical 5-FU.[51] In a prospective randomized study of 55 participants with multiple AKs on the face or scalp, participants were assigned to receive either combination laser ablation with the Er:YAG and CO_2 lasers down to the level of the papillary dermis or 5-FU cream 5% applied twice daily for 2 to 7 weeks until an appropriate clinical inflammatory response was achieved. At 12 months follow-up, the laser treatment group achieved significantly (P=.048) higher mean lesion clearance rates (91.1%) as compared to the 5-FU arm (76.6%) and significantly (P=.003) higher sustained complete clearance rates (59.3%) as compared to 5-FU (29.2%). The proportion of participants with an improvement in photoaging score at 12 months follow-up approached statistical significance (P=.07), with 74% of the laser-treated group showing improvement as compared to 43% of the 5-FU–treated group. Long-term, cosmetically unappealing side effects such as erythema and hypopigmentation occurred notably more often in the laser-treated group as compared to the 5-FU group.[51] In summary, ablative lasers appear to be a highly effective therapy for AK but at the cost of increased risk for AEs such as permanent pigmentary changes, prolonged erythema lasting up to several months, and scarring.[50,52-55]

Fractional photothermolysis is a relatively new advancement in the field of laser therapy that has received FDA approval for the treatment of AK.[56] This treatment works by creating multiple noncontiguous microscopic columns of thermal injury while sparing adjacent zones of viable tissue.[57] Although there are limited studies involving the use of such lasers in the treatment of AK, initial findings suggest that 1927-nm thulium lasers may be more effective than 1550-nm erbium lasers in achieving lesion clearance. A trial of 14 participants who received 5 laser treatments with a 1550-nm fractionated erbium-doped fiber laser reported an average reduction in AK counts of 66.2% at 3 months follow-up and a 55.6% reduction at 6 months follow-up. A participant-determined marked or very significant improvement of lesions was reported in 83% of participants at 1 month posttreatment but only in 44% of participants at 6 months posttreatment.[58] A similar trial of 24 participants treated with up to 4 treatment sessions of the fractionated 1927-nm thulium laser reported an 87.3% reduction in number of AKs at 3 months follow-up and an 86.6% reduction at 6 months follow-up.[56] The primary advantage of fractional laser therapy is a faster recovery period generally lasting only 2 or 3 days as compared to 2 weeks or more with traditional ablative lasers, thus limiting the amount of time a patient must tolerate cosmetically unappealing erythema.[59,60] The quick recovery time has been attributed to the fractional laser's ability to preserve the stratum corneum and skin barrier, which also helps reduce the risk for other AEs such as scarring and infection.[56,59-61] Additional studies are needed to better assess the true efficacy of fractional laser therapy, but treatment with the fractional 1927-nm thulium laser appears to be a promising and well-tolerated therapeutic option for treatment of AK with similar efficacy to traditional ablative lasers but with a lower risk of AEs.

Photodynamic Therapy—Photodynamic therapy (PDT) is an FDA-approved treatment that involves the use of a topical photosensitizing agent such as 5-aminolevulinic acid (ALA) or methyl aminovulinate (MAL) before exposure to an activating light source to generate reactive oxygen species that lead to cell death.[62-65] Multiple PDT regimens with varying combinations of photosensitizers, incubation time, and light sources have been studied, but a 2012 Cochrane review determined that treatment with conventional formulations of MAL and ALA with either blue- or red-light PDT were similarly efficacious for treatment of individual AKs as compared to vehicle with blue- or red-light PDT. One exception was that longer incubation time (ie, 4 hours) with ALA resulted in better results than shorter incubation times (ie, 0.5, 1, 2 hours) with ALA.[66]

Standard PDT treatment with MAL also has consistently demonstrated superior efficacy in achieving complete clearance rates in addition to superior cosmetic outcomes over treatment with either cryotherapy, DFS, or 5-FU.[67-73] Three studies in particular noted an excellent or good investigator-determined cosmetic outcome in 96% to 98% of participants treated with MAL-PDT.[69,71,74] Photodynamic therapy with ALA also has been reported as superior over CO_2 laser ablation for AK reduction as well as both patient and investigator overall satisfaction.[75]

More recently, several methods of improving photosensitizer delivery have been studied, which have demonstrated remarkable efficacy at achieving lesion clearance over standard cream formulations or application routines. One such method involves the use of gentle heating to increase photosensitizer uptake. In a split-extremity study of 20 participants who were treated with 20% ALA under occlusion for 1 hour with one side heated to 38.8°C, the heated side demonstrated significant (P<.0001) efficacy at achieving higher median clearance rates over control when evaluated at 2 and 6 months posttherapy.[76] Notably, occlusion of ALA in itself during the incubation period also has been demonstrated to significantly (P<.0001)

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improve clearance rates.[77] Another method involves the use of a new nanoemulsion-based formulation of ALA gel, known as BF-200 ALA, which has demonstrated remarkable efficacy over standard MAL cream and placebo in a long-term follow-up analysis of 2 prospective, randomized, controlled trials.[78] In a similar vein, 3 prospective randomized trials with a minimum follow-up time of 3 months demonstrated that MAL-PDT in combination with fractional ablative laser pretreatment has significant ($P<.02$ in all trials) efficacy over MAL-PDT without pretreatment in achieving complete AK clearance. Although the cosmetic outcomes were good or excellent in 87% to 100% of patients, they were not significantly different from stand-alone MAL-PDT treatment in any of the trials.[79-81] However, pretreatment with microneedling in MAL-PDT has been shown to achieve superior cosmetic outcomes over MAL-PDT without microneedling, according to one small split-face study of 10 participants.[82]

Overall, PDT is an excellent therapeutic option that is able to provide efficacious clearance of AKs as well as superior cosmetic outcomes. Common AEs of PDT include burning, itching, and stinging during therapy, but pain intensity decreases dramatically upon termination of illumination, with cessation of most symptoms by 12 hours posttherapy.[73] Permanent pigmentation changes have been reported to occasionally occur following PDT therapy.[81]

Conclusion

When determining which therapy to use in a patient, clinicians must take into account a variety of factors such as patient preference, cost of treatment, availability, tolerance for AEs, and the need for field therapy. Although all therapies discussed within this article are effective and reasonable treatment choices, patients who are particularly concerned about cosmetic outcomes would most likely benefit from either IMQ or PDT, as the data for cosmetic outcomes with these therapies are the strongest. Combination or sequential treatments may be required in some cases and all patients should be monitored for lesion recurrence regardless of treatment choice. A summary of the therapies and key studies discussed here is available online in the eTable.

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APPENDIX

Efficacy, Cosmetic Outcomes, and Cosmetic Considerations for Actinic Keratoses Treatments

Reference (Year)	Study Design	Treatment Arm(s)	Reduction in Mean or Median Lesion Count	Complete Clearance	Cosmetic Outcome	Most Common AEs and Cosmetic Considerations
Topical 5-FU						
Askew et al[11] (2009)	Systematic review of 5 studies	5-FU cream 5% 1–2 times daily for 1–7 wk (N=423)	4–52 wk PT: average, 79.5%; range, 59.2%–100%	4–52 wk PT: average, 49.0%; range, 0%–96.0%	N/A	N/A
Jorizzo et al[13] (2002)	RD, DB, VC, PG, MC study	(A) 5-FU cream 0.5% once daily for 1 wk (n=47); (B) 5-FU cream 0.5% once daily for 2 wk (n=46); (C) 5-FU cream 0.5% once daily for 4 wk (n=45); (D) vehicle once daily for 1, 2, or 4 wk (n=69)	4 wk PT: (A) 69.5%, (B) 86.1%, (C) 91.7%, (D) 21.6%	4 wk PT: (A) 14.9%, (B) 37.0%, (C) 57.8%, (D) 0%	4 wk PT: significant ($P<.001$) improvement with active treatment compared to vehicle (PD)	Facial irritation (50%), erythema (42%), and dryness (36.2%); little to no irritation present by 4 wk PT
Chemical Peels						
Lawrence et al[16] (1995)	Split-face study	Split face treatment (N=15): (A) left side, single application of Jessner solution and 35% TCA to mild erythema and faint frost; (B) right side, 5-FU cream 5% twice daily for 3 wk	1 mo PT: (A) 75%, (B) 75%; 6 mo PT: (A) 75%, (B) 86%; 12 mo PT: (A) 70%, (B) 74%	N/A	6 wk PT: 80% of patients self-reported both treatment arms produced considerable cosmetic improvement (PD)	1 participant experienced erythema for 3 mo PT with chemical peel; on average, effects (ie, erythema, mild desquamation) lasted 10 d PT; 60% of patients preferred ease of use of chemical peel over 5-FU
DFS						
Rivers et al[23] (2002)	RD, DB, VC, PG, MC study	(A) DFS 3% for 30 d (n=49); (B) vehicle gel for 30 d (n=49); (C) DFS 3% for 60 d (n=48); (D) vehicle gel for 60 d (n=49)	N/A	30 d PT: (A) 31%, (B) 10%, (C) 14%, (D) 4%	30 d PT: complete improvement in 31% of participants with active treatments vs 10% with placebo (ID); complete improvement in 29% of participants with active treatments vs 10% with placebo	Pruritus (36%), rash (35%), and dry skin (26%)

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Reference (Year)	Study Design	Treatment Arm(s)	Reduction in Mean or Median Lesion Count	Complete Clearance	Cosmetic Outcome	Most Common AEs and Cosmetic Considerations
Wolf et al[24] (2001)	RD, DB, VC study	(A) DFS 3% for 90 d (n=58); (B) vehicle gel for 90 d (n=59)	N/A	30 d PT: (A) 50%, (B) 20%	30 d PT: 47% of participants in active treatment reported complete lesion improvement vs 19% in placebo (ID); 41% of participants in active treatment reported complete lesion improvement vs 17% in placebo (PD)	Pruritus (55%), dry skin (36%), rash (33%), and erythema (26%)
IMQ						
Hadley et al[30] (2006)	Meta-analysis of 5 studies	N=1293: (A) IMQ cream 5% 2–3 times per wk for 12–16 wk; (B) vehicle	N/A	8–14 wk PT: (A) 50.0%, (B) 4.7%	N/A	Erythema (27%), scabbing (21%), flaking (9%), erosion (6%), edema (4%), and weeping (3%)
Swanson et al[32] (2014)	RD, DB, VC, PG, MC study	(A) IMQ cream 3.75% (n=160); (B) IMQ cream 2.5% (n=160); (C) vehicle cream (n=159); all once daily for two 2-wk treatment cycles with a 2-wk no-treatment interval in between cycles	8 wk PT: (A) 81.8%, (B) 71.8%, (C) 25.0%	8 wk PT: (A) 35.6%, (B) 30.6%, (C) 6.3%	8 wk PT: all treatments showed improvement over baseline, with IMQ cream 3.75% treatment arm approximately achieving a much improved photodamage score (ID)	N/A
Krawtchenko et al[33] (2007)	RD, PG study	(A) IMQ cream 5% 3 times per wk for 4 wk (n=26), (B) 1–2 courses of cryosurgery for 20–40 s (n=25), (C) 5-FU ointment 5% twice daily for 4 wk (n=24)	N/A	8 wk PT: (A) 85%; 6 wk PT: (B) 68%; 4 wk PT: (C) 96%; 12 mo PT: (A) 73%, (B) 4%, (C) 33%	12 mo PT: excellent cosmetic outcome (ID and PD) in (A) 81%, (B) 4%, (C) 4%	Mild atrophy, irregular pigmentation, and hypopigmentation

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(continued)

Reference (Year)	Study Design	Treatment Arm(s)	Reduction in Mean or Median Lesion Count	Complete Clearance	Cosmetic Outcome	Most Common AEs and Cosmetic Considerations
IM						
Anderson et al[34] (2009)	RD, DB, VC, PG, SC study	(A) IM gel 0.025% for 3 d (n=50); (B) IM gel 0.05% for 3 d (n=57); (C) vehicle gel for 3 d (n=60); (D) vehicle gel for 1 d followed by IM gel 0.05% for 2 d (n=55)(all once-daily application)	8 wk PT: (A) 75.0%, (B) 100%, (C) 0%, (D) 83.3%	8 wk PT: (A) 40.0%, (B) 54.4%, (C) 11.0%, (D) 43.6%	8 wk PT: significantly ($P<.0001$) higher satisfaction with cosmetic outcomes in active treatment arms compared to vehicle (PD)	Erythema (34%), flaking (29%), pigmentation changes (20%), and crusting (9%); AEs most intense around day 5 PT but generally resolve within 2–4 wk
Lebwohl et al[36] (2012)	RD, DB, VC, PG, MC study	(A) IM gel 0.015% once daily for 3 d on face or scalp (n=277); (B) vehicle gel once daily for 3 d on face or scalp (n=270); (C) IM gel 0.05% once daily for 2 d on trunk or extremities (n=226); (D) vehicle gel once daily for 2 d on trunk or extremities (n=232)	57 d PT: (A) 83%, (B) 0%, (C) 75%, (D) 0%	57 d PT: (A) 42.2%, (B) 3.7%, (C) 34.1%, (D) 4.7%	N/A	Erythema, flaking, scaling, crusting, swelling, vesiculation, and ulceration; most application-site reactions were resolved by 12 d PT; the short duration of treatment resulted in very high (>98%) adherence to the therapy, contributing to the effectiveness of IM
Dermabrasion						
Coleman et al[43] (1996)	Retrospective review	Dermabrasion (N=23)	N/A	1, 2, 3, 4, 5 y PT: 96%, 83%, 79%, 64%, 54%	N/A	N/A
Cooley et al[44] (1997)	Split-face study	(A) dermabrasion to pinpoint bleeding followed by 25% TCA, 1 layer to light frost, on the left side of face (n=2); (B) Jessner solution, 4 layers to light frost, and 35% TCA, 1 layer to light frost, or dermabrasion alone on the right side of face (n=2)	7–90 d PT: nearly complete eradication of histologically assessed AKs in all treatments	N/A	7–90 d PT: combination treatment with TCA and dermabrasion provided excellent cosmetic results and greater cosmetic improvement as compared to Jessner and TCA alone (ID)	Erythema, occasional pigmentary imbalance with all treatments that generally resolved by 30 d PT; combination treatment with TCA and dermabrasion associated with longer healing time, duration of erythema, and occasional pigmentary imbalance

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Reference (Year)	Study Design	Treatment Arm(s)	Reduction in Mean or Median Lesion Count	Complete Clearance	Cosmetic Outcome	Most Common AEs and Cosmetic Considerations
Cryotherapy						
Thai et al[47] (2004)	RD, PG, MC study	Freezing time per lesion: (A) 1–5 s (n=122); (B) 5–10 s (n=67); (C) 10–15 s (n=51); (D) 15–20 s (n=55); (E) >20 s (n=128)	N/A	3 mo PT: (A) 39%, (B) 75%, (C) 80%, (D) 69%, (E) 83%	3 mo PT: excellent or good cosmetic outcome in 94% of all treatment groups (ID and PD)	Stinging, pain, or burning (52%), erythema (16%); edema (10%); all AEs resolved within 1 wk PT; of complete response lesions: hypopigmentation (29%), hyperpigmentation (6%), tissue defect (5%), and scarring (2%); incidence of hypopigmentation increased with freezing time
Zane et al[48] (2014)	RD, PR, PG study	(A) freeze time of 10–20 s until a 1–2 mm perilesional frozen rim (n=102); (B) CO_2 laser, 500-microsecond pulses at 2.3 W with 50 Hz repetition rate, 2–3 passes (n=98)	N/A	3 mo PT: (A) 71.6%, (B) 65.3%	3 mo PT: excellent or good cosmetic outcome (ID) in (A) 86.3%, (B) 92.2%; PD: excellent or good cosmetic outcome in (A) 93.1%, (B) 95.3%	Erythema, edema, serous and hemorrhagic vesicles, and blisters
Laser Therapy						
Hantash et al[15] (2006)	RD, PG study	(A) CO_2 laser, 2 passes, 6 W and 5 W respectively (n=8); (B) 30% TCA to frost (n=10); (C) 5-FU cream 5% twice daily for 3 wk (n=9)	3 mo PT: (A) 92%, (B) 89%, (C) 83%	N/A	N/A	No AEs were noted in any of the treatment arms
Trimas et al[49] (1997)	PR study	CO_2 laser, 16–18 W, 6-mm spot size, 70–150-μm depth, 1–2 passes (N=14)	N/A	6–24 mo PT: 100%	All participants reported satisfaction (PD)	Mild transient hyperpigmentation and erythema; average time for complete resolution of erythema was 7 wk with a range of 4–12 wk
Jiang et al[50] (2000)	PR study	Er:YAG 2940-nm laser, 2.0 J, 5-mm spot size, 2–3 passes (N=5)	3 mo PT: 93%	N/A	3 mo PT: improved facial skin appearance (PD)	Exudation, crusting, and erythema; erythema lasted 3–6 wk PT

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(continued)

Reference (Year)	Study Design	Treatment Arm(s)	Reduction in Mean or Median Lesion Count	Complete Clearance	Cosmetic Outcome	Most Common AEs and Cosmetic Considerations
Ostertag et al[51] (2006)	RD, PG study	(A) 5-FU cream 5% twice daily for 4 wk (n=27), (B) Er:YAG laser, 7–28 J/cm^2, and CO_2, 2–4 W, 10–12 pulses per second (n=28)	6 mo PT: (A) 79.2%, (B) 94.4%; 12 mo PT: (A) 76.6%, (B) 91.1%	N/A	12 mo PT: improved photoaging score (ID) in (A) 43%, (B) 74%	Pain, irritation, erythema, edema, and hypopigmentation; significantly ($P<.05$) more side effects with laser therapy that may last up to 1 year or longer
Weiss et al[56] (2013)	PR study	Up to 4 treatments at 2–6 wk intervals with a fractionated 1927-nm thulium laser, 5–20 mJ (N=24)	1, 3, and 6 mo PT: 91.6%, 87.3%, 86.6%	N/A	1 and 6 mo PT: average of marked to very significant improvement in photodamage (ID and PD)	Erythema and swelling resolved by 3 mo PT
Katz et al[58] (2011)	PR study	5 sessions of 1550-nm fractionated erbium-doped fiber laser, 20–70 mJ, 8–10 passes (N=14)	1, 3, and 6 mo PT: 73.1%, 66.2%, 55.6%	N/A	1 mo PT: marked or very significant clinical improvement of lesions (45% [ID], 83% [PD]); 6 mo PT: marked or very significant clinical improvement of lesions (36% [ID], 44% [PD])	Erythema and edema resolved within 4–7 d PT
PDT						
Freeman et al[69] (2003)	RD, DB, PC, PG study	Scales and crusts were removed with curette prior to treatment; (A) 160 mg/g occluded MAL cream applied for 3 h before illumination with red-light PDT, 570–670 nm, 50–250 mW/cm^2, 10 min, 75 J/cm^2 light dose, therapy was repeated after 7 d (n=88); (B) placebo cream applied for 3 h before illumination with red-light PDT, 570–670 nm, 50–250 mW/cm^2, 10 min, 75 J/cm^2 light dose, therapy was repeated after 7 d (n=23); (C) cryotherapy with a single freeze-thaw cycle (n=89)	N/A	3 mo PT: (A) 91%, (B) 30%, (C) 68%	3 mo PT: excellent cosmetic outcome (ID) in (A) 83%, (B) N/A, (C) 51%; excellent cosmetic outcome (PD), (A) 76%, (B) N/A, (C) 56%	Burning/stinging (81%), erythema (42%), edema (15%), and skin peeling (10%); median duration of AEs was 1 wk

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Reference (Year)	Study Design	Treatment Arm(s)	Reduction in Mean or Median Lesion Count	Complete Clearance	Cosmetic Outcome	Most Common AEs and Cosmetic Considerations
Pariser et al[71] (2003)	RD, DB, PC, MC study	Scales and crusts were removed with curette prior to treatment: (A) 160 mg/g occluded MAL cream applied for at least 3 h before illumination with noncoherent red light, 570–670 nm, 50–200 mW/cm^2, 75 J/cm^2 light dose, therapy repeated after 1 week (n=42); (B) placebo cream applied for at least 3 h before illumination with noncoherent red light, 570–670 nm, 50–200 mW/cm^2, 75 J/cm^2 light dose, therapy repeated after 1 week (n=38)	N/A	3 mo PT: (A) 82%, (B) 21%	3 mo PT: cosmetic outcome excellent or good in 97% of active treatment arm (ID); cosmetic outcome excellent or good in 91% of active treatment arm (PD)	Burning (27%), erythema (22%), crusting (16%), pain (10%), blisters (8%), edema (6%), and stinging (6%); AEs resolved within 9 d of treatment completion
Szeimies et al[74] (2002)	RD, PG study	Scales and crusts were removed with curette prior to treatment: (A) cryotherapy with liquid nitrogen spray, 2 freeze-thaw cycles (n=100); (B) 160 mg/g occluded MAL cream applied for 3 h before illumination with noncoherent red light, 570–670 nm, 70–200 mW/cm^2, 75 J/cm^2 light dose, therapy repeated after 1 wk (n=102)	N/A	3 mo PT: (A) 75.3%, (B) 68.7%	3 mo PT: excellent or good cosmetic outcome (ID) in (A) 80.9%, (B) 96.3%; excellent or good cosmetic outcome (PD) in (A) 91.1%, (B) 98.2%	Burning sensation, skin pain, and crusting

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Reference (Year)	Study Design	Treatment Arm(s)	Reduction in Mean or Median Lesion Count	Complete Clearance	Cosmetic Outcome	Most Common AEs and Cosmetic Considerations
Willey et al[76] (2014)	Split-extremity study	Scales and crusts were removed with curette prior to treatment: (A) 20% occluded 5-ALA applied to upper or lower extremity (randomly assigned), incubated at room temperature (27.7°C–33.4°C) for 1 h before illumination with blue light, 10 J/cm^2, 1000 s, 2–4 in away (n=20); (B) 20% occluded 5-ALA applied to upper or lower extremity (randomly assigned), incubated with a heating pad (36.4°C–40.6°C) for 1 h before illumination with blue light, 10 J/cm^2, 1000 s, 2–4 in away (n=20)	2 mo PT: (A) 70.5%, (B) 88.0%; 6 mo PT: (A) 67.0%, (B) 88.0%	N/A	2 mo PT: significant ($P<.0001$) global improvement on heated side vs control (PD); 6 mo PT: nonsignificant global improvement on heated side vs control (ID)	Erythema, stinging/burning, oozing/crusting, dyspigmentation, scaling, and edema
Choi et al[79] (2015)	RD, PG study	Scales and crusts were removed with curette prior to treatment: (A) pretreatment with 2940-nm Er:YAG AFL, 300–550-μm depth, level 1 coagulation, 1 pulse, 22% density followed by 160 mg/g occluded MAL cream applied for 2 h before illumination with red light, 632 nm (n=29); (B) same as treatment arm A, but with a 3 h occlusion time (n=31); (C) 160 mg/g occluded MAL cream applied for 3 h before illumination with red light, 632 nm, 37 J/cm^2 light dose (n=33)	N/A	12 mo PT: (A) 67.5%, (B) 84.8%, (C) 51.1%	12 mo PT: excellent or good cosmetic outcome (PD), (A) 90.2%, (B) 87.0%, (C) 80.6%	Erythema, postinflammatory hyperpigmentation, edema, itching, oozing, and bleeding

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(continued)

Reference (Year)	Study Design	Treatment Arm(s)	Reduction in Mean or Median Lesion Count	Complete Clearance	Cosmetic Outcome	Most Common AEs and Cosmetic Considerations
Ko et al[80] (2014)	RD, PG study	Scales and crusts were removed with curette prior to treatment: (A) 160 mg/g occluded MAL cream applied for 3 h before illumination with red light, 632 nm, 5 cm away, 9 min (n=22); (B) Er:YAG 2940-nm fractionated laser, 300–550 μm depth, level 1 coagulation, 1 pulse, 22% density used, followed by MAL-PDT as in treatment arm A (n=23)	N/A	3 mo PT: (A) 61.2%, (B) 86.9%	24 wk PT: excellent or good cosmetic outcome (ID), (A) 96%, (B) 95%; excellent or good cosmetic outcome (PD), (A) 96%, (B) 91%	Erythema and hyperpigmentation; erythema decreased slowly over 12 wk after FL-PDT and over 8 wk with MAL-PDT; hyperpigmentation decreased slowly over 24 wk after FL-PDT and over 20 wk with MAL-PDT; side effects more frequent in FL-PDT group
Togsverd-Ho et al[81] (2012)	RD, PG study	Scales and crusts were removed with curette prior to treatment: (A) 160 mg/g occluded MAL cream applied for 3 h before illumination with red light, 632 nm, 37 J/cm^2 light dose (n=15); (B) AFL, 10 mJ per pulse, single pulse, 0.12-mm spot size, 5% density before receiving treatment arm A (n=15)	N/A	3 mo PT: (A) 67%, (B) 90%	3 mo PT: excellent or good cosmetic outcomes in 100% of patients for all treatment groups (ID and PD)	Pain, erythema, crusting, long-term pigmentary changes; inflammatory side effects were more prevalent with AFL-PDT than PDT alone

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Reference (Year)	Study Design	Treatment Arm(s)	Reduction in Mean or Median Lesion Count	Complete Clearance	Cosmetic Outcome	Most Common AEs and Cosmetic Considerations
Torezan et al[82] (2013)	Split-face study	Scales and crusts were removed with curette prior to treatment: (A) 160 mg/g occluded MAL cream applied for 90 min before illumination with red light, 50 mW/cm^2, 37 J/cm^2 light dose on half of face (n=10); (B) immediately after MAL cream was applied, a disposable microneedling roller with 192 needles of 1.5-mm length and 0.1-mm width was passed 7–8 times in each direction until uniform erythema and pinpoint bleeding was achieved before receiving treatment arm A on opposite half of face (n=10)	90 d PT: (A) 86%, (B) 90%	N/A	90 d PT: treatment arm B showed greater improvement in global assessment for mottled pigmentation, coarse wrinkles, fine lines, roughness, and sallowness	Erythema, edema, crusting, pain, and bacterial infection; mean time to resolution of AEs was 5 d with normal MAL-PDT and 10 days with microneedling-assisted MAL-PDT

Abbreviations: 5-FU, 5-fluorouracil; PT, posttreatment; N/A, not applicable; RD, randomized; DB, double-blind; VC, vehicle controlled; PG, parallel group; MC, multicenter; PD, participant determined; TCA, trichloroacetic acid; DFS, diclofenac sodium; ID, investigator determined; IMQ, imiquimod; IM, ingenol mebutate; SC, single center; AE, adverse event; AK, actinic keratosis; PR, prospective; Er:YAG, erbium-doped:YAG; PDT, photodynamic therapy; PC, placebo controlled; MAL, methyl aminolevulinate; 5-ALA, 5-aminolevulinic acid; AFL, ablative fractional laser; FL, fractionated laser.

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