

ORIGINAL ARTICLE

Comparison of therapeutic agents' short-term effects on facial and scalp actinic keratosis: A network meta-analysis

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Abstract

Background: Care for actinic keratosis (AK) can be improved with more knowledge on the relative of effect of indicated therapies.

Objectives: Using network meta-analyses, we quantitatively determined the comparative “short-term” effects of interventions in adults with facial and scalp AK.

Methods: On February 28, 2023, evidence from the peer-reviewed literature was systematically obtained from OVID, the Cochrane Central Register of Controlled Trials and [ClinicalTrials.gov](https://www.clinicaltrials.gov). We analyzed data from studies published in English, of a trial design, and investigating the effect of an actinic keratosis monotherapy. Patient complete clearance, patient partial clearance or lesion-specific clearance across adults were analyzed at 8–12 weeks after therapy. Patient complete clearance pertained to proportion of participants who experienced complete clearance of actinic keratosis lesions; patient partial clearance corresponded to percentage of subjects who achieved at least 75% clearance of actinic keratosis lesions; lesion-specific clearance represented the percentage of all lesions that were cleared. In the main (i.e., base) analyses, nodes were analyzed only at the level of the agent.

Results: Data from a total of 84 studies were used—across which 22 active agents were identified. Estimates of interventions' surface under the cumulative ranking curve rankings and (pairwise) relative effects were estimated. Across the three outcomes, fluorouracil 5% was ranked the most effective.

Conclusions: Our work is the first to provide information on covariate-adjusted relative effects of actinic keratosis therapies— including the more recently reported treatments—for the face and scalp; this knowledge may help physicians and patients make more informed decisions.

KEYWORDS

actinic keratosis, face and scalp, network meta-analysis, short-term efficacy, treatment

1 | INTRODUCTION

Actinic keratosis (AK), the third most common reason to visit a dermatologist,¹ is majorly caused by chronic exposure to ultraviolet radiation^{1,2}; it is a concerning condition as it can—if untreated (or incompletely treated)—advance to skin cancer (i.e., cutaneous squamous cell carcinoma).^{3,4} This condition's prevalence varies geographically; for instance, in Europe and the United States, the reported prevalence rates vary between 1.4%–37.5% and 17.3%–29.3%, respectively.^{5–8}

AK interventions can be broadly categorized into lesion-targeted therapies or field-targeted therapies.⁹ To address evidence gaps which, in turn, can aid in providing optimal care, we compared the short-term effects of therapies for facial and scalp AK in adults; a secondary aim of the current study was to determine the relative short-term safety of AK interventions.

2 | MATERIALS AND METHODS

We performed a systematic review with network meta-analyses (NMAs)—and the reporting thereof was in accordance with the “Preferred Reporting Items for Systematic Reviews and Meta-analyses” guideline for NMAs¹⁰; in addition, our work was also guided by recommendations from the literature.^{11–13} The protocol for this study was published in the “international platform of registered systematic review and meta-analysis protocols”(INPLASY) (Appendix S1). All analyses were conducted in *RStudio* (version 2022.02.3+492).¹⁴ We also reviewed clinical guidelines to inform the conduct of our work, and Wessely et al.'s critical appraisal of existing guidelines for AK care made the German Association of Scientific Medical Societies S3 guidelines our choice of reference for clinical guidelines.^{12,15}

2.1 | Search process

Quantitative evidence was extracted from eligible studies after systematically searching the peer-reviewed literature through electronic databases (i.e., OVID and Cochrane Central Register of Controlled Trials) and a trial registry ([ClinicalTrials.gov](https://clinicaltrials.gov)), on February 28, 2023. Evidence was also identified through reference mining. Deduplication was performed using the “Systematic Review Accelerator Deduplicatpor.”¹⁶ The screening of full-text, titles, and abstracts was managed by Rayyan software.¹⁷ The screenings and data extraction were each independently conducted by two authors (SPR and SH-N)—and disagreements were resolved through discussion with a third author (AKG). Collated data included information pertaining to authorship, therapeutic regimen, and patients' demographic information (e.g., age and sex).

2.1.1 | Identification of eligible studies

In light of the patient-intervention/comparator-outcome framework,¹⁸ an identified study's data was eligible for analyses if it was:

(i) of a trial design (randomized or non-randomized), (ii) published in English, and (iii) investigated the impact of an AK monotherapy in terms of three outcomes (we selected outcomes quantified within 8–12 weeks posttreatment), namely, “patient complete clearance,” “patient partial clearance,” and “lesion-specific clearance.” With the exception of “methyl aminolevulinate-mediated photodynamic therapy (PDT-MAL) with laser,” “diclofenac and hyaluronic acid (DHA) gel,” and “fluorouracil 0.5% with salicylic acid 10%,” studies that investigated combination therapy were excluded; we made these three exceptions to our eligibility criteria a priori (i.e., before the start of the systematic search) as we deemed them clinically relevant.

2.1.2 | Definition of outcome variables

Primary outcomes

In our study, “patient complete clearance” corresponded to proportion of patients who achieved complete clearance of AK lesions within 8–12 week post-therapy; likewise, “patient partial clearance” represented the percentage of subjects whose AK lesions were cleared by at least 75% within 8–12 weeks after treatment; “lesion-specific clearance” referred the percentage of AK lesions across all patients (i.e., percentage of total lesion count at baseline) that was cleared within 8–12 weeks posttreatment.

For each primary outcome, we conducted network-wide evaluation of evidence quality using the “Confidence in Network Meta-Analysis” (CINeMA) tool: risk of bias across nodes was summarized as “average risk of bias”; reporting bias was set to low throughout; the cut-off for a clinically important effect size was a value greater than 1.00.¹⁹

Secondary outcomes

After eligible studies were identified, we reviewed them to obtain any data pertaining to discontinuation of an AK therapy (due to any adverse event) within 8–12 weeks after treatment.

2.2 | Quantitative analyses

Our analyses amalgamated randomized and non-randomized (i.e., observational) evidence through naïve pooling—an approach the literature supports.²⁰ For each of our primary outcomes, we produced a network plot, the visual depiction of interventions that have been compared in head-to-head trials. We checked statistical consistency for the main analyses using node-splitting analyses—where non-significant ($p \geq 0.05$) estimates indicated that no inconsistency has been detected. We conducted a main (i.e., “base”) analysis and a sensitivity analysis for each primary outcome. Wherever possible, the intention-to-treat principle was applied. In all analyses, significance level (i.e., alpha) was set to 5%. For our primary outcomes, the surface under the cumulative ranking curve (SUCRA) values estimated from main and sensitivity analyses were presented in “kilom plots.”²¹

Node-splitting analyses is a quantitative technique whose results are used to determine whether direct and indirect evidence

are statistically consistent. An agents SUCRA value is a ranking metric that quantifies its relative “impact”—be it in terms of “effectiveness” or “safety”; the value of SUCRA is between 0 (or 0%) and 1 (or 100%).

2.2.1 | Geometry of our networks

Nodes were analyzed at the “agent-level” in our main analyses: so, interventions with same agent (e.g., imiquimod 5%) but different regimens (e.g., two times per week for 16 weeks vs. three times per week for 4 weeks) were collapsed into a single node.^{22,23}

2.2.2 | Network meta-analyses

For our four outcomes, a Bayesian NMA, with uniform priors, was conducted. Fixed-effects estimates were chosen because their model fit—as per deviance information criterion values—were better than those of the random-effects model. Given that proportions were compared for all outcomes, the binomial likelihood (logit link) was used. The NMAs were conducted with the *multinma* (Phillippo, 2022) R package which uses the “Stan” programming language; each NMA estimated relative effects for every possible pairwise comparison; relative effects were reported as mean difference of the log odds—along with their corresponding 95% credible interval (CI). Agents' SUCRA values were also estimated. If the mean difference and lower bound of the confidence interval is a positive value, the difference between the two interventions is statistically significant.

2.2.3 | Sensitivity analyses

We examined whether results of our main analyses would starkly differ if regimen variation (i.e., the different dosages) was accounted for. Hence, for our sensitivity analyses, we extended the main analyses by conducting a covariate-adjusted NMA (i.e., a network meta-regression); covariates were the following three exploratory variables: frequency of treatment, duration of treatment and the range of AKs evaluated in the study (which was somewhat “proxy” variable for number of AK lesions at baseline).

3 | RESULTS

3.1 | Eligible studies

The schematic in Figure 1 summarizes the search process for the identification of 243 studies during screening and reference mining, of which data from 84 studies were used across all analyses; study characteristics are detailed Table S1. A bibliography of the 84 studies is provided in Appendix S2. The main NMA for patient complete clearance, patient partial clearance and lesion-specific clearance

used data from 58, 30 and 52 of the 84 trials (Table S1). Most of the studies were randomized—and of a whole-head design (Table S1). Network-wide evaluation of evidence quality, for our primary outcomes, have been provided in Tables S2–S4. For all our primary outcomes, results from node-splitting analyses showed that there were no major disagreements between direct and indirect evidence (Appendix S3).

3.2 | Relative effect of therapies

3.2.1 | Network

Across the 84 eligible studies, the following 22 unique agents were identified: (i) hexyl aminolevulinate-mediated photodynamic therapy (PDT-HAL), (ii) PDT-MAL with daylight / artificial daylight/ artificial white light (i.e., we grouped daylight, artificial daylight, and artificial white light together), (iii) PDT-MAL with blue light, (iv) PDT-MAL with red light, (v) PDT-MAL with laser, (vi) aminolevulinic acid-mediated photodynamic therapy (PDT-ALA) with blue light, (vii) PDT-ALA with red light, (viii) PDT-ALA with 10% ALA-gel (10% ALA-gel is a nanoemulsion with hydrogen chloride gel), (ix) fluorouracil 5%, (x) imiquimod 5%, (xi) imiquimod 3.75%, (xii) imiquimod 2.5%, (xiii) resiquimod, (xiv) ingenol disoxate gel, (xv) cryotherapy (which is also sometimes referred to as cryosurgery), (xvi) tirbanibulin ointment, (xvii) carbon dioxide laser ablation, (xviii) ingenol mebutate, (xix) fluorouracil 0.5%, (xx) DHA gel, (xxi) trichloroacetic acid, and (xxii) fluorouracil 0.5% combined with salicylic acid 10%. In the networks for patient partial clearance, patient complete clearance and lesion-specific clearance, the effects of 16, 19, and 19 unique agents were compared. The kilim plot in Figure 2 presents these interventions' SUCRA values from both main and sensitivity analyses. Furthermore, after examining distribution of variables as per study characteristics, we deemed our networks to be transitive.

3.2.2 | Relative efficacy of AK therapies

The network graph for patient complete clearance is presented in Figure 3; the league table in Figure 4 presents the pairwise relative effects, in terms of complete clearance, across a subset of the agents identified. Network plots for the other two outcomes are presented in Figures S1 and S2. Relative effects for pairwise comparisons across all agents—from both main and sensitivity analyses of the primary outcomes—are also presented in the Tables S5–S10.

Across all primary outcomes, fluorouracil 5% was ranked the most effective across main analyses—while placebo/vehicle was ranked the least effective (Figure 2). All active agents, across the respective primary outcomes were significantly ($p < 0.05$) more effective than placebo/vehicle (Figure 4; Tables S5, S7, and S9).

Resiquimod was significantly ($p < 0.05$) more effective than imiquimod 2.5% (mean difference in log odds = 1.4, 95% CI: 0.78–2.00) and imiquimod 3.75% (mean difference in log odds 1.1, 95%

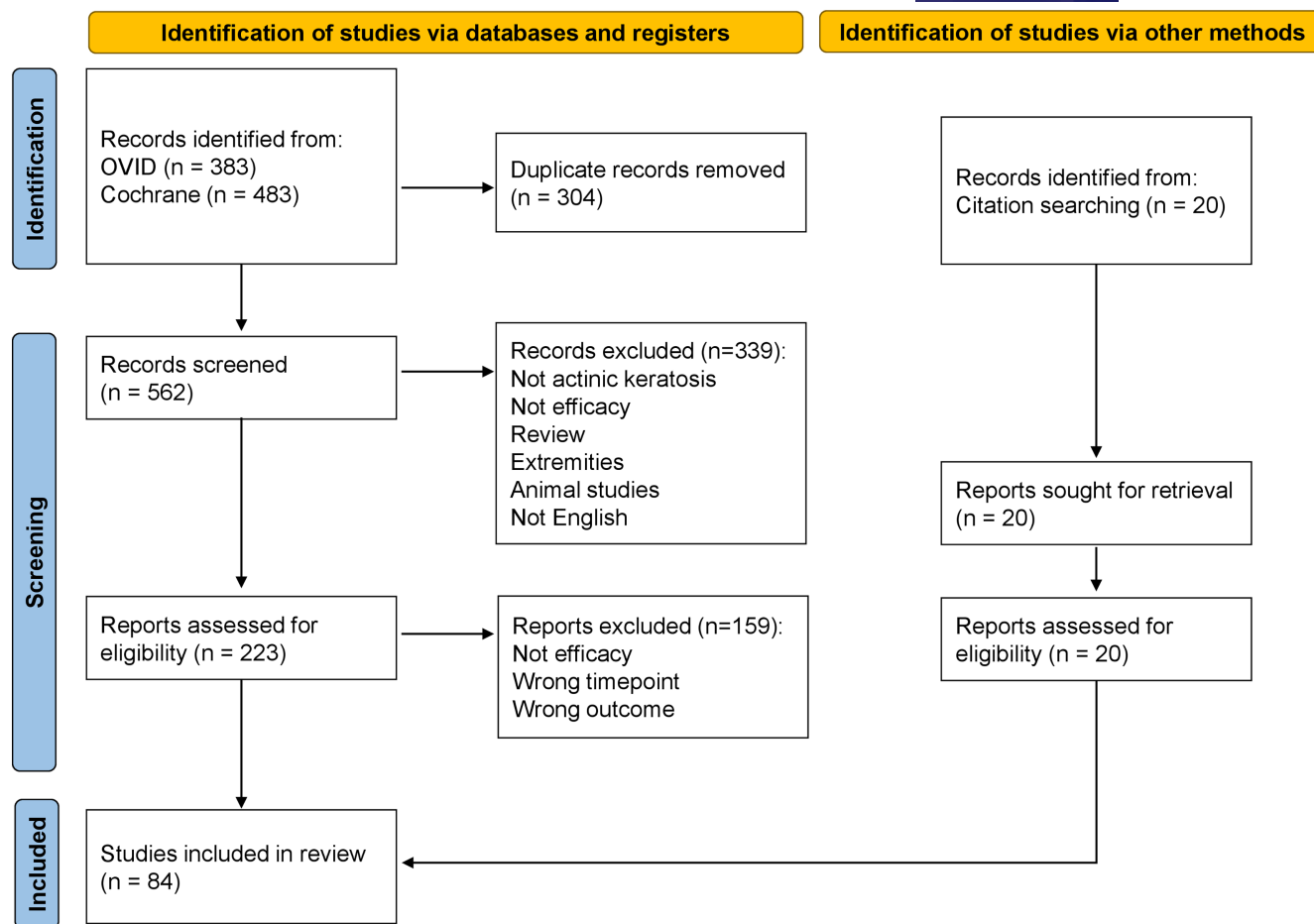


FIGURE 1 Schematic for the identification of studies whose data were used for analyses.

CI: 0.50–1.72) in terms of patient complete clearance; however, the effect of resiquimod, for this primary outcome, did not significantly ($p \geq 0.05$) differ from that of the imiquimod 5% (Table S5). These findings for the three concentrations of imiquimod and resiquimod were similar for patient partial clearance (Table S7). For lesion-specific clearance, there was no outcome data for resiquimod (Table S9).

For patient complete clearance and patient partial clearance, imiquimod 5% was significantly ($p < 0.05$) more effective than the 3.75% concentration (mean difference in log odds = 1.1, 95% CI: 0.5–1.6)—whose effect, in turn, was superior ($p < 0.05$) to the 2.5% concentration (mean difference in log odds = 0.3, 95% CI: 0.02–0.5) (Tables S5 and S7).

Fluorouracil 5% was significantly ($p < 0.05$) more effective than cryotherapy in terms of patient complete clearance (mean difference of log odds = 1.9, 95% CI: 0.7–3.4), patient partial clearance (mean difference of log odds = 0.8, 95% CI: 0.2–1.5), and lesion-specific clearance (mean difference of log odds = 3.1, 95% CI: 2.7–3.5) (Figure 4; Tables S5, S7, and S9).

Among the identified agents, DHA gel was the least effective—in terms of patient complete clearance and lesion-specific clearance: in other words, all the other comparators were significantly ($p < 0.05$) more effective than DHA gel. Outcome data for patient partial clearance insofar as DHA gel was absent (Tables S5 and S9).

For patient complete clearance, the effects of PDT-ALA with blue or red light were not significantly different ($p \geq 0.05$) (Table S5). However, for lesion-specific clearance, PDT-ALA with red light was more effective than with blue light (mean difference of log odds = 0.7, 95% CI: 0.5–0.9) (Table S9).

The SUCRA values and estimates of relative effects from our sensitivity analysis highly corroborated those of main analyses (Tables S6, S8 and S10).

3.3 | Relative safety of AK therapies

For all-cause discontinuation rate within 8–12 weeks post-therapy, outcome data was available for all 22 unique agents. The SUCRA rankings thereof are presented in increasing order of safety in Appendix S4; lower SUCRA values corresponds to lower rates of discontinuation. All pairwise comparisons for relative safety are presented in Table S11. Patients treated with the ingenol disoxate gel were the least likely to discontinue from treatment, and is statistically different from that of placebo/vehicle (Table S11); this difference could be explained by patients assigned to the placebo/vehicle arm experiencing inadequate treatment response or disease relapse that led to study withdraw.

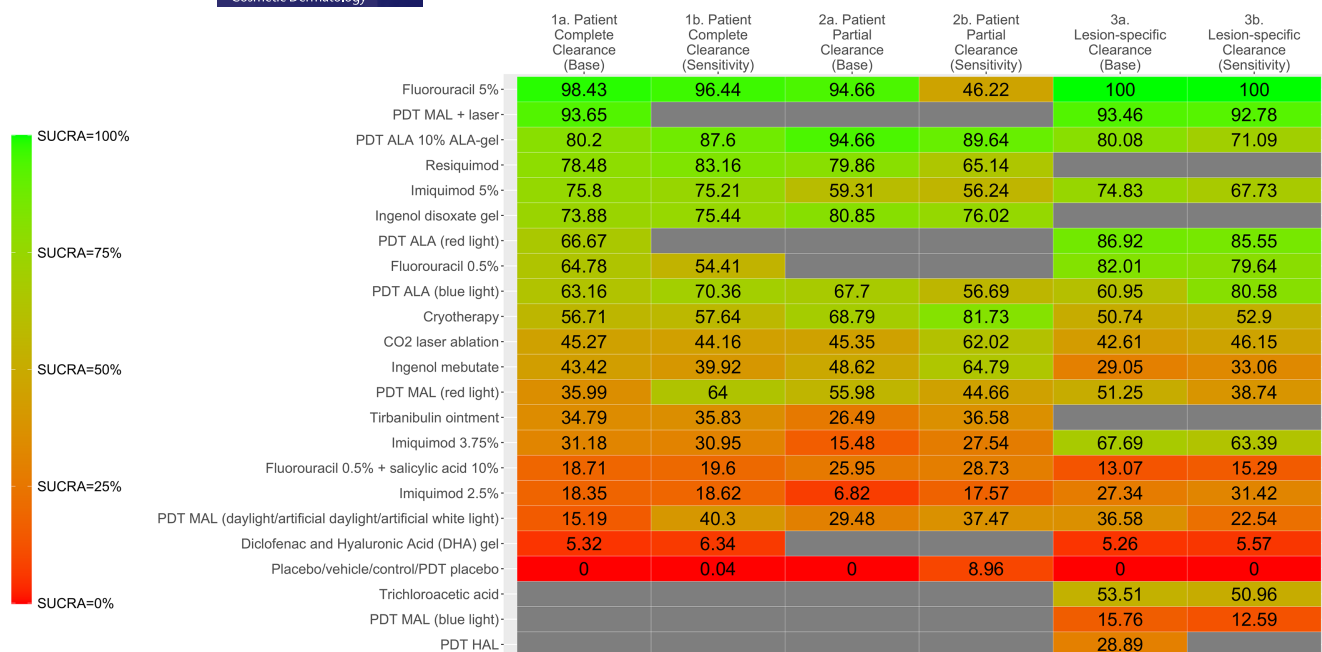


FIGURE 2 Agents' surface under the cumulative ranking curve (SUCRA) values from main (i.e., base) and sensitivity analyses. All agents are listed in the decreasing order of SUCRA values from main (i.e., base) analysis for patient complete clearance (i.e., arranged based on the probability of achieving 100% clearance of AK lesions with 8–12 weeks of therapy). In base analyses, nodes were analyzed at the level of the agent; however, the sensitivity analyses extended the main analyses by adjusting for covariates (i.e., frequency and duration of therapy, number of AK lesions at baseline). PDT-ALA, aminolevulinic acid-mediated photodynamic therapy; DHA, diclofenac and hyaluronic acid; PDT-HAL, hexyl aminolevulinate-mediated photodynamic therapy; PDT-MAL, methyl aminolevulinate-mediated photodynamic therapy.

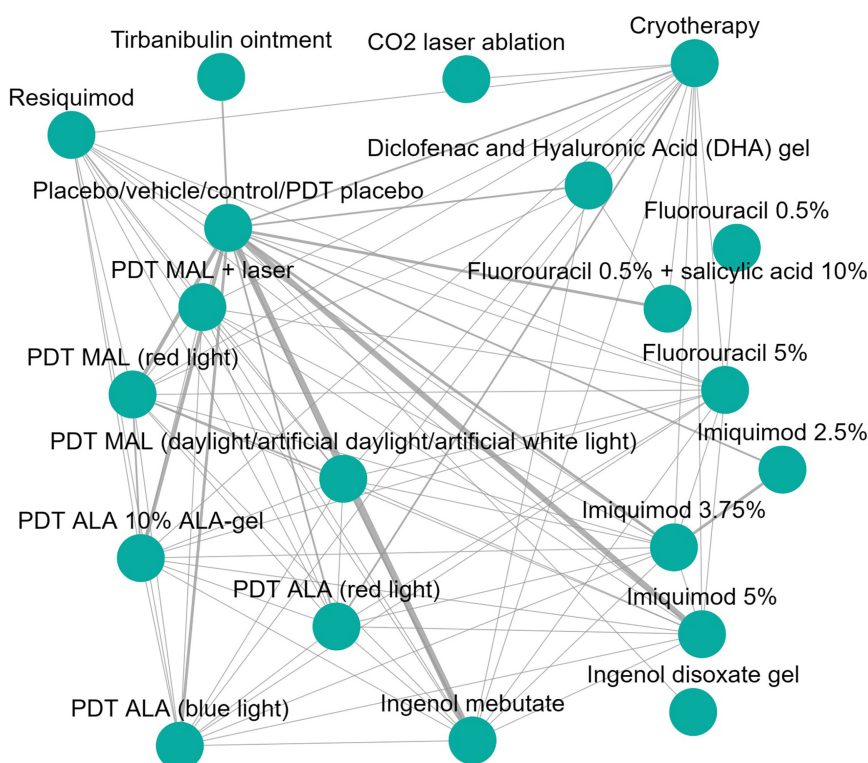


FIGURE 3 Network plot for patient complete clearance. Direct comparisons between interventions for the treatment of AK is depicted within a network plot; each node represents an intervention of interest, and an edge is represented by a line between nodes that corresponds to head-to-head comparisons (i.e., direct evidence) from included studies. PDT-ALA, aminolevulinic acid-mediated photodynamic therapy; DHA, diclofenac and hyaluronic acid; PDT-HAL, hexyl aminolevulinate-mediated photodynamic therapy; PDT-MAL, methyl aminolevulinate-mediated photodynamic therapy.

4 | DISCUSSION

Using the network meta-analytic technique, we attempted to address some of the current knowledge gaps in the AK literature

by providing statistical evidence for therapeutic agents whose effects have not been empirically investigated. We conducted an NMA study to determine the relative impact of AK therapies. The outcome measures for which we conducted quantitative evidence

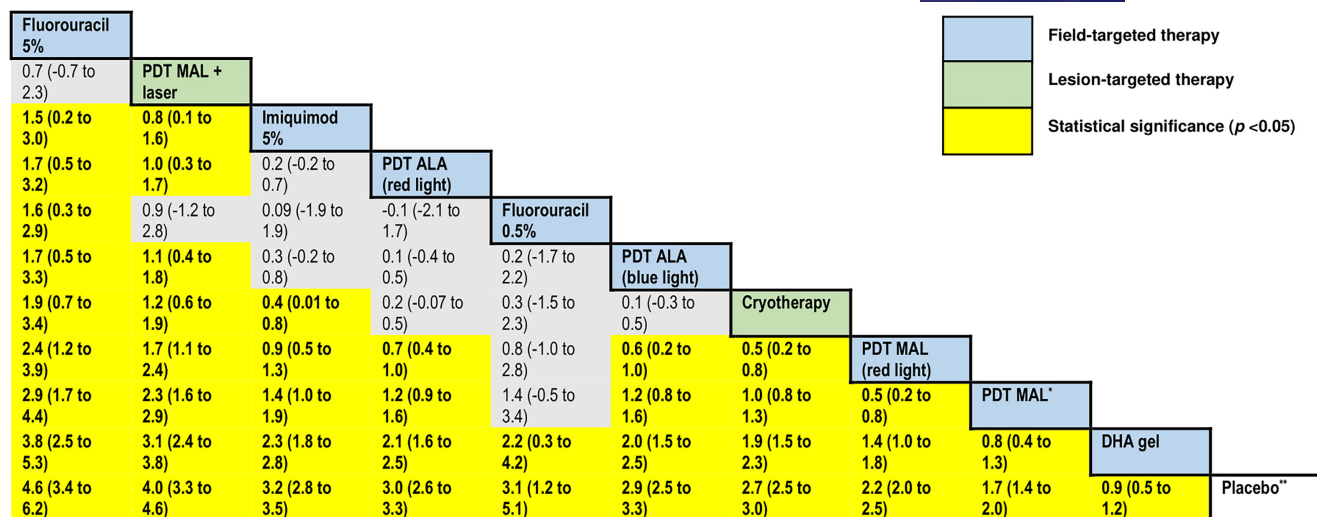


FIGURE 4 League table for the relative effects of actinic keratosis therapies for patient complete clearance (results from main analysis). This league table presents the pairwise effect of 12 (i.e., 11 agents + placebo/vehicle) of the 20 interventions identified for “patient complete clearance.” Herein, the point estimates (whose 95% credible interval are in parentheses) correspond to the mean difference in log odds. *PDT MAL (daylight/artificial daylight/artificial white light); **Placebo/vehicle/control/PDT placebo. PDT ALA, aminolevulinic acid-mediated photodynamic therapy; DHA, diclofenac and hyaluronic acid; PDT HAL, hexyl aminolevulinate-mediated photodynamic therapy; PDT MAL, methyl aminolevulinate-mediated photodynamic therapy.

syntheses are—as the German S3 guideline states—“critical effectiveness endpoints.”¹² Furthermore, two of our three primary outcomes were congruous with two of the six core outcomes that Reynolds et al.—after a Delphi consensus process—recommended for AK trials, namely, complete clearance of AKs, and percentage of AKs cleared.^{24,25} Though our eligibility criteria did include observational data, the majority of the included 84 studies were randomized.

Our findings reiterate results of other studies. In a single-blinded randomized trial, Jansen et al. found patients treated with fluorouracil 5% to have the highest probability of maintaining treatment response ($\geq 75\%$ AK clearance) compared to imiquimod 5%, MAL-PDT and ingenol mebutate 0.015%.²⁶ Previous NMA studies also reported fluorouracil 5% to be the most efficacious^{27,28}; additionally, the therapeutic impact of this agent was shown to be superior to cryotherapy and fluorouracil 0.5% combined with salicylic acid 10%.²⁸ Our results, along with those of previous NMAs,^{27–29} address the questions raised by Zouboulis—who inquired on cryosurgery’s therapeutic impact vis-à-vis other AK therapies.³⁰

Through the inclusion of newer studies, our work serves as an extension of a recently published NMA²⁹; for instance, inclusion of the trial by Meierhofer et al. that investigated PDT-ALA with 10% ALA-gel.³¹ Furthermore, by specifying the outcome assessment timepoint at 8–12 weeks, the design of our NMA minimizes time-varying confounding separate from previous NMAs.^{28,32}

Among the different doses of a given agent (e.g., imiquimod) our results showed a positive dose-dependent relationship. Furthermore, our statistical findings support Farr et al.’s theoretical expositions on resiquimod’s superiority over imiquimod.³³ In light of comments by Dirschka and Szeimies, the network meta-regressions of our

sensitivity analyses incorporated—as an exploratory variable—proxies for number of AK lesions at baseline: the authors’ comments critiqued other related studies on the consideration of this variable as it was essentially argued that such variable is correlated with disease severity which, in turn, can be an effect modifier.^{34,35}

PDT-ALA was significantly more effective than PDT-MAL in terms of patient complete clearance and lesion-specific clearance. PDT-ALA using the red light is also significantly different from blue light for lesion-specific clearance. Furthermore, the combinational use of laser with PDT-MAL therapy demonstrated a more favorable efficacy profile compared to PDT-MAL monotherapy, as well as PDT-ALA monotherapy.³⁶

One limitation of the current study is that evidence in non-English language was excluded from our work. Furthermore, we could not account for relevant effect modifiers—such as sunscreen use and frequency of ultraviolet radiation exposure,^{6,37–39} as constituent studies did not quantify them; there were also a scarce number of studies that utilized the Olsen grading system to classify AKs. Due to unstandardized reporting, we opted to use the all-cause study discontinuation rate instead of rates of specific safety signals which may limit the utility of our work for the treating physician. Lastly, results of the CINeMA evaluation identified sources of study bias concerning heterogeneities and incoherence likely due to our naïve-pooling of randomized and non-randomized evidence; however, results of our sensitivity analyses were in concordance with the main analyses. Further prospectively designed head-to-head studies are warranted to confirm our findings.

When there are several isolated hyperkeratotic AKs, lesion-directed therapies may be suitable; however, field-targeted treatments are able to treat less hyperkeratotic lesions as well as the surrounding actinically damaged skin. Compliance with therapy is in

part determined by whether the treatment is in office (cryotherapy, in-office PDT) or needs to be delivered at home; number and frequency of topical applications, and the adverse-effects profile.^{9,40,41}

To conclude, we addressed knowledge gaps pointed in the evidence base for AK therapies by using an arguably rigorous methodological approach; furthermore, the congruence of results between our main and sensitivity analyses supported the certainty of our findings. The singular timeframe for our outcomes not only contributes to the rigor of our approach, but also could help in prognoses: valid information on the agents' therapeutic impact at a specific time period can more accurately help quantify the risk estimates for development of malignancy—where malignancy is a consequence of having untreated (or poorly treated) AKs.^{3,4} Our results can be used to update clinical practice guidelines; future works can investigate the long-term effects of therapies for facial and scalp AKs.

5 | CONCLUSION

The study offers insights into the covariate-adjusted relative effects of various facial and scalp actinic keratosis therapies, including the latest treatments. The SUCRA values for 22 therapeutic agents indicate that fluorouracil 5% was ranked the most effective in terms of three outcomes: (a) patient complete clearance, (b) patient partial clearance, and (c) lesion-specific clearance within 8–12 weeks after treatment.

AUTHOR CONTRIBUTIONS

Conceptualization: AKG; data curation: MAB, TW, SPR, SH-N; formal analysis: MAB; investigation: AKG, MAB, TW, SPR; methodology: MAB, TW, SPR; project administration: AKG; resources: AKG; supervision: AKG, MT; validation: TW, SPR; visualization: AKG, MT; writing—original draft preparation: AKG, MAB, TW, MT; writing—review and editing: MAB, TW, SPR, SH-N, GM, VP, MT.

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CONFLICT OF INTEREST STATEMENT

AKG, MAB, TW, SPR, MT, and SH-N have no conflict of interest to declare. GM has served as a speaker and/or consultant and/or has been involved in scientific advisory boards for AbbVie, Almirall, Alumis, Bristol Myers Squibb, Celgene, Dermavant Sciences, Inc., DUSA/Sun, Eli Lilly, Evelo, Galderma, Horizon, Incyte, Janssen, LEO Pharma, Nobel-pharma, Ortho/Bausch Health, Organogenesis, Pfizer, Trevi, and UCB Biopharma. VP has no personal financial ties with any pharmaceutical company. He has received honoraria for speaker and/or advisory board member roles from AbbVie, Celgene, Janssen, Kyowa Kirin Co. Ltd, LEO Pharma, Novartis, Pfizer, Sanofi, UCB, and Union Therapeutics. In his role as Department Division Director of Dermatology at the University of Toronto, VP has received departmental support in the form of unrestricted educational grants from AbbVie, Bausch Health, Celgene, Janssen, LEO

Pharma, Lilly, L'Oréal, NAOS, Novartis, Pfizer, Sandoz and Sanofi in the past 36 months.

DATA AVAILABILITY STATEMENT

Supporting data are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The authors declare human ethics approval was not needed for this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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