Photodynamic Therapy with Topical Aminolevulinic Acid vs Placebo in the Treatment of Actinic Keratosis

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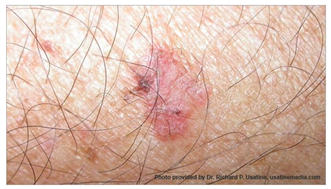
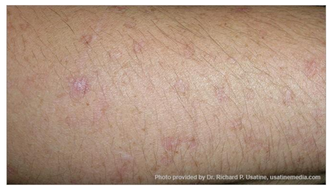
Introduction

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 can progress into squamous cell carcinoma (SCC).[1] SCC is the second most common type of 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 treatment of AKs, especially in widespread cases.[3] Although cryotherapy is one of the most common treatments for single lesions, field treatment with topical agents is preferred for subclinical lesions and diffuse disease. Topical agents include fluorouracil, imiquimod, and diclofenac.[3] These agents cause photosensitivity, erythema, edema, erosions and pain for the entire duration of treatment.[3] Although convenient, they 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 compliance. The provider applies a photosensitizing agent, called 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 healthy skin cells are unaffected, as they do not absorb the phototoxic agents. Although patients experience discomfort during treatment, side effects are 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.

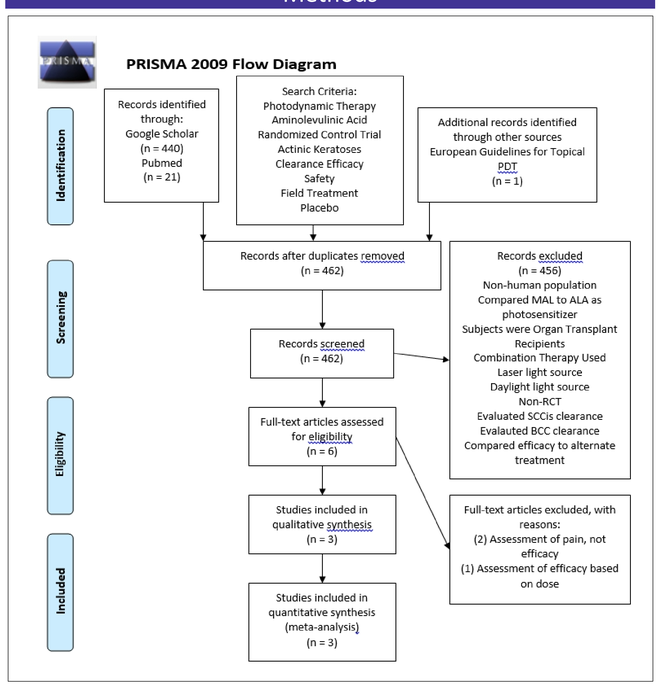




Clinical Question

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?

Methods



Results

Table 1: 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/cm²)	Blue light (10 J/cm²)	Blue light (10 J/cm²)
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

Table 2: Overview of Results

	Subjects with 100% AKCR Week 8		Subjects with 100% AKCR Week 12		Subjects with ≥ 75% AKCR Week 8		Subjects with ≥ 75% AKCR Week 12	
	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

Table 3 : 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

Discussion

An overview of the 3 studies is provided (Table 1). 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. Piaquadio 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 study also had far longer incubation times (14-18 hours compared to 2 hours). All three studies used the same light source and time of exposure to light.

All three studies reported 100% and 75% AKCR (Table 2). 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. 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 a 100% AKCR did not warrant a second treatment. The number of subjects with ≥ 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.

Conclusion

PDT with topical ALA offers an effective treatment alternative for individuals with AK's 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 remained 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.

Acknowledgements

We would like to thank Dr. Massey for her unending wisdom and her constant supply of baked goods. We love biostats.

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