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Photodynamic therapy with topical aminolevulinic acid vs placebo in the treatment of actinic keratosis

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Abstract:

Objective: Assessing the effectiveness of photodynamic therapy with aminolevulinic acid versus placebo in the complete clearance rate of actinic keratosis. **Design:** Systematic literature review. **Methods:** An initial literature search was performed using Google Scholar using terms "photodynamic therapy", "aminolevulinic acid," "randomized control trial", "actinic keratosis", "clearance efficacy", "safety", "field treatment", and "placebo". An additional search using PubMed was performed using the same terms. Studies were excluded if they were performed on non-human subjects, did not use aminolevulinic acid as their photosensitizer, used organ transplant recipients, compared efficacy to alternate treatment modalities, used alternative light source such as laser or daylight, or if they evaluated the clearance rates of squamous cell carcinoma in situ or basal cell carcinoma. The final studies were selected based on their relation to our clinical question. **Results:** Pariser et al found that the median actinic keratosis clearance rate at week 12 for aminolevulinic acid treated subjects ranged from 68% to 79% compared to 7% with placebo. Complete clearance rate at week 12 for the treatment group ranged from 17% to 30% compared to 2% in the placebo group. Piacquadio et al found 75% clearing of treated lesions at week 8 was 77% and 89% at week 12 compared to 18% and 13%, respectively for the placebo group. Taub found that 73% of patients who received aminolevulinic acid achieved at least 50 percent reduction in lesion count when compared to only 13% in the placebo group.
Conclusion: All three randomized vehicle-controlled studies demonstrated efficacy and safety for actinic keratosis clearance rates when compared to placebo.

Introduction:

Actinic keratoses (AK) are rough, scaly lesions consisting of dysplastic keratinized epithelium that occur on chronically sun exposed skin commonly affecting the head, neck and arms.[1] AKs lie on one end of a spectrum of dysplastic keratinocytes, which can progress into squamous cell carcinoma in situ (SCCis), invasive squamous cell carcinoma (SCC), and finally metastatic SCC.[1] SCC is the second most common skin cancer, with over 1 million cases diagnosed annually in the United States and accounts for over 5000 deaths per year.[2]

Currently, there is no widely accepted algorithm for the treatment of AKs, especially in widespread, diffuse cases.[3] Although cryotherapy is perhaps the most common treatment for single lesions, field treatment with topical agents is often preferred for subclinical lesions and diffuse disease. Topical agents include 5-FU, imiquimod, and diclofenac.[3] These agents cause

local skin reactions, including photosensitivity, erythema, edema, erosions and pain for the entire duration of treatment.[3] Although convenient, these agents require longer duration of therapy and therefore prolonged side effects, making adherence difficult.[3]

Alternatively, photodynamic therapy (PDT) is an in-office field treatment for subclinical and clinical AKs that does not require long-term patient compliance. The provider applies a photosensitizing agent, aminolevulinic acid (ALA), that preferentially absorbs into hyperproliferative cells.[3] The treatment area is then exposed to non-irradiating blue light, resulting in cellular destruction.[3] It is important to note that normal skin cells are unaffected, as they do not absorb the phototoxic agents. Although patients will experience discomfort during treatment, side effects are generally well-tolerated and short lived with better cosmesis.[3] This review aims to evaluate the lesion response rate and safety of PDT with ALA, compared to PDT without ALA for the treatment of AK.

Methods:

An initial search of Google Scholar was performed in September 2020 using the terms photodynamic therapy, aminolevulinic acid, randomized control trial, actinic keratosis, clearance efficacy, safety, field treatment, and placebo. Limits included English. This yielded 440 results. An additional search was done on PubMed, using the same search criteria, which yielded 21 results. An additional record was identified in the references of the article *European Guidelines for Topical PDT*. These results were screened and excluded based on the criteria of Table 1. This left 6 full text articles that were assessed for eligibility, three of which were excluded based on the reasons listed in Table 2.

Table 1 : Reasons for Screened Article Exclusion	
Non-human population	Daylight used as light source
Compared MAL to ALA as the photosensitizing agent	Non-RCT
Subject population was Organ Transplant Recipients (OTR)	Evaluated SCCis clearance
Combination therapy evaluated	Evaluated BCC clearance
Laser light source used	Compared efficacy to alternate treatment

Table 2 : Reasons for Full-Text Article Exclusion
Assessment of pain, not efficacy (2)
Assessment of efficacy based on dose of ALA (1)

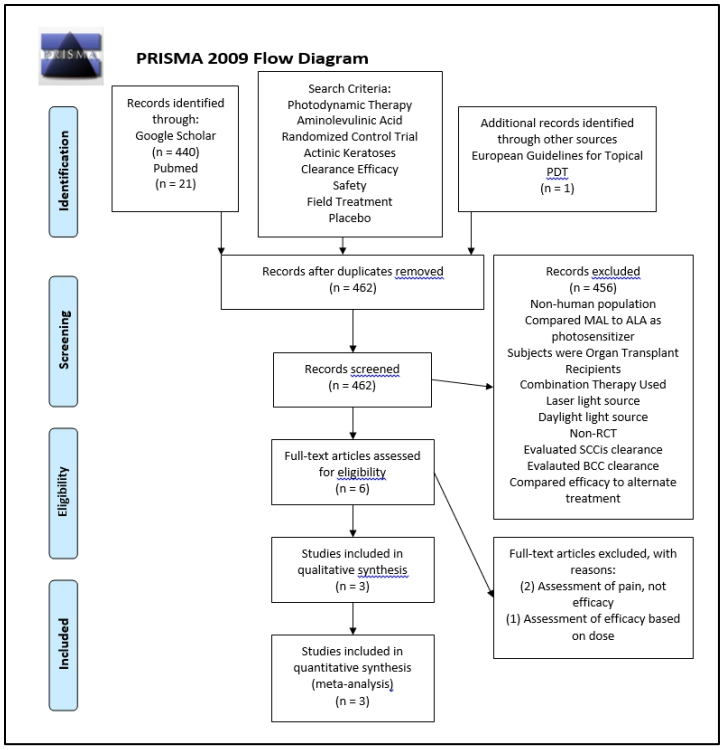

Figure 1 : PRISMA diagram

Results:

Study # 1

Randomized Vehicle-Controlled Study of Short Drug Incubation Aminolevulinic Acid Photodynamic Therapy for Actinic Keratoses of the Face or Scalp. Pariser et al.[4]

Objective: To assess the effectiveness and tolerability of aminolevulinic acid photodynamic therapy (ALA-PDT) on broad areas of affected skin with short duration incubation times.

Study design: This was a randomized vehicle-controlled study of two hundred thirty-five male and non-pregnant female subjects greater than 18 years old, who were enrolled in a multicenter study spanning 13 different sites. See table 1 for exclusion criteria. Two hundred and thirty four subjects (211 males and 23 females) had a mean age of 68 years old (range 40-88 years) and Fitzpatrick skin type I (6%), II (44%), III (43%), IV (6%), and V (0.4%) were included in the efficacy analysis (intention to treat population). See table 4 for descriptions of Fitzpatrick skin types I-VI. Two hundred thirty-one of the total enrolled participants (98%) completed the study.

Participants were randomized into one of 5 treatment groups: broad application of ALA with 1, 2 or 3 hour incubations prior to blue light, spot application of ALA 2 hours prior to blue light, or vehicle (VEH) before blue light application (placebo control). For spot treatment, 2 applications of ALA or VEH were applied to individual AKs; for broad application treatment, the first

application was applied to individual AKs with 2 additional broad applications followed by blue light (BLU-U photodynamic Therapy illuminator) administration to the treatment area for 1000 seconds (16 minutes, 40 seconds) for a total dose of $10J/cm^2$. Follow up was performed at 24 to 48 hours and 2, 4, 8, 12, and 24 weeks after initial treatment. If there was any evidence of remaining AKs at 8 weeks, an additional treatment was performed. Participants were instructed to avoid direct sunlight and bright indoor light to the treatment area for 36 hours post treatment. Additionally, subjects were advised to wear physical sunblock containing titanium dioxide (TiO_2) and/or zinc oxide (ZnO) with sun protection factor (SPF) of 15+ to treatment areas.

Table 3 : Exclusion Criteria for Pariser et al
Grade 3 AK within treatment area
Lesion suspicious or proven for skin cancer within treatment area
History of cutaneous photosensitization
Any condition associated with immunosuppression
Keratolytics including >5% urea, alpha hydroxyl acids
>2% salicylic acid within 2 days of initiation of treatment
Cryotherapy within previous 4 weeks
Microdermabrasion, ablative laser, ALA-PDT, chemical peels, 5-fluorouracil, diclofenac, imiquimod within previous 8 weeks
2 or more ALA-PDT treatments or systemic retinoid use within the previous 6 months.

Table 4 : Fitzpatrick Skin Type		
Skin Type	**Typical Features**	**Tanning Ability**
I	Pale white skin, blue/green eyes, blond/red hair	Always burns, does not tan
II	Fair skin, blue eyes	Burns easily, tans poorly
III	Darker white skin	Tans after initial burn
IV	Light brown skin	Burns minimally, tans easily
V	Brown skin	Rarely burns, tans darkly easily
VI	Dark brown or black skin	Never burns, always tans darkly

Study results: The absolute AK count at baseline and median actinic keratoses clearance rate (AKCR) were measured at 8, 12, and 24 weeks (see figure 1). Most subjects in each treatment group received both ALA-PDT and vehicle PDT (VEH-PDT) treatment of AKs of the face and scalp. The median AKCR by week 12 was 71.4 (+/- 34.8)% for ALA with broad area application for 1-hour incubation (ALA-BA1), 73.6 (+/- 31.1)% for ALA broad area application for 2-hour incubation (ALA-BA2), 78.6 (+/- 30.5)% for ALA broad area application with 3 hour incubation (ALA-BA3), 68.3 (+/-39.4)% for ALA spot application with 2 hour incubation (ALA-SP2), and 7.1 (+/-44.3)% for VEH. The median AKCR was significantly greater for all ALA groups when compared to VEH during all time intervals. Table 2 depicts complete AK clearance rate defined

as no lesions remaining. Complete clearance for ALA groups ranged from 15% (7/48) in ALA-BA2 to 30% (14/47) in ALA-BA1 at 12 weeks compared to 2% (1/46) for VEH.

At the final visit, week 24, subjects also rated their overall satisfaction with improvement of the appearance of treatment areas. A 4-point scale (0=no improvement/worsening, 3= excellent). 79% (147/185) subjects treated with ALA-PDT rated moderate to excellent improvement when compared to baseline and 35% (16/46) subjects treated with VEH-PDT reported moderate or excellent improvement when compared to baseline.

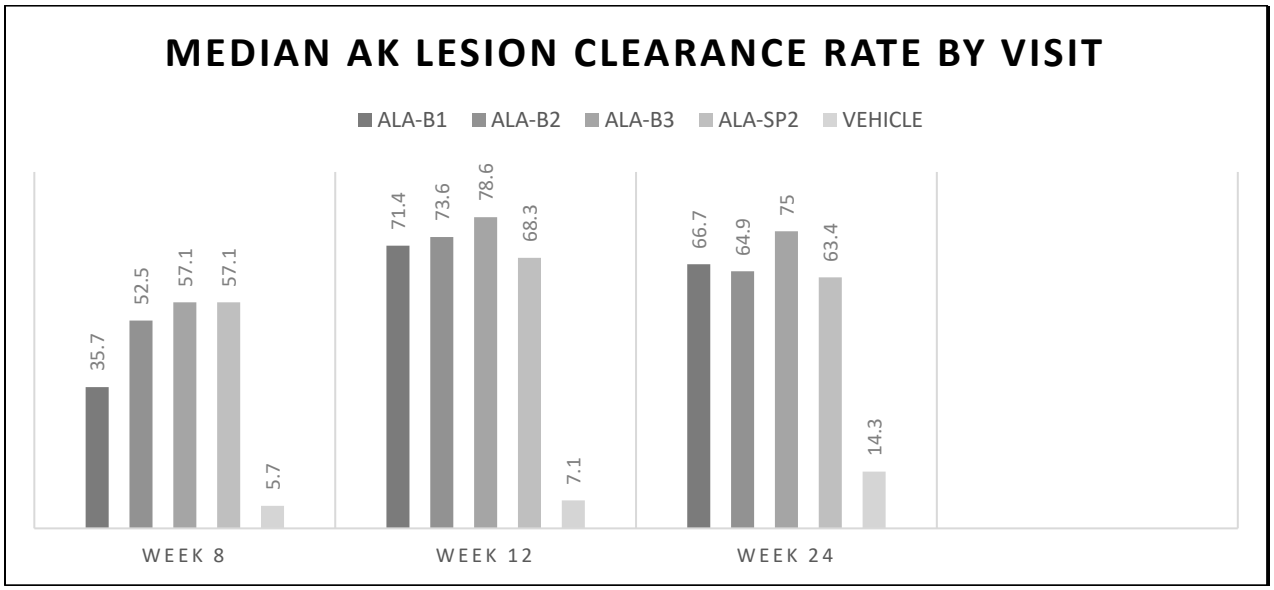

Figure 2: Median AK Clearance rate by visit for Pariser et al.

Table 5 : Subjects with 100% AK clearance rate at 8, 12, and 24 weeks					
	ALA-BA1 (N=47)	ALA-BA2 (N=48)	ALA-BA3 (N=47)	ALA-SP2 (N=46	VEH (N=46)
Week 8, N (%)	3 (6.4)	7 (14.6)	8 (17)	4 (8.7)	0 (0.0)
Week 12, N (%)	14 (29.8)	7 (14.6)	13 (27.7)	8 (17.4)	1 (2.2)
Week 24, N (%)	11 (23.4)	3 (6.3)	12 (25.5)	2 (4.3)	1 (2.2)
ALA-BA1, aminolevulinic acid broad area application, 1-hour incubation; ALA-BA2, aminolevulinic acid broad area application, 2-hour incubation; ALA-BA3, aminolevulinic acid broad area application, 3-hour incubation; ALA-SP2, aminolevulinic acid spot application, 2-hour incubation; VEH, vehicle application.					

Study Critique: A strength of the study is that it included analysis of Fitzpatrick skin types I-V, therefore including darker skin types such as brown skin. In addition, the study participants were randomized into one of 5 treatment groups with comparable sample sizes per group. The use of intention to treat (ITT) population was used in the efficacy analysis. ITT helps to preserve the original randomization and to avoid potential bias during analysis.

A major inconsistency noted in this study is the large discrepancy between male and female participants. As mentioned in the article, this may be partly due to the fact that males have a

higher tendency to develop AKs which is likely influenced by a higher total lifetime sun exposure rate and a lower adherence to photoprotective measures to the scalp and face.

Additionally, the study excluded participants with advanced AKs. While this allows for standardization of the subjects, it would be helpful to evaluate the efficacy of ALA and PDT on advanced AKs that already have a higher risk of progressing to SCCis. This type of data could be extrapolated further to determine efficacy of blue light for diffuse advanced AKs and SCCis.

Study #2:
Photodynamic Therapy with Aminolevulinic Acid Topical Solution and Visible Blue Light in the Treatment of Multiple Actinic Keratoses of the Face and Scalp. Piacquadio et al.[5]

Objective: To determine the efficacy and safety of PDT using 20% weight/volume ALA and visible blue light for treatment of multiple AK of the face and scalp.

Study design: The study included results from 2 independent, identical, phase 3 clinical trials which were presented as a single research effort. This study was a randomized placebo-controlled, uneven parallel-group study of 243 participants (40 females, 203 males) at 16 different sites with Fitzpatrick skin types of I (29%), II (50%), III (20%), IV (2%) in the ALA group and Fitzpatrick skin types I (32%), II (37%), III (27%), IV (3%) in the vehicle group. The participants were randomized at each center in a 3:1 drug-vehicle ratio to receive either topical ALA (n = 181) or a vehicle (n=62) followed by blue light PDT within 14 to 18 hours of application. The topical ALA or vehicle was twice applied to individual AK lesions by an unblinded investigator.

Efficacy assessments were performed by a blinded investigator at follow up visits that occurred at 24 hours, 1, 4, 8, and 12 weeks post PDT. Lesions that remained at 8-week appointment were re-treated according to the original randomization. Patients who were retreated returned at 24 hours, and again at 1-week post second treatment.

Ninety-six percent (233/243) completed the study. Reasons for not completing the study included: noncompliance (4 patients in the ALA group, 2 in the vehicle group), patients who requested withdrawal (1 in the ALA group), death unrelated to the study (1 in the ALA group), and other (1 patient in the ALA group, 1 patient in the vehicle group).

Table 6 : Exclusion Criteria for Piacquadio
History of cutaneous photosensitization or porphyria, hypersensitivity to porphyrins, or photodermatosis
Use of photosensitizing drugs within a given time frame of study start
Very hyperkeratotic, grade 3 (on a 0-3 scale) AK lesions among the target lesions
Use of topical medications such as corticosteroids, alpha-hydroxy acids, or retinoid use on the face or scalp within 2 weeks before study entry

Systemic steroid therapy within 4 weeks before study entry
Cryotherapy to the target lesions
Laser resurfacing, chemical peels, topical application of fluorouracil or masoprocol for the treatment of AKs within 2 months before study entry
Systemic treatment with chemotherapeutic agents, psoralens, immunotherapy, or retinoid use within 2 months be- fore study entry.

Study Results: The main outcome measured was clinical response based on lesion clearing at week 8, however, complete response rates for patients with 100% AK clearing were measured at 8 weeks and 12 weeks. At 8 weeks, 66% (109/166) of patients who received ALA had a 100% clearance rate when compared to 11% (6/55) with the vehicle. At 12 weeks, 73% (109/149) of patients who received ALA had a 100% clearance rate compared to 8% (4/52) for vehicle ($P < 0.001$ at weeks). The ALA response rate at week 12 included 30% (55/181) of patients who required a second treatment at 8 weeks. Individual AK lesions, independent of how many lesions were treated with ALA, cleared at 8 weeks were 83% (1046/1258) compared to 91% (1019/1114) at 12 weeks. The response rate for vehicle treatment was 31% (139/455) at 8 weeks and 25% (109/428) at 12 weeks. The 95% confidence interval for the difference in response rates between 8 and 12 weeks was 47.9% to 57.3% and 61.6% to 70.4%, respectively. Data in table 7 also includes total number of lesions treated.

Table 7 : Subjects with 100% AK clearance rate at 8 and 12 weeks

	ALA Group	Vehicle Group
Total No. of patients treated	181	62
Week 8	109/166 (66%)	6/55 (11%)
Week 12*	109/149† (73%)	4/52 (8%)
Total No. lesions treated	1403	506
Week 8	1046/1258 (83%)	139/455 (31%)
Week 12*	1019/1114 (91%)	109/428 (25%)

*week 12 response rates include 55 (30%) of 181 patients who received a second treatment.
† Week 12 response rate for patients with only 1 treatment was 87%; week 12 response rate for patients with 2 treatments was 41%.

Study Critique: Strengths of this study includes the study design of being an investigator-blinded randomized placebo-controlled study. Additional strengths include the analysis of individual lesions being treated. This helped to provide larger numbers for data analysis.

This study was hindered by the small sample size and the method used to randomize the participants. As a result of this type of randomization, an unequal number of participants received treatment versus vehicle. Additionally, the rationale for the use of a 3:1 drug-vehicle ratio was not discussed in the research article.
The investigators applying the photosensitizing agent were unblinded, which could create some bias during the application of the medication. While the use of spot treatment and counting the number of lesions is helpful to quantify the efficacy of ALA and PDT, the methods do not

provide efficacy on field treatment, which would theoretically be more effective in treating subclinical AKs and diffuse disease. There may be some selection bias here as well, since patients were excluded if they had evidence of advanced AKs and investigators only spot treated clinically significant lesions.

Another hindrance of this article is that the study only included people of lighter skin tones. Although the study used the Fitzpatrick skin type I through IV, it did not include Fitzpatrick skin types V and VI, which includes brown, dark brown and black skin. Additionally, there was no delineation as to whether the skin types I-IV included only European descent or if it expanded to other "white races" such as South Asian, Middle Eastern and North African descent. Furthermore, there was no description of the locations of the 16 sites where the studies were performed. This has potential to impact study results as these locations could be experiencing seasonal variations and also discrepancies in the strength of ultraviolet rays from the sun. Lastly, the study had a large discrepancy between male and female study participants without explanation.

Study #3:
A Randomized, Blinded, Bilateral intraindividual, Vehicle-Controlled Trial of the Use of Photodynamic Therapy with 5-Aminolevulinic Acid and Blue Light for the Treatment of Actinic Keratoses of the Upper Extremities. Taub et al.[6]

Objective: To determine and compare the efficacy and tolerability of photodynamic therapy using 20% 5-ALA with blue light versus ALA vehicle with blue light for treatment of AKs on the dorsal hand and forearm.

Study Design: This study was a randomized, blinded, bilateral intraindividual, vehicle controlled study of 15 participants (11 females, 4 males), ages 42-79 (mean age 55.8 years), of Fitzpatrick skin types I-III with four or more AK lesions on the dorsal sides of both hands and forearms. See Table 6 for exclusion criteria.

Participants were randomized to receive ALA (active product) on one dorsal hand and forearm and vehicle (placebo) on the contralateral dorsal hand and forearm. Both ALA and vehicle were first applied to individual AK lesions, then allowed to dry. A second application was then applied evenly and liberally in small circles to cover the entire dorsal hand and forearm surface and allowed to dry. The entire treatment area was then occluded with plastic wrap and latex gloves, then allowed to incubate for 120 minutes. After incubation, all treated surfaces were washed with mild cleanser and water. Surfaces were then exposed to blue light for 1000 seconds (16 min, 40 seconds), which provided approximately 10J/cm2 of 417-nm spectral peak light at 10 mW/cm2 output.

A total of two treatments were completed 8 weeks apart (visits 1 and 3). Follow up evaluation was done 48 hours after treatment (visits 2 and 4), and a final evaluation was done approximately 4 weeks after completion of the 2nd treatment (visit 5). Efficacy was evaluated by

the number of lesions present at baseline, visit 3, and visit 5. All 15 subjects completed the study.

Table 8 : Exclusion Criteria for Taub
Pregnancy or Lactation
History of cutaneous photosensitization
Porphyria
Hypersensitivity to porphyrins or photodermatosis
Any conditions with associated immunosuppression (e.g., HIV, systemic malignancy)
Skin condition that was unsafe, could interfere with study evaluation, or would require treatment that could interfere
Fitzpatrick Skin Types V-VI
Enrollment in another study
Tanning or excessive sunlight during study period
Use of keratolytics including urea (>5%), alpha hydroxy acids (>5%), salicylic acid (>2%) within 2 days of initiation of treatment
Retinoids (tazarotene, adapalene, tretinoin, and retinol) within 4 weeks of initiation of treatment
Cryotherapy, microdermabrasion, ablative laser, or chemical peel treatment within 8 weeks of enrollment
Use of 5-fluouracil, imiquimod, or 5-aminolevulinic acid PDT 6 months before study initiation
Systemic retinoids within 6 months of study initiation
Systemic immunosuppression within 3 months of study initiation

Study Results: The main study outcome was median lesion count at 4 weeks after the 2nd treatment (visit 5), which was significantly lower than at baseline in both ALA and vehicle sides. The mean lesion count reduction were 58.4% and 24.8% for ALA and vehicle sides, respectively. The reduction was significantly greater for the ALA-treated side than the vehicle-treated side (P=0.0004) by the paired *t* test. While the mean lesion count reduction was significant, only one participant achieved 100% clearance rate at the 5th visit on the ALA-treated side.

Table 9 : Results of Taub Study		
	ALA Side	Vehicle Side
Subjects with 100% AK Clearance Rate		
Week 8 (visit 3)	0/15 (0%)	0/15 (0%)
Week 12 (visit 5)	1/15 (6.7%)	0/15 (0%)
Subjects with ≥75% AK Clearance Rate		
Week 8 (visit 3)	2/15 (13.3%)	0/15 (0%)
Week 12 (visit 5)	3/15 (20%)	1/15 (6.6%)

Study Critique: Some advantages of this study include its use of contralateral placebo, which would theoretically reduce any subject-subject variability. This does have a drawback, since most adults obtain more sun exposure on one side of the body when driving over their lifetime,

and it is not clear if every subject had the same side of the body treated with ALA versus the vehicle. Another advantage is that they study does not exclude advanced AKs.

While this study did enroll a higher percentage of females than males as compared to the previous studies, it is hindered by the small sample size. There is no mention of the number of lesions treated per subject, only that all subjects had at least 4 clinical AK lesions on both forearms and hands. Additionally, it is not clear if researchers were blinded at application of the photosensitizer or at evaluation.

Discussion:

Actinic keratosis is a common condition that carries the risk of progression to squamous cell carcinoma. Treatment and prevention of AKs can therefore reduce the incidence of a malignancy that carries the potential for metastasis. Multiple treatments exist to treat AKs, but are limited by their efficacy, patient compliance, and side effects that often include skin irritation, pain, and erythema. The purpose of this review is to determine if photosensitization with ALA and blue light exposure is effective and tolerable in the treatment of AKs.

An overview of the 3 studies is provided (Table 10). While Pariser et al had five different groups, each with difference incubation times, only the data for the 2 hour incubation group has been used to compare results, as it is similar to the Taub study. The Pariser et al and Taub studies are most similar to each other – with relatively similar age groups, manner of application, and incubation time. The Pariser et al and Piacquadio et al studies were similar in their study size, gender, treatment area, and blinding. Piacquadio et al differed heavily between the two by only spot treating clinically visible AKs, unlike the others who also applied the ALA with a broad application (field treatment). The Piacquadio et al study also incubated for far longer (14-18 hours, compared to 2 hours). All three studies used the same light source and time of exposure to light.

Table 10 : Overview of Studies

	Pariser et al	**Piacquadio et al**	**Taub et al**
Patients, N	234	243	15
Age	40 – 80 years old (mean 60)	35 - 89 years old (mean 66.5)	42 – 79 years old (mean 55.8)
Gender	M – 211 F – 23	M – 203 F – 40	M – 4 F – 11
Skin Types	Fitzpatrick Types I - V	Fitzpatrick Types I – IV	Fitzpatrick Types I – III
Application	One spot treatment for visible AKs, then two broad applications	Two spot treatment applications for visible AKs	One spot treatment for visible AKs, then one broad application
Treatment Areas	Face or scalp	Face or scalp	Upper extremities
Control	Randomized control group with vehicle application	Randomized control group with vehicle application	Intraindividual control with vehicle application on contralateral side

Incubation Time with ALA	2 hours	14-18 hours	2 hours
Occlusion with Incubation	No	No	Yes
Light Source	Blue light (10 J/cm^2)	Blue light (10 J/cm^2)	Blue light (10 J/cm^2)
Time Exposed to Light	1000 s	1000 s	1000 s
Total Number of Treatments per Subject	2 treatments only in those with remaining lesions at week 8	2 treatments only in those with remaining lesions at week 8	2
Blinding	At efficacy assessment	At efficacy assessment	Unclear
Statistical Analysis	Intention to Treat	Per-protocol	Unknown

It should be noted that Taub failed to disclose if the investigators were blinded at the efficacy assessments, even though the study title implies use of blinding. Additionally, Taub included occlusion of the photosensitizer (with plastic wrap and gloves) during incubation, which theoretically improves efficacy of treatment.

The statistical analyses differed as well. Pariser et al employed intention to treat analysis, and used last-observation-carried-forward for dropouts or missing data. Piacquadio et al used per-protocol analysis, excluding patients if they did not return for their light treatment within 14-18 hours, or if their light treatment did not last at least half the prescribed course (1000 seconds). Patients whose visits fell outside the predefined treatment window, or if they had missing responses were excluded from analysis of that visit. Taub did not explicitly state which statistical analysis was used, however, all 15 subjects completed the study.

All three studies reported 100% and 75% AKCR, which are summarized in Table 11. Piacquadio et al had the highest rate of 100% clearance at both weeks 8 and 12. This is likely due to the 14-18 hour incubation period, as compared to the 2 hour incubation period used in the other studies. Pariser et al had the highest rate of ≥75% AKCR at weeks 8 and 12. Note that in subjects with 100% AKCR, there was minimal difference between weeks 8 and 12 in Pariser et al and Piacquadio et al – likely because those who had already responded 100% did not warrant a second treatment. The number of subjects who had ≥ 75% AKCR in these studies did improve between weeks 8 and 12, suggesting that subsequent treatment continued to increase AKCR, although seemingly by a lower percentage. This is in contrast to the Taub study, which treated all subjects with a second treatment, therefore increasing the number of subjects who were able to achieve 100% AKCR at week 12.

Table 11: Overview of Results

	Subjects with 100% AKCR at Week 8		Subjects with 100% AKCR at Week 12		Subjects with ≥ 75% AKCR at Week 8		Subjects with ≥ 75% AKCR at Week 12	
Study	ALA	VEH	ALA	VEH	ALA	VEH	ALA	VEH
Pariser et al	7/48 (14.5%)	0/46 (0%)	7/48 (14.5%)	1/46 (2.1%)	13/48 (27.1%)	1/46 (2.2%)	24/48 (50%)	5/46 (10.9%)

Piacquadio et al	109/166 (65.6%)	6/55 (10.9%)	109/149 (73.1%)	4/52 (7.7%)	19/166† (11.4%)	4/55† (7.2%)	24/149† (16.1%)	3/52† (5.7%)
Taub et al	0/15 (0%)	0/15 (0%)	1/15 (6.6%)	0/15 (0%)	2/15 (13.3%)	0/15 (0%)	3/15 (20%)	1/15 (6.6%)
*p value was only calculated based on mean lesion reduction (p = 0.0004), not 100% clearance rate †Values actually published included the number of subjects with 100% AKCR – values in this table reflect subjects who had more than 75% AKCR, but less than 100% AKCR								

The p-values for all studies were significant, although the p-value provided by Taub was calculated based on mean lesion count reduction, which is not applicable to just the 100% or 75% AKCR comparisons.

All studies reported side effects of stinging and burning during treatment which subsided after treatment. Erythema and edema were also common, and improved with time. This response is comparable to that of topical treatments used in treatment of AKs, such as topical 5-fluorouracil, imiquimod, and diclofenac gel. However, ALA with blue light can be done in office and does not require any daily application of medication. Compliance with topical medications can be poor, since patients will avoid applying the medication once they realize the skin reaction it causes.

As noted previously in the results section, a critique of the studies was the exclusion of darker skin types. While patients of darker skin are less likely to develop AKs and skin cancers from sun exposure, all patients can develop cutaneous SCC from human papillomavirus (HPV) infection[7]. Clinicians and researchers have begun exploring the use of ALA with blue light in treating cutaneous SCCis and superficial basal cell carcinoma (although recurrence rates are higher). This treatment could perhaps in the future extend to treat cutaneous SCC caused by HPV. In that case, the treatment should also be tested on patients of darker skin types.

Conclusion:

Clinical Question: In adults with diagnosed actinic keratosis, is the treatment with photodynamic therapy (PDT) and topical aminolevulinic acid (ALA) as effective as placebo in inducing complete lesion response?

Overall, PDT with topical ALA offers an effective treatment alternative for individuals with AKs on chronically sun exposed skin affecting the head, neck, arms and hands. Topical ALA with PDT can be safely performed in office on single lesions or multiple lesions with minor adverse side effects that are noted to improve and resolve over time. Additionally, lesions that remain after an initial treatment may safely undergo additional treatments to the affected area to further improve AK clearance rates and diminish the progression to squamous cell carcinoma.

Further research should be performed to include the full spectrum of Fitzpatrick skin types (I-VI), larger sample sizes, and longer lengths of follow up to fully assess the long-term efficacy of PDT with ALA. Additionally, further investigation on the shortest effective incubation time may help to improve side effects such as stinging and burning associated with treatment.

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