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Aminolevulinic Acid 20% Solution Combined With Photodynamic Therapy for Treatment of Actinic Keratoses: A Review

Joe Gorelick MSN FNP-C,[a] Scott Freeman MCMS PA-C[b]

[a]California Skin Institute, San Jose, CA
[b]Advanced Dermatology, St. Petersburg, FL

ABSTRACT

Actinic keratoses (AK) are lesions with potential to transform into nonmelanoma skin cancers. Numerous methods are available for treatment of AK. Here, we review clinical trial data on the use of photodynamic treatment combined with the sensitizing agent aminolevulinic acid 20% solution (ALA-PDT) for AK management. Although treatment guidelines for AK vary in their specific recommendations, efficacy of ALA-PDT is considered comparable or better relative to other FDA-approved treatments for AK. It is generally well tolerated and has a very acceptable long-term safety profile. ALA-PDT is typically recommended for patients who have multiple AKs and is associated with improved cosmetic outcomes compared with cryotherapy. Patients who undergo treatment with ALA-PDT should receive thorough education regarding the risks and benefits of treatment, the treatment regimen and the importance of adhering to it, how to manage local reactions, and signs and symptoms that warrant further evaluation.

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INTRODUCTION

Actinic keratoses (AK) are dysplastic epidermal lesions resulting from long-term sun exposure that have potential to progress to nonmelanoma skin cancer (NMSC), particularly squamous cell carcinoma (SCC).[1,2] They are a manifestation of abnormal keratinocyte proliferation and differentiation.[3]

AKs may be considered visible evidence of a photo-damaged field with changes predisposing the patient to development of NMSC.[4] However, AKs may also spontaneously resolve or remain stable without malignant transformation.[3] In one study of 169 patients with 7784 AKs, 5.6% of patients progressed to develop SCC or basal cell carcinoma (BCC) within 5 years.[4,5] Another study predicted that patients with an average of 7.7 AKs had a 10% risk of developing SCC within 10 years.[3] Further, roughly two-thirds of primary SCCs, one-third of primary BCCs, and 60% to 80% of invasive SCCs arose in AK lesions.[4,5]

The prevalence of AK varies from 6% to 60% among populations and appears to be increasing.[2] Factors increasing risk for AK include age, skin phototype, lifestyle, and occupation (eg, working outdoors), geographical location, history of skin cancer, and immunosuppressed status.[2] Development of AK is more likely in patients whose skin burns easily (eg, phototype I) compared with those who rarely burn (eg, phototype VI).[6] They primarily occur on areas of skin that experience chronic sun exposure, particularly the head and neck, followed by the upper extremities.[3] The total direct costs associated with AK in 2004 were estimated at $1.2 billion, with the majority of these costs resulting from outpatient visits to health care providers for treatment.[4]

Although some AKs are associated with sensations of itching or tenderness, most are generally asymptomatic.[3] Patients often describe the lesions as rough "sandpaper"-like patches. AKs are graded using a 3-point scale: grade 1 lesions are visible and palpable, grade 2 lesions are usually red and scaly, and grade 3 lesions are thicker, hyperkeratotic lesions that can be difficult to differentiate from early SCCs.[3] Presence of a single lesion may be associated with development of multiple lesions in the future.[3] When multiple AKs are present, they are considered to be evidence of "field change," ie, an area of skin with extensive actinic damage.[3]

Overview of Treatment Options for Actinic Keratoses

The goals of AK treatment are to eliminate existing AKs and minimize risk of recurrence and progression to SCC.[2] Available treatment options include photodynamic therapy (PDT) with photosensitizing agents; topical agents such as 5-fluorouracil, imiquimod, diclofenac, and topical retinoids; cryosurgery;

curettage; laser therapy; and systemic therapy (eg, systemic retinoids). Light sources for PDT include red- and blue-spectrum; red narrow-spectrum sources require less illumination time and may be associated with a higher rate of response.[3] The addition of photosensitizing agents to PDT induces apoptosis and necrosis of target tissue. Factors that influence treatment selection include efficacy, potential for side effects, number of lesions, grade, location of lesions, response to previous therapy, cosmetic impact, regimen flexibility and convenience, availability, patient preference, and cost.[1,3]

Treatments can be directed to specific lesions or the entire "field." When isolated lesions are treated, for example, with cryotherapy, underlying subclinical actinic damage may not be visualized. By using field therapy techniques, both clinical and subclinical lesions receive treatment, achieving more comprehensive clearance of actinic damage.

Neither surgical excision nor biopsy is routinely performed.[7] Biopsy may be appropriate if NMSC or other conditions such as Bowen's disease cannot be ruled out with clinical evaluation and dermoscopy.[8]

Treatment Guidelines for AK

Several treatment guidelines for treatment of AK have been published, including Canadian, European, British, Italian, and Swiss guidelines.[3,7-10] Additional treatment guidelines are available for patients at higher risk of SCC.[11] There is significant heterogeneity among the organization and structure of available guidelines. For example, Canadian guidelines recommend surgical excision or curettage for isolated AKs and state that topical treatments including 5-FU, imiquimod, or ingenol mebutate (discontinued in 2020[12]) may be used for isolated or clustered AKs (4 or more), whereas PDT or other field-directed therapies are recommended for clustered AKs.[7] British guidelines provide an "A" recommendation for several therapies: diclofenac, cryotherapy, PDT with either 5-aminolevulinic acid or its methyl ester (methyl aminolevulinate; MAL) as a photosensitizing agent, 5-FU, imiquimod, or ingenol mebutate. Treatments with a "B" recommendation include laser resurfacing, chemical peels, dermabrasion, and other topical agents.[3,13] Tirbanibulin—approved by the FDA for AK treatment in December 2020—is not yet included in treatment guidelines.[14]

Some guidelines suggest that treating AK is not always required; however, experts are divided on this issue.[3] Guidelines from the British Association of Dermatologists indicate that patient preference and clinical circumstances (eg, extent, duration, symptoms, and risks for skin cancer) should be considered when determining whether to treat AK.[3] In contrast, Canadian treatment guidelines state that AKs should be treated due to their chance of progression to SCC and because they can be difficult to distinguish from early SCC.[7] The Progressing Evidence in AK (PEAK) Working Group recommends treatment of AK by default, especially in patients at increased risk of NMSC,[2] although direct evidence that AK treatment prevents progression to NMSC is lacking.[2] AK lesions that progress to SCC following treatment may have been SCC lesions that were initially diagnosed as AK and had a deep component that persisted through treatment.[15] In the clinical setting, in light of the potential for malignancy, most identified AKs are treated.

A comprehensive review of available guidelines is beyond the scope of this article. In general, cryotherapy is the most widely recommended treatment for isolated AKs, whereas field therapies (5-FU, imiquimod, PDT with a photosensitizing agent, and likely tirbanibulin when added to guidelines) are recommended for multiple AKs.[13] PDT for AK is considered highly effective, with efficacy at least comparable to other FDA-approved treatments. It is associated with improved cosmetic outcomes compared with cryotherapy.[16]

Aminolevulinic Acid 20% Solution Combined With Photodynamic Therapy (ALA-PDT)

Mechanism of Action of ALA-PDT

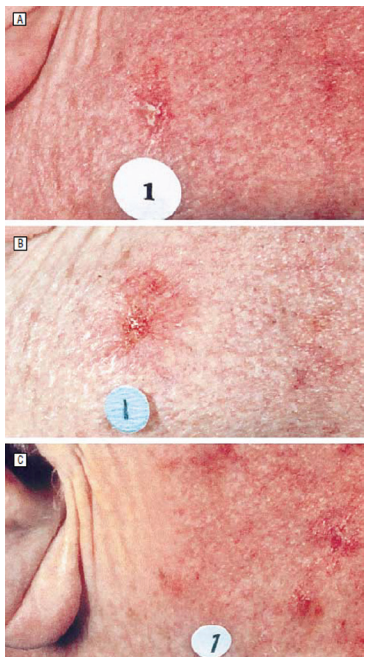
Due to its encouraging efficacy and safety profile, including favorable cosmetic outcomes, and field-directed nature, PDT with 5-aminolevulinic acid 20% solution as a photosensitizer (ALA-PDT) is often used in treatment of AK. 5-aminolevulinic acid is a prodrug that is absorbed and metabolized to protoporphyrin IX (PpIX). When PDT of the appropriate wavelength is applied, a cytotoxic reaction produces reactive oxygen species (ROS), resulting in apoptosis and necrosis of the treated lesion with minimal damage to untreated skin.[15,17]

Clinical Efficacy of ALA-PDT

Per US labeling, ALA-PDT combining 5-aminolevulinic acid 20% solution plus blue light illumination using the BLU-U Blue Light Photodynamic Therapy Illuminator is indicated for photodynamic therapy (treatment) of minimally to moderately thick AKs of the face or scalp, or AKs of the upper extremities.[18] In several phase 3 or 4 clinical trials, ALA-PDT was highly effective for treatment of minimally to moderately thick AKs when used as directed (Table 1).[1,15,19,20] Initial trials investigated safety and efficacy of ALA-PDT for the treatment of AK on the face and scalp, while more recent trials have addressed AK on the upper extremities.[15]

In a phase 3 multicenter trial conducted by Piacquadio et al, 243 patients with 4 to 15 AK lesions on the face or scalp were randomized to treatment with PDT and either ALA or vehicle.[19] At 8 weeks after treatment, ≥75% of AK lesions were cleared in 77% of patients receiving ALA-PDT vs 18% receiving vehicle-PDT (P<0.001).[19] Complete response rates (100% clearance) at 8 weeks occurred in 66% of ALA-PDT treated patients vs 11% of vehicle-PDT treated patients (P <0.001).[19] Photographs from a

FIGURE 1. Case example from phase 3 trial of 20% aminolevulinic acid solution followed by photodynamic therapy using blue light. (A) Pretreatment, (B) 24 hours posttreatment, (C) 8 weeks posttreatment. Reproduced with permission from Piacquadio, et al. *Arch Dermatol.* 2004;140:41–46.



case example are reproduced as Figure 1.

Tschen et al, conducted a phase 4 open-label study of 110 patients with 6 to 12 AKs on the face or scalp.[20] Patients were treated with ALA-PDT and followed with monthly visits for 12 months. Any treated lesions that remained at month 2 were retreated with ALA-PDT; 66% of these patients received a second treatment at month 2. Lesions that did not respond to treatment were biopsied at month 3.[20] Seventy-six percent (76%) of target lesions were completely cleared at month 1 and 72% at month 2; complete clearance peaked at month 4 at 86% of lesions and then declined gradually to 78% of all lesions at month 12. The percent of patients with complete clearance (100% of target lesions) was 67% at month 3 and declined to 40% at month 12. Beginning at month 6, clearance rates were slightly higher in patients with skin types I and II compared with skin types III and IV.[20] The percentage of lesions that cleared was similar for grade 1 and grade 2 lesions.

Jiang et al, investigated treatment with ALA-PDT or vehicle-PDT in patients with 4 to 15 grade 1 or 2 AKs on one upper extremity.[15] Among patients who received a second treatment, the mean AK lesion clearance rate in patients who received ALA was 69.1% at week 12, compared with 29.9% in vehicle-treated patients (P<0.0001).[15] The number of patients who experienced complete clearance was also significantly greater in those who received ALA vs vehicle (P=0.0001).[15]

In a post hoc analysis of a phase 3 study of 269 patients with 4–15 grade 1–2 AKs on an upper extremity, patients were treated with ALA-PDT or vehicle-PDT, applied twice. Treatment was also applied at week 8 if lesions were present in the treatment area.[1] At weeks 8 and 12, AK clearance rates were significantly greater in patients who received ALA-PDT vs vehicle-PDT. At week 12, the clearance rates were 80.6% in those receiving ALA-PDT and 45.5% in those receiving vehicle-PDT. Cumulative disease area cleared was also greater in those who received ALA-PDT. Results were similar across all baseline lesion sizes.[1]

Efficacy in High-Risk Patients

Piacquadio conducted a phase 2 trial in patients at high risk for progression to NMSC. Patients had 4–15 facial AKs grade 1–3 and had been previously been treated for NMSC in a sun-exposed area.[21] A total of 166 patients underwent cryotherapy at screening and then were randomized to treatment with ALA-PDT or vehicle-PDT applied 2 times (baseline and week 4) or 3 times (baseline, week 4, and week 24).[21] Compared with vehicle-PDT treatment, ALA-PDT treatment performed 3 times significantly reduced the rate of new and recurrent AKs at 52 weeks.[21] Complete clearance rates at week 52 were 36% for ALA 2x, 37.5% for ALA 3x, and 18.9% for vehicle ($P \leq 0.01$ for each ALA treatment vs vehicle).[21]

Clinical Safety

The safety profile of ALA-PDT includes consideration of the immediate and short-term effects of PDT, ALA, and ALA-PDT as well as potential long-term effects of treatment, particularly the development of NMSC. However, long-term NMSC rates have only been reported in more recent trials.

Early-Onset Side Effects

Common early-onset side effects of PDT include pain and local skin reactions (erythema, edema, desquamation, and pustules). These effects often occur within hours or days of exposure to PDT and can negatively impact patient satisfaction.[17]

In the trial of patients with AK on the face or scalp by Piacquadio et al, adverse events (AEs) were similar in patients treated with either ALA or vehicle.[19] The overwhelming majority of AEs (92%) were mild or moderate; 97% of AEs were considered unrelated to ALA treatment. The most common AEs related to treatment were headache, dry skin, and conjunctivitis.[19] Patient discomfort due to PDT (eg, stinging and burning during PDT treatment) was reported by >90% of patients receiving ALA-PDT; only 28% reported any discomfort after 24 hours. Other common local responses included erythema, edema, crusting, pruritis, and scaling.[19] Rates of SCC or BCC diagnosis following treatment were not reported.

In the open-label study reported by Tschen et al, AEs associated with PDT were common immediately after treatment; 95% of

TABLE 1.

Summary of Efficacy Results of ALA Phase 3 and 4 Trials			
Endpoint	**ALA-PDT**	**VEH-PDT**	***P* value vs VEH**
Patients with upper extremity AKs[1]			
Mean clearance rate of treated upper extremity AKs at week 8	67.3	37.2	<0.0001
Mean clearance rate of treated upper extremity AKs at week 12	80.6	45.5	<0.0001
Percent of patients with cumulative disease area cleared at week 8	67.8	37.2	<0.0001
Percent of patients with cumulative disease area cleared at week 12	82.4	42.6	<0.0001
Patients with upper extremity AKs[15]			
Mean clearance rate of treated upper extremity AKs at week 8	53.4	26.3	<0.0001
Mean clearance rate of treated upper extremity AKs at week 12	69.1	29.9	<0.0001
Percent of patients with cumulative disease area cleared at week 8	25.9	9.0	<0.0001
Percent of patients with cumulative disease area cleared at week 12	31.1	12.7	<0.0001
Patients with face and scalp AKs[19]			
Percent of patients with ≥75% clearance at week 8	77	18	<0.001
Percent of patients with ≥75% clearance at week 12	89	13	<0.001
Percent of patients with complete disease area cleared at week 8	66	11	<0.001
Percent of patients with complete disease area cleared at week 12	73	8	<0.001
High-risk patients with facial AK[21]			
Lesion recurrent rate at week 52	ALA 2x: 7.7 ALA 3x: 6.1	15.5	0.0004 for ALA 2x <0.0001 for ALA 3x
Mean duration of response, weeks	ALA 2x: 35.9 ALA 3x: 33.3	25.9	NR

AK, actinic keratoses; ALA, aminolevulinic acid; NR, not reported; PDT, photodynamic therapy; VEH, vehicle.

patients experienced erythema, and 79% experienced edema.[20] ALA treatment increased the rate of stinging/burning from 16% at baseline to 64% during the incubation period following application and prior to light treatment; 96% of patients reported stinging/burning during light treatment. These side effects all subsided at follow-up visits, when rates were lower than those observed at baseline.[20] The AK recurrence rate was 24% (162/688); 139 were biopsied. Rates of SCC or BCC diagnosis among biopsied lesions were 7% and 0.7%.

In the upper extremity trial by Berman et al, ALA-PDT was generally well tolerated, and reactions to treatment were nonserious and resolved within several weeks. Compared with vehicle pretreatment, ALA pretreatment increased the incidence and severity of side effects associated with PDT, including erythema, edema, stinging/burning, scaling, dryness, and oozing/vesiculation/crusting. No clinically significant AEs were reported in either treatment group.[1] Similar results were found by Jiang et al; the incidence of erythema appeared more

TABLE 2.

Summary of Safety Results of ALA Phase 3 and 4 Trials		
Endpoint	**ALA-PDT**	**VEH-PDT**
Berman et al.—Patients with upper extremity AKs[1]		
Patients diagnosed with SCC	9 lesions in 7 patients	3 lesions in 3 patients
Patients diagnosed with BCC	0	4 lesions in 3 patients
Jiang et al.—patients with upper extremity AKs[15]		
Patients diagnosed with SCC	2	1
Patients diagnosed with BCC	NR	NR
High-risk patients with facial AK[21]		
Patients diagnosed with SCC	ALA 2x: 6 ALA 3x: 3	7
Patients diagnosed with BCC	ALA 2x: 4 ALA 3x: 2	5

AK, actinic keratoses; ALA, aminolevulinic acid; BCC, basal cell carcinoma; NR, not reported; PDT, photodynamic therapy; SCC, squamous cell carcinoma; VEH, vehicle.

frequent in patients treated with ALA than vehicle.[15]

Late-Onset Adverse Events

PDT has been associated with hyperpigmentation and scarring in rare cases; however, the most concerning potential AE is development of NMSC, also a rare event.[17] Because patients with AK are already predisposed to NMSC, it is difficult to associate PDT with NMSC pathogenesis. However, PDT could potentially mediate development of NMSC via generation of ROS or immunosuppressive effects.[17] Therefore, careful assessment of NMSC rates in patients receiving PDT treatment is warranted (Table 2).

In the upper extremity trial by Berman et al, 16 skin carcinomas were diagnosed; 9 SCCs were diagnosed in 7 patients receiving ALA-PDT (all with a prior history of SCC), and 3 SCCs were diagnosed in patients receiving vehicle-PDT.[1] Three BCCs were diagnosed in patients who received vehicle-PDT.[1] In the trial by Jiang et al, new SCC developed in 2 patients who received ALA and one who received vehicle; all had a previous history of SCC.[15] In the study of high-risk patients conducted by Piacquadio et al, there were a total of 27 NMSCs reported during follow-up; the rate was significantly lower in patients who received ALA-PDT 3 times compared with patients who received vehicle.[21]

Patient Education for ALA-PDT

Patient education related to the use of ALA-PDT for the treatment of AK should begin with a discussion of the risks and benefits of treating AK. Patients with AK should be educated that they have evidence of sun damage and are at risk for development of NMSC. Regardless of treatment decisions, education should include information about signs and symptoms that require further evaluation, including bleeding or painful lesions, and lesions that grow or begin to protrude.[3] Risks and benefits of available treatment options should also be discussed.

Several barriers hinder use of field therapy with ALA-PDT, including the time needed to explain the treatment regimen, properly apply the treatment, address the immediate pain and inflammation, and ensure that patients adhere to requirements associated with the regimen.[4] Benefits of ALA-PDT include that it is more convenient and less invasive than surgery, is not associated with long-term side effects, and results in little to no scarring. Additionally, it avoids potential adherence issues that may arise with treatments applied exclusively by the patient.

If treatment with ALA-PDT is selected, it is important to educate patients about the regimen. ALA treatment must be applied prior to PDT treatment; the specific incubation time depends on the location. Patients should be advised that if they are unable to return for the PDT treatment during the appropriate period after applying the solution, they should avoid exposure of the photosensitized lesions to sunlight for at least 40 hours. Patients should also be advised to avoid medications that enhance the phototoxic reaction to PDT, such as St. John's wort, griseofulvin, thiazide diuretics, sulfonylureas, phenothiazines, sulfonamides and tetracyclines.[18]

It is imperative that clinicians provide patients with comprehensive education regarding proper home care following ALA-PDT treatment. Patients must remain indoors and avoid all direct sunlight (even sitting by a window) for 36 hours. If patients must go outside, appropriate protective apparel such as a wide-brimmed hat, long-sleeved shirt, and gloves may be used to protect the skin from sunlight and other bright light; sunscreen will not be effective.[18] Patients should wash the treated area twice daily with a gentle cleanser and apply moisturizer 4 times daily. If the treated area is painful, patients may use nonprescription analgesics (ie, acetaminophen or ibuprofen) and apply ice packs for 5–10 minutes every few hours. Patients should be advised to expect redness and for the skin to feel dry and tight. Makeup may be used if desired once any crusting has healed. When patients go outdoors after the first 36 hours, they should use broad spectrum sunscreen that provides a physical barrier such as zinc oxide or titanium dioxide.[16]

CONCLUSION

ALA-PDT is effective and well tolerated for the treatment of AK located on the face, scalp, and upper extremities. Clinical trials have found dramatically improved rates of AK clearance following treatment with ALA-PDT compared with PDT applied with vehicle alone. Field therapy for AK with a treatment such as ALA-PDT is supported for patients with multiple AKs and may reduce the risk for future occurrence of NMSC. Patients treated with ALA-PDT require thorough education to ensure that they adhere to all treatment recommendations and are prepared to manage local reactions. Additionally, regardless of whether patients receive treatment with ALA-PDT, all patients with AK should be educated regarding signs and symptoms that may indicate progression to NMSC and require further evaluation.

DISCLOSURES

JG is a consultant, advisor, and/or speaker for AbbVie, Inc.; Beiersdorf; Celgene Corporation; Dermira; Eli Lilly and Company; Encore Dermatology, Inc.; Foamix Pharmaceuticals Ltd; LEO Pharma; Mayne Pharma; Novartis Pharmaceuticals; Ortho Dermatologics, Inc.; Primus Pharmaceuticals; PruGen Pharmaceuticals; Regeneron Pharmaceuticals, Inc.; Sanofi-Genzyme; Sun Pharmaceutical Industries, Inc.; and UCB S.A. SF is a consultant, advisor, and/or speaker for AbbVie, Inc.; Eli Lilly and Company; Novartis, and UCB.

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REFERENCES

1. Berman B, Bhatia N, Piacquadio D, et al. Efficacy of aminolevulinic acid 20 % solution photodynamic therapy in the treatment of actinic keratoses on the upper extremities: A post hoc analysis of a phase 3, randomized, vehicle-controlled trial. *Photodiagnosis Photodyn Ther.* 2020;32:102013.
2. Cerio R, Dirschka T, Dreno B, et al. Actinic keratosis, a chronic, progressive disease: Understanding clinical gaps to optimise patient management. *Acta Derm Venereol.* 2017;97(8):997-998.
3. de Berker D, McGregor JM, Mohd Mustapa MF, et al. British Association of Dermatologists' guidelines for the care of patients with actinic keratosis 2017. *Br J Dermatol.* 2017;176(1):20-43.
4. Del Rosso JQ, Kircik L, Goldenberg G, Brian B. Comprehensive management of actinic keratoses: practical integration of available therapies with a review of a newer treatment approach. *J Clin Aesthet Dermatol.* 2014;7(9 Suppl S2-S12):S2-S12.
5. Criscione VD, Weinstock MA, Naylor MF, et al. Actinic keratoses: Natural history and risk of malignant transformation in the Veterans Affairs Topical Tretinoin Chemoprevention Trial. *Cancer.* 2009;115(11):2523-2530.
6. Sachdeva S. Fitzpatrick skin typing: applications in dermatology. *Indian J Dermatol Venereol Leprol.* 2009;75(1):93-96.
7. Poulin Y, Lynde CW, Barber K, et al. Non-melanoma skin cancer in Canada chapter 3: Management of actinic keratoses. *J Cutan Med Surg.* 2015;19(3):227-238.
8. Peris K, Calzavara-Pinton PG, Neri L, et al. Italian expert consensus for the management of actinic keratosis in immunocompetent patients. *J Eur Acad Dermatol Venereol.* 2016;30(7):1077-1084.
9. Werner RN, Stockfleth E, Connolly SM, et al. Evidence- and consensus-based (S3) Guidelines for the Treatment of Actinic Keratosis - International League of Dermatological Societies in cooperation with the European Dermatology Forum - Short version. *J Eur Acad Dermatol Venereol.* 2015;29(11):2069-2079.
10. Hofbauer G, Anliker M, Boehncke WH, et al. Swiss clinical practice guidelines on field cancerization of the skin. *Swiss Med Wkly.* 2014;144:w14026.
11. Richard MA, Amici JM, Basset-Seguin N, et al. Management of actinic keratosis at specific body sites in patients at high risk of carcinoma lesions: expert consensus from the AKTeam of expert clinicians. *J Eur Acad Dermatol Venereol.* 2018;32(3):339-346.
12. PharmaLetter T. Denmark's LEO Pharma initiates Picato phase-out. 2020; https://www.thepharmaletter.com/article/denmark-s-leo-pharma-initiates-picato-phase-out. Accessed March 10, 2021.
13. Fleming P, Zhou S, Bobotsis R, Lynde C. Comparison of the treatment guidelines for actinic keratosis: A critical appraisal and review. *J Cutan Med Surg.* 2017;21(5):408-417.
14. Almirall. Almirall announces FDA approval of Klisyri® (tirbanibulin), a new innovative topical treatment for actinic keratosis. 2020; https://www.almirall.com/newsroom/news/almirall-announces-fda-approval-of-klisyri%C2%AE-tirbanibulin-a-new-innovative-topical-treatment-for-actinic-keratosis. Accessed March 10, 2021.
15. Brian Jiang SI, Kempers S, Rich P, et al. A randomized, vehicle-controlled phase 3 study of aminolevulinic acid photodynamic therapy for the treatment of actinic keratoses on the upper extremities. *Dermatol Surg.* 2019;45(7):890-897.
16. Ozog DM, Rkein AM, Fabi SG, et al. Photodynamic therapy: A clinical consensus guide. *Dermatol Surg.* 2016;42(7):804-827.
17. Borgia F, Giuffrida R, Caradonna E, et al. Early and late onset side effects of photodynamic therapy. *Biomedicines.* 2018;6(1).
18. Levulan Kerastick [product label]. Sun Dermatology W, MA. March 2018.
19. Piacquadio DJ, Chen DM, Farber HF, et al. Photodynamic therapy with aminolevulinic acid topical solution and visible blue light in the treatment of multiple actinic keratoses of the face and scalp: investigator-blinded, phase 3, multicenter trials. Arch Dermatol. 2004;140(1):41-46.
20. Tschen EH, Wong DS, Pariser DM, et al. Photodynamic therapy using aminolaevulinic acid for patients with nonhyperkeratotic actinic keratoses of the face and scalp: phase IV multicentre clinical trial with 12-month follow up. *Br J Dermatol.* 2006;155(6):1262-1269.
21. Piacquadio D, Houlihan A, Ferdon MB, et al. A randomized trial of broad area ALA-PDT for field cancerization mitigation in high-risk patients. *J Drugs Dermatol.* 2020;19(5):452-458.

AUTHOR CORRESPONDENCE

Joe Gorelick MSN FNP-C

E-mail:..... jgorelick1@me.com