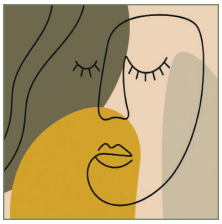

Acne Vulgaris in Skin of Color: A Systematic Review of the Effectiveness and Tolerability of Current Treatments

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Acne vulgaris is a common dermatosis frequently encountered in general dermatology and presents significant health-related quality of life and psychological challenges. Clinical studies on acne vulgaris in skin of color are limited; thus, it is likely that treatment recommendations to patients with darker skin types are drawn from trial data based on Caucasian skin. The aim of this study was to systematically review the effectiveness and tolerability of treatments used to treat acne vulgaris in patients with skin of color. A literature search was performed in the PubMed, Embase, and Scopus bibliographic databases, with a total of 1,477 retrieved articles, of which 1,316 were excluded after initial screening. Of the 93 studies assessed, 55 studies met our inclusion criteria (28 randomized controlled trials, 4 cohort studies, 6 post-hoc analyses, and 12 other interventional trials). The studies reported a total of 21,202 patients. Most studies explored topical therapies (23 studies) and photodynamic therapy (13 studies). Other treatments included laser/light therapy, systemic therapy, chemical peels, and radiofrequency and microneedling. In general, the different treatment modalities offered an improvement in lesion count and were well tolerated, with no report of major adverse events. However, due to limited evidence, we were unable to draw firm conclusions from the results of this review to guide decisions in practice, particularly with respect to long-term outcomes, in patients with skin of color and acne vulgaris. **KEYWORDS:** Acne, medical dermatology, ethnicity

Ethnic dermatology represents a new area of study focusing on common dermatological presentations that can manifest differently in patients with skin of color compared to those of lighter skin types. Ethnic skin, or skin of color, refers to people categorized as having Fitzpatrick Skin Types (FPS) III to VI, typically with African, Native American, Asian, Middle Eastern, or Hispanic backgrounds.[1] Acne vulgaris (AV) typically affects the face and torso and is characteristically centered on the pilosebaceous unit.[2] AV is among the most common dermatological conditions for which patients with skin of color present for medical attention in primary care.[3] In a landmark prevalence study (including female patients only), Perkins et al[4] concluded that AV was most prevalent in female patients of African-American descent with FPS V to VI (37%) or Hispanic descent with FPS III to IV (32%), followed by patients of Asian (30%), Caucasian (24%), or Continental Indian (23%) descent. Prevalence of acne subtype was comparable between ethnic groups, except in Asian skin, which had a higher number of inflammatory lesions (IL) compared to comedonal lesions (CL) (20% vs. 10%), and Caucasian skin, in which CL was more prevalent than IL (14% vs. 10%).[4] Patients from African American or Hispanic descent showed higher prevalence of hyperpigmentation (65% and 48%, respectively) compared to patients of Caucasian, Asian, or Continental Indian, descent (25%, 18%, and 10%, respectively).[4] According to the Global Burden Disease Study, AV is the tenth leading cause of disability-adjusted life years (DALYs) in the 15 to 19-year-old subgroup across developed countries, of which there is a global incline, suggesting an unmet dermatology need globally for AV (Figure 1).[5]

The pathophysiology of AV in skin of color is similar to that observed in Caucasian skin, comprising the well-known quartet of excessive sebum production, abnormal follicular keratinisation and plugging, proliferation of *Propionibacterium acnes* (*P. acnes*), and exaggerated inflammatory response.[3] Nodulocystic acne is more common in Caucasian and Hispanic subjects than in African-American subjects.[6] Post-inflammatory hyperpigmentation (PIH), defined as an acquired hypermelanotic process following inflammation or trauma,[7] is more pronounced in patients with skin of color, particularly among those

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with FPS IV to VI; however, PIH frequently goes unrecognized by clinicians, which is likely related to the lack of representation of skin of color in dermatology photography resources and other educational materials.[8] The hyperpigmentary changes associated with acne can last substantially longer than the acne lesions themselves, and epidermal lesions can take up to 6 to 12 months to heal, while lesions deeper in the dermis can last for years.[9,10] In a study of 30 female African-American patients, Falder et al[11] reported that inflammation was histologically evident in all types of acne lesions, of which even simple comedones displayed a mild degree of inflammation. Inflammation was also evident some distance away from index lesions, a condition termed *satellite inflammation*. Additionally, pomade acne is more common in patients with skin of color,[12] due to the frequent use of hair products containing potent acnegens.[13] Interestingly, He et al[9] provided primary data on a possible association of the CYP17-34T/C polymorphism and the development of severe acne in Chinese subjects, and, in a later study, described two new susceptibility loci—1q24.2 and 11p11.2—that were associated with more severe acne.[10] The aim of the current systematic review was to summarize the efficacy and safety of available AV treatments in patients with skin of color. Our review was designed and performed in accordance with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions,[14] as well as the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[15]

METHODS

Data sources, search strategy, and design overview. Relevant studies were identified in the PubMed, Embase, and Scopus bibliographic databases, using the search strategy outlined in Appendix 1. Studies were eligible for inclusion if they were published on or after January 1, 2001, were written in English, and involved human participants only. Finally, a manual search was performed by reviewing the references of the included studies.

Selection criteria. Study inclusion criteria were as follows:

- Participants diagnosed with AV of the face, head, and/or neck.
- Participants with skin of color included in study (using predefined eligibility criteria outlined in Appendix 1).
- All grades of acne severity included in study
- Treatment comprised topical, mechanical, or systemic agent
- Outcome measures assessing efficacy and safety were utilized.

The complete inclusion and exclusion criteria are outlined in Appendix 2.

This systematic review included all FPS, rather than restricting our search to FPS IV to VI. Our search criteria (seen in Appendix 1) included any article that referenced skin of color or any associated terms. FPS was not specified in all retrieved articles; however, this did not lead to exclusion if an article included certain search terms (e.g., *non-Caucasian*, *Japanese*, among others). The authors made a conscious decision not to exclude articles that failed to specify FPS as we believe this may have led to the omission of significant findings. Studies in which FPS was specified are presented in Table 1.

Screening of studies. The titles, abstracts, and full texts of the retrieved articles were screened independently by two reviewers. Randomized, controlled trials (RCTs), cohort studies, case control studies, cross-sectional surveys, and case series with at least three patients were included. Articles were excluded if they focused on acne diagnoses other than AV (e.g. acne rosacea, acne conglobate), if the full text was unavailable, if the outcomes of patients with skin of color were not discussed separately from those of lighter-skinned patients, and if no data pertaining to efficacy were available.

Data collection. Data collection was led by two authors, and disagreements were resolved by discussion and consensus with a third author. The following information was extracted from the included studies: first author, year of publication, study country of origin, study design, number of patients, and primary and secondary outcomes. Extracted data were entered into a pregenerated standard Microsoft® Excel (Microsoft Corporation, Redmond, Washington, USA) file. Due to the heterogeneity of the study designs, participants, interventions, and reported outcomes, a formal meta-analysis was not performed.

Outcome measures. The primary outcome measure was the change in total lesion count (TLC). Secondary outcome measures included the following other validated and nonvalidated measures of effectiveness: Evaluator's Global Severity Score (EGSS), Acne Severity Index (ASI), Acne Global Severity Scale (AGSS), Global Acne Evaluation (GAE), Global Acne Assessment Score (GAAS), and adverse events (AEs). Treatment success was defined by the authors of each individual study according to their study protocols (summarized in Appendix 4).

Assessment of bias. Risk of bias was assessed using the Cochrane Collaboration Tool for RCTs[16] and ROBINS-I[17] for non-RCTs, and each study was assigned a risk of bias described as low, moderate, serious, or critical (Appendix 3). Assessment of the quality of included studies was based upon the CASP tools[18] and Oxford CEBM Levels of Evidence.[19]

Ethical considerations. Ethical approval was not required for this systematic review. We used publicly accessible data, and the work was conducted in accordance with the standards outlined in the Good Clinical Practice guidelines.

RESULTS

Summary of article types. The literature search produced 1,477 articles; 1,316 were excluded after assessment of the titles and abstracts. Ninety-three studies underwent full review, of which 55 studies met the inclusion criteria. Figure 2 illutrates the PRISMA flow chart for study inclusion. The final studies included 29 RCTs[20–48] (5 nonblinded,[20–24] 13 single-blinded, [25–37] 11 double-blinded[38–48]), four cohort studies[49–52] (3 retrospective,[49–51] 1 prospective[52]), four pilot studies,[53–56] six post-hoc analyses,[57–62] and 12 other interventional trials.[63–73] Ten studies were of a split-face design.[29,30,32,35,37,40,45,46,48,67] The included studies reported a total of 21,202 patients.

Regarding interventions, 23 studies[20,25–28,30,31,38–44,53,57–64] evaluated topical therapies, 14 studies[22–24,32–34,49,54,55,66,67,74] evaluated photodynamic therapy, seven studies[29,35,36,47,68–70] evaluated laser/light therapy, one study[51] evaluated systemic therapy, three studies evaluated chemical peels,[21,38,45] three studies evaluated

TABLE 1. Effectiveness and tolerability outcomes (all outcomes reported pertain to those at final follow-up visit unless otherwise stated)

AUTHOR, YEAR	PATIENTS (N)	TREATMENT(S)	EFFECTIVENESS	SAFETY	STUDY LIMITATIONS
TOPICAL RETINOIDS					
Cook-Bolden et al,[57] 2019	766	Tretinoin 0.05% lotion vs. vehicle lotion	**Lesion count** • Mean % reduction in IL 60.1% and NIL count 53% in intervention group vs. 51.1% and 38.7% with vehicle **Treatment success** • ≥2 grade reduction in EGSS achieved by 19.6% vs. 12.7%	**Tolerability** • Common reported: application site pain, dryness, erythema, scaling, and burning	Need to expand on blinding procedure in original trials; no clear exclusion criteria provided; post-hoc analysis; short duration of follow-up
Lain et al 2019,[58]	1,640	Tretinoin 0.05% lotion vs. vehicle lotion	**Lesion count** • Black/African-American male patients: mean % reduction in IL of 58.2% in tretinoin group vs. 52.1% in Caucasian male patients (*P*=0.346) vs. 41% in vehicle group (*P*=0.033) and reduction in NIL of 49.1% in tretinoin group vs. 45.9% in Caucasian male patients (*P*=0.522) vs. 24% in vehicle group (*P*=0.006) • Black/African-American female patients: mean % reduction in IL of 57.3% in tretinoin group vs. 56.2% in Caucasian female patients (*P*=0.879) vs. 52% in vehicle group (*P*=NR) and reduction in NIL of 49.3% in tretinoin group vs. 56.2% in Caucasian female patients (*P*=0.236) vs. 36% in vehicle group (*P*=NR) **Treatment success** • Black/African-American male patients: achieved in 18.0% in tretinoin group vs. 15.4% in Caucasian male patients (*P*=0.522) vs. 10% in vehicle group • Black/African-American female patients: achieved in 23.0% in tretinoin group vs. 23.3% in Caucasian female patients (*P*=0.946) vs 15% in vehicle group	*Not all data reported separately for ethnic vs Caucasian patients* **Tolerability** • Treatment-related AEs more frequent in female (5.2%) vs male (10.6%) patients (*P*=0.008) • Application site dryness in 2.6% Black/African-American participants (all female) • Erythema and pruritus reported in 30–40% patients (all ethnicities) **Withdrawals** • Treatment discontinued due to treatment-related AEs in 0.6% male vs. 2.5% female patients (NR according to ethnicity)	Short duration of follow-up; ITT analysis; no clear exclusion criteria; post-hoc analysis; safety outcomes poorly reported according to ethnicity; inconsistent reporting of P values especially when statistical significance not achieved; very large numbers of Caucasian patients
Kubota et al,[25] 2012	66	4/52 of 1% clindamycin phosphate gel 2x/day and 0.1% adapalene gel 1x/day, then 4/52 0.1% adapalene 1x/day vs. 4/52 of 0.1% adapalene for 2/52	**Lesion count** • Reduction in mean IL and NIL counts from 11.6±0.8 to 6.9±0.7, and from 7.5±0.7 to 4.6±0.5, respectively **Treatment success** • Decrease in mean acne severity score from 2.0±0.1 to 1.4±0.1 (*P* <0.05) **QoL** • Total mean QoL score and mean scores of emotion and function domains improved significantly (*P*<0.05) from 41.5, 67.6, and 15.5 at baseline to 21.2, 29.7, and 7.2, respectively	**Local AEs** • 60 subjects experienced 60 local AEs (erythema, scaling, pruritus, burning • Most local events were mild or moderate **Withdrawals:** • No subject withdrawals due to AEs	Small study size; short duration of follow-up

A/BPO: adapalene/benzoyl peroxide; AE: adverse event; ALA: aminolaevulinic acid; BPO: benzoyl peroxide; C/BPO: clindamycin/benzoyl peroxide; CDLQI: Children's Dermatology Life Quality Index; CI: confidence interval; DL: diode laser; DLQI: Dermatology Life Quality Index; EGSS: Evaluator's Global Severity Score; Excellent or good therapeutic effect: >50% reduction in lesion count); FMR: fractional microneedle radiofrequency; FPS: Fitzpatrick skin type; GA: glycolic acid; GAGS: Global Acne Grading System; GAI: Global Assessment of Improvement; GIS: Global Improvement Score; ICG: idocyanine green; IGA: Investigator's Global Assessment; IGA: Investigator's Global Assessment; IL: inflammatory lesion count; IPL: Intense pulsed light; ISGA: Investigator's Static Global Assessment; ITT: Intention To Treat; JS: Jessner's solution; KAGS: Korean Acne Grading System; LED: light emitting diode; LFTs: liver function tests; MAL: Methyl aminolevulinate; NIL: non-inflammatory lesion count; NR: not reported; OR: odds ratio; PIH: post-inflammatory hyperpigmentation; QoL: Quality of Life; rhGEF: topical epidermal growth factor; SA: salicylic acid; SD: standard deviation; TLC: total lesion count

TABLE 1 (CONTINUED). Effectiveness and tolerability outcomes (all outcomes reported pertain to those at final follow-up visit unless otherwise stated)

AUTHOR, YEAR	PATIENTS (N)	TREATMENT(S)	EFFECTIVENESS	SAFETY	STUDY LIMITATIONS
TOPICAL ANTIBIOTICS					
Kawashima et al,[38] 2017	607	BPO 2.5% vs. BPO 5% vs. placebo	**Lesion count** • Median % reduction in IL for 2.5% BPO, 5% BPO, and placebo were 72.7%, 75.0%, and 41.7% ($P<0.001$), respectively • Median % reduction for TL for 2.5% BPO, 5% BPO and placebo were 62.2%, 67.9% and 28.6% ($P<0.001$) • Median % reduction in NIL for 2.5% BPO, 5% BPO and placebo were 56.5%, 68.2% and 21.9% ($P<0.001$), respectively	**Percent of patients who experienced AEs** • Incidence of AE with a possible causal relation was 37.3% for 2.5% BPO, 38.7% for 5% BPO, and 12.9% for placebo • No cases of death or severe AE **Local AEs** • 2.5% BPO: skin exfoliation (19.1%), application site erythema (13.7%), application site irritation (8.3%), application site pruritus in (3.4%), contact dermatitis (2.5%) • 5% BPO: skin exfoliation (23.5%), application site irritation (12.3%), application site erythema (10.8%) , application site pruritus (2.5%) • Placebo: skin exfoliation (8.0%) **Withdrawals** • 13 patients discontinued due to AE (6, 5, and 2 for 2.5% BPO, 5% BPO, and placebo, respectively)	No patient satisfaction measures; short duration of follow-up; different denominator for efficacy (n=607) and AEs (n=609)
Kawashima et al,[20] 2017	458	BPO 2.5% vs. BPO	**Lesion count** • Mean % reduction in IL and NIL: 63.6% and 54.3% compared to 43.5% and 38.1% with vehicle ($P=0.001$ and $P=0.008$, respectively) **Treatment success** • ≥2 grade improvement in EGSS achieved by 36.5% in C/BPO group vs. 28.3% in vehicle group ($P=0.326$)	**Treatment-emergent AEs** • In C/BPO group, treatment-emergent AEs infrequent and unrelated to treatment (n=4, nasopharyngitis and headache); in vehicle group AEs considered related to treatment (n=2, facial pain, swelling of face) **Local AEs** • Mild-to-moderate tolerability issues in C/BPO group **Withdrawals** • No study withdrawals due to AEs	Post-hoc analysis; unclear whether ITT used for all outcomes; no analysis of White vs. non-White patients
Alexis et al,[59] 2017	136	Clindamycin phosphate 1.2%/ BPO 3.75% vs. vehicle	**Lesion count** • At 12 weeks, greatest reduction in median TLC, median IL count, and median NIL count in 2.5% BPO and 5% BPO groups, reductions of 62.1% vs. 66.9%, 68.2% vs. 72.7%, and 75% vs. 83.3%, respectively • At 52 weeks, median reduction in TLC in 2.5% and 5% BPO groups were 75.3% and 80.4%, respectively **Microbiology** • Microbial assays carried out in 238/458 patients; *Propionibacterium acnes (P. acnes)* and *Staphylococcus epidermidis (S. epidermidis)* detected in 179 and 111 patients, respectively; assay repeated at Week 52 on 87 of remaining 393 participants; *P. acnes* and *S. epidermidis* detected in 65 and 39 patients, respectively.	**Percent of patients who experienced AE:** • 84% in the 2.5% BPO group, 87.2% in the 5% BPO group, and 85.6% in total • 52.2% (239/458) AEs among entire study group had a possible causal relationship to BPO • AEs included skin exfoliation, local irritation, erythema, dryness, pruritis, contact dermatitis, xeroderma, blepharitis, erythema of eyeline, urticaria, intertrigo and eczema **Monitoring** • No significant change in clinical laboratory tests in both groups.	Post-hoc analysis; unclear whether ITT used for all outcomes; no analysis of White vs. non-White patients

A/BPO: adapalene/benzoyl peroxide; AE: adverse event; ALA: aminolaevulinic acid; BPO: benzoyl peroxide; C/BPO: clindamycin/benzoyl peroxide; CDLQI: Children's Dermatology Life Quality Index; CI: confidence interval; DL: diode laser; DLQI: Dermatology Life Quality Index; EGSS: Evaluator's Global Severity Score; Excellent or good therapeutic effect: >50% reduction in lesion count); FMR: fractional microneedle radiofrequency; FPS: Fitzpatrick skin type; GA: glycolic acid; GAGS: Global Acne Grading System; GAI: Global Assessment of Improvement; GIS: Global Improvement Score; ICG: idocyanine green; IGA: Investigator's Global Assessment; IGA: Investigator's Global Assessment; IL: inflammatory lesion count; IPL: Intense pulsed light; ISGA: Investigator's Static Global Assessment; ITT: Intention To Treat; JS: Jessner's solution; KAGS: Korean Acne Grading System; LED: light emitting diode; LFTs: liver function tests; MAL: Methyl aminolevulinate; NIL: non-inflammatory lesion count; NR: not reported; OR: odds ratio; PIH: post-inflammatory hyperpigmentation; QoL: Quality of Life; rhGEF: topical epidermal growth factor; SA: salicylic acid; SD: standard deviation; TLC: total lesion count

TABLE 1 (CONTINUED). Effectiveness and tolerability outcomes (all outcomes reported pertain to those at final follow-up visit unless otherwise stated)

AUTHOR, YEAR	PATIENTS (N)	TREATMENT(S)	EFFECTIVENESS	SAFETY	STUDY LIMITATIONS
TOPICAL ANTIBIOTICS, continued					
Xu et al,[26] 2016	1,016	Clindamycin phosphate 1%/BPO 5% vs. clindamycin only	**Lesion count** • Mean % reduction in TLC 72% (C/BPO) and 67% (clindamycin) (*P*=0.003) • Mean % reduction in IL count 78% (C/BPO) and 75% (clindamycin) (non-significant) Mean % reduction in NIL count 67% (C/BPO) and 60% (clindamycin) (*P*=0.019) **Treatment success** • Improvement of ≥2-grade in ISGA score achieved in 30.2% (C/BPO) vs. 22.7% (clindamycin) (*P*=0.018) **QoL measures** • DLQI and CDLQI reduced from baseline in both treatment groups (DLQI total score: C/BPO -5.4 and clindamycin -4.7; CDLQI total score: C/BPO -4.1 and clindamycin -4.5)	**Percent of patients who experienced AE** • Overall incidence of AEs higher in C/BPO group (14.4%) than in clindamycin group (7.9%) • Majority of AEs were mild-to-moderate intensity • Incidence of drug-related AEs was 8.6% in C/BPO group vs. 1.2% in clindamycin group • No deaths reported **Local AEs** • Most common drug-related AE associated with C/BPO treatment was application site erythema, pruritus, and pain **Withdrawals** • 16 patients discontinued study: 2.4% from C/BPO group and 0.8% clindamycin group, primarily due to application site reaction (swelling, erythema, and pruritus)	Single blinding; short duration of follow-up; no placebo arm; sex numbers do not match to reported participants
Amar et al,[63] 2015	20	Clindamycin phosphate 1.2%/ BPO 2.5% gel	**Lesion count** • Mean % reduction in IL count, NIL count and TLC of 76%, 62%, and 71% respectively (*P*<0.0002) **Treatment success** • IGA reduced to "clear" or "almost clear" in 70% participants (*P*=0.0001), all patients experienced ≥1 grade improvement in IGA • PIH severity improved by ≥1 grade in 95% participants	**Number of patients who experienced AE** • 10 participants experienced a total of 21 AEs • No serious AEs; only 1 AE possibly related to study drug (facial tattoo tightening), which resolved by end of study **Local AEs** • Erythema, dryness, peeling, oiliness minimal at baseline and resolved within 4/52 of treatment	Nonblinded study; no control arm; small population sample; short duration of follow-up; no definition of AEs provided
Kawashima et al,[27] 2015	800	Clindamycin phosphate 1.2% / BPO 3.0% OD vs BD vs clindamycin BD	**Lesion count** • Mean TLC reduction of -57.5±26.7 in C/BPO OD group vs -60.4±34.6 in C/BPO BD group vs -48.9±34.9 in clindamycin BD group **Treatment success** • ≥2-grade improvement in ISGA score achieved by significantly more patients from Week 4 with C/BPO 3.0% OD or BD than with clindamycin BD (*P*<0.05)	**Treatment-emergent AEs** • Most AEs were mild or moderate in severity • Severe AEs occurred in two patients (erythema plus face swelling, and contact dermatitis) in C/BPO OD group • No deaths or serious AEs occurred **Local AEs** • Issues of tolerability (dry skin, contact dermatitis, erythema, pruritus, skin exfoliation, skin irritation, eczema, facial pain, burning) higher for C/BPO OD (24.0%) or BD (35.1%) than for clindamycin BD (9.0%) **Withdrawals** • Permanent discontinuations in 8.3% patients receiving C/BPO OD, 9.1% receiving C/BPO BD and 2.3% receiving clindamycin BD	Short duration of follow-up; multiple analyses at various timepoints and between subgroups; single-blinding

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TABLE 1 (CONTINUED). Effectiveness and tolerability outcomes (all outcomes reported pertain to those at final follow-up visit unless otherwise stated)

AUTHOR, YEAR	PATIENTS (N)	TREATMENT(S)	EFFECTIVENESS	SAFETY	STUDY LIMITATIONS
TOPICAL ANTIBIOTICS, continued					
Kawashima et al,[39] 2014	360	BPO 3% vs. vehicle	**Lesion count** • Absolute reduction in TLC of -44.0±32.34 in BPO group vs. -22.2±34.02 in vehicle group (P<0.001) • Difference of adjusted mean absolute change -8.6 (95% CI, -11.1 to -6.2; P<0.001) for IL counts, and -12.3 (95% CI, -16.5 to -8.2; P<0.001) for NIL counts, in favor of BPO **Treatment success** • ≥2-grade improvement in ISGA score achieved in significantly higher proportion of BPO (19%) group than with vehicle (1%) (P< 0.001)	**Percent of patients who experienced AE** • Incidence of AE higher for BPO (58%) than for vehicle (47%) • All AEs were mild or moderate • No severe or serious AE or deaths reported **Local AEs** • Drug reactions (facial pain, pruritus, dry skin, contact dermatitis, erythema, and skin irritation) more frequent for BPO (30%) than for vehicle (5%) **Withdrawals** • Permanent discontinuation of 12 patients (7%) in BPO group vs. 5 patients (3%) in vehicle group	Short duration of follow-up; no active comparator
Cook-Bolden et al,[60] 2012	458	Clindamycin phosphate 1.2%/ BPO 2.5% vs. clindamycin only vs. BPO only vs vehicle	**Lesion count** • Mean % reduction in IL counts of 71.6% (C/BPO), 57.1% (clindamycin only, P=0.001), 58.4% (BPO only, P<0.001), 47.6% (vehicle, P<0.001) • Lesion reduction in Hispanic population greater than in overall acne population **Treatment success** • IGA of "clear" or "almost clear" in 33.1% of C/BPO group vs. 11.5% in vehicle group (P=0.003)	**Local AEs** • No subjects experienced severe local signs or symptoms • Overall mean scores of 0 (none) for burning and stinging, and 0.1 for itching, scaling ,and erythema (where 1.0=mild) in C/BPO group **Withdrawals** • No patient withdrawals due to AEs	Post-hoc analysis; short duration of follow-up; FPS not reported (Hispanic may include White patients)
Callender VD,[61] 2012	797	Clindamycin phosphate 1.2%/ BPO 2.5% vs. vehicle	**Lesion count** • Median % reduction in IL, NIL, and TLC of 63%, 50%, and 52.4% in FPS I–III vs. 65%, 47%, and 51.4% in FPS IV–VI **Treatment success** • EGSS of "clear" or "almost clear" of 29.8% in FPS I–III vs. 27.2% in FPS IV–VI	**Local AEs** • No severe local AEs or symptoms **Tolerability** • Mean scores for burning and stinging of 0 (none), 0.1 for itching and scaling, and 0.1 or 0.2 for erythema with no increased irritation in FPS IV–VI group **Withdrawals** • No participants withdrew due to erythema, scaling, itching, burning, or stinging	Post-hoc analysis; Comparisons made between FPS subgroups, with little mention of results from vehicle arm; Inclusion of patients with FPS I
Jung et al,[40] 2011	34	1% nadifloxacin cream vs. vehicle cream	**Lesion count** • Reduction in IL from 8.7±4.2 to 2.7±2.4 (P<0.001) with nadifloxacin cream vs. to 8.4±6.2 with vehicle • Reduction in NIL from 21.4±15.4 to 11.1±7.2 vs. to 18.6±8.6 with vehicle **Treatment success** • Baseline acne severity grade of 2.69 decreased to 0.98 (P<0.001) and 2.44 (P=0.57) with nadifloxacin and vehicle cream, respectively	**Local AEs** • Mild erythema (n=4) and dryness (n=2), which resolved spontaneously on nadifloxacin side	Small study size; unclear enrolment process; short duration of follow-up

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TABLE 1 (CONTINUED). Effectiveness and tolerability outcomes (all outcomes reported pertain to those at final follow-up visit unless otherwise stated)

AUTHOR, YEAR	PATIENTS (N)	TREATMENT(S)	EFFECTIVENESS	SAFETY	STUDY LIMITATIONS
COMBINED TOPICAL RETINOID AND ANTIBIOTIC					
DuBois et al,[64] 2019	50	Adapalene 0.3%/ BPO 2.5%	**Treatment success** • 56% participants had IGA 0–1 • 87% had good to excellent improvement in GAI **QoL** • Participants reporting "no effect at all" of acne on QoL increased 15% to 55%, participants reporting "very large" to "extremely large effect" of acne on QoL reduced 28% to 4%; 75% satisfied or very satisfied with treatment effectiveness	**Percent of patients who experienced AE** • 4% reported pruritus; 4% reported PIH change; 2% reported skin irritation; 2% reported cheilitis, eschar and papular rash • No serious or severe AEs **Withdrawals** No AEs leading to discontinuation	Prospective, open-label design; Small number of patients; Single-arm study
Hayashi et al,[28] 2018	349	Clindamycin phosphate 1.2%/ BPO 3.0% ON vs. clindamycin 1.2% BD/adapalene 0.1% ON	**Lesion count** • Mean reduction in TLC, IL counts, and NIL counts after C/BPO or adapalene/ clindamycin of -80.7±34.04 vs. -78.1±36.33, -27.2±11.02 vs. -25.6±11.71 and -53.5±28.4 vs. -52.5±31.46, respectively **Treatment success** • ≥2-grade improvement in ISGA score achieved in 37% C/BPO vs. 27% adapalene/clindamycin	**Percent of patients who experienced AE** • Overall incidence in C/BPO group (31%) lower than adapalene/clindamycin group (56%) • Most AEs were mild or moderate in severity • One serious AE (duodenal ulcers) unrelated to study treatment in C/BPO 3% group **Local AEs** • Application-site dryness (24%), pain (9%), and erythema (6%) in adapalene/clindamycin group vs. application-site dryness (9%) and pruritus (3%) in C/BPO group **Withdrawals** • 2% in both groups - all due to application-site events	Single blinding; short duration of follow-up; no placebo arm; multiple subgroup analyses; variable reporting of *P* values
Alexis et al,[62] 2017	286	Adapalene 0.3%/ BPO 2.5% vs. vehicle	**Lesion count** • Mean change in IL count in FPS I–III of -62.1% in A/BPO vs. -28.7% in vehicle group, in IV–VI group -63.7% vs. -45.0% in vehicle group (*P*<0.001) • Mean change in NIL count in FPS I–III of -63.6% in A/BPO group vs. -32.9% in vehicle group, in IV–VI group -61.1% in A/BPO group vs -34.0% in vehicle group (*P*<0.001)	**Percent of patients who experienced AE** • Most common AEs in A/BPO group: nasopharyngitis (6.5%), skin irritation (4.1%) **Local AEs** • Scores of "none" or "mild" for FPS I–III erythema (90.3% A/BPO vs. 92.3% vehicle), scaling (98.3% A/ BPO vs. 100% vehicle), dryness (95.6% A/BPO vs. 100% vehicle), stinging/burning (99.1% A/BPO vs. 100% vehicle) • Scores of "none" or "mild" for FPS IV–VI erythema (100% A/BPO vs. 91.3% vehicle), scaling (97.5% A/ BPO vs. 91.3% vehicle), dryness (98.2% A/BPO vs. 95.7% vehicle), stinging/burning (100% A/BPO vs. 100% vehicle)	Post-hoc analysis; inclusion of FPS I patients and patients w/ darker skin types; multiple subgroup analyses
Kim et al,[30] 2013	23	Adapalene 0.1%/ BPO 2.5% vs. Adapalene 0.1%	**Lesion count** • Decrease in IL and NIL counts more remarkable on A/BPO side compared to adapalene side (5.9±2.5 and 4.9±3.2 vs. 13.1±7.1 and 9.7±4.1, respectively) (*P*=0.023)	**Local AEs** • Erythema 8.7% both sides, scaling 17.4% A/BPO vs. 13.0% adapalene, dryness 13.0% A/BPO vs. 8.7% adapalene, stinging/burning 4.3% both sides	Small study size; short duration of follow-up; single-blinded study; no ITT analysis

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AUTHOR, YEAR	PATIENTS (N)	TREATMENT(S)	EFFECTIVENESS	SAFETY	STUDY LIMITATIONS
COMBINED TOPICAL RETINOID AND ANTIBIOTIC, continued					
Takigawa et al,[31] 2013	188	Adapalene 0.1%/ nadifloxacin 1% vs. adapalene 0.1% monotherapy	**Lesion count** • Mean reduction in IL count 66% adapalene/ nadifloxacin group vs. 51% adapalene group (*P*=0.0056) **Treatment success** • Excellent or good therapeutic effect 73.8% adapalene/nadifloxacin group vs. 59% adapalene group (*P*=0.02496)	**Local AEs** • No systemic AEs • Dryness and burning most frequently reported local effects and mostly mild **Withdrawals** • 1 patient in adapalene/nadifloxacin group withdrew due to severe skin irritation	No exploration of limitations within manuscript; per-protocol analysis rather than ITT; short duration of follow-up; no placebo group
Callender et al,[41] 2012	33	Clindamycin phosphate 1.2%/ tretinoin 0.025% vs. vehicle	**Lesion count** • Mean IL count reduced 5.5±6.56 clindamycin/tretinoin group vs. 4.1±11.36 (*P*=0.05) vehicle group • Mean NIL count reduced 21.3±22.60 clindamycin/tretinoin group vs. 12.8 (±40.08) (*P*=NS) in vehicle group **Treatment success** • EGSA of 0 or 1 ("clear" or "almost clear") 47% clindamycin/tretinoin vs. 27% (vehicle) (*P*=NS) • ≥1-point improvement in PGA score 80% clindamycin/tretinoin and 53% vehicle	**Local AEs** • Severity scores 0 or 1 reported in 85–100% patients for scaling, erythema, burning, stinging, itching **Withdrawals** • Periorbital edema of moderate severity possibly related to clindamycin/tretinoin gel	Small sample size; short follow-up period; use of cleansing bar and sunscreen as potential confounders; inconsistent reporting of *P* values
Schmidt et al,[42] 2011	2,010	Clindamycin phosphate 1.2%/ tretinoin 0.025% vs. clindamycin only	**Lesion count** • Mean % decrease in lesion counts >clindamycin/tretinoin group (range: 46.9–67.1%) vs. clindamycin group (range: 36.8–59.1%) for all FPS	**Local AEs** • AEs not reported according to FPS • Investigator-based evaluations: clindamycin/ tretinoin group exhibited >scaling and dryness than participants in clindamycin-only arm • Erythema scores for both groups were similar • No reports of hypo- or hyper-pigmentation	Limitations not explored; unclear where study conducted (multicenter sites not stated); short duration of follow-up; AEs not presented according to FPS
TOPICAL DAPSONE					
Taylor et al,[43] 2018	4,327	Dapsone 7.5% vs. vehicle	**Lesion count** • Percent reduction in IL count FPS I–III -54.2% dapsone group vs. -46.1% vehicle group; FPS IV–VI -56.0% dapsone group vs. -51.1% vehicle group (*P*≤0.01) • Percent reduction TLC FPS I–III -48.8% dapsone group vs. -41.2% vehicle group; FPS IV–VI -49.6% dapsone group vs. -45.2% vehicle group **Treatment success** • ≥1 grade improvement in GAAS achieved in FPS I-III 76.6% in dapsone group vs. 62.8% in vehicle group (*P*<0.001); in FPS IV–VI 76.6% dapsone group vs. 67.9% vehicle group (*P*<0.001)	**Percent of patients who experienced AE** • Safety population (n=432)— similar rate of treatment-related AEs, serious AEs, and AEs leading to discontinuation (treatment-related AEs: 3.4% vs. 3.5% FPS I–III; 3.6% vs. 3.3% FPS IV–VI; serious AEs: 0.3% vs. 0.5% FPS I–III; 0.4% vs. 0.3% FPS IV–VI) **Local AEs** • Similar rates of investigator-reported erythema and scaling and patient-reported stinging/ burning across 2 subgroups, typically mild in severity **Withdrawals** • AEs leading to discontinuation: 0.4% vs. 0.4% FPS I–III; 0.2% vs. 0.2% FPS IV–VI	Post-hoc analysis; short duration of follow-up; inconsistent use of *P* intervals and standard error

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TABLE 1 (CONTINUED). Effectiveness and tolerability outcomes (all outcomes reported pertain to those at final follow-up visit unless otherwise stated)

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TOPICAL DAPSONE, continued					
Draelos et al,[44] 2017	1,850	Dapsone 7.5% gel OD vs. vehicle	**Lesion count** • Mean % change in IL count (-57.6% dapsone group vs. -53.0% vehicle group); NIL count (-48.6% dapsone group vs. -43.5% vehicle group); TLC (-51.9% vs. 47.0%)	**Percent of patients who experienced AE** • 16.7% dapsone group vs .15.2% vehicle group **Local AEs** • Dryness 1.6% dapsone vs. 1.3% vehicle, pruritus 1.5% dapsone vs. 0.6% vehicle, erythema 0.4% dapsone vs. 0.7% vehicle, pain 0.8% dapsone vs. 1.5% vehicle	Post-hoc analysis of PIH outcomes; short duration of follow-up; complete inclusion/exclusion criteria from original studies not reported; inconsistent P value reporting
Alexis et al,[53] 2016	67	Dapsone 5%	**Lesion count** • TLC reduced 52% **Treatment success** • Mean change in GAAS: -1.2 (95% CI, -1.4, -1.0, $P<0.001$)	**Percent of patients who experienced AE** • 20.6% reported ≥1 AE • No AE considered treatment-related • One serious AE (spontaneous termination of pregnancy) but considered unrelated to treatment **Local AEs** • Burning (1.6%), erythema (9.5%), dryness (15.9%), peeling (11.1%), oiliness (11.1%)	Different number of patients included for data analysis at different time points; small sample size; short study duration; open-label; no control arm
CHEMICAL PEELS					
How et al,[45] 2020	36	Jessner's solution peel vs. SA 30% peel	**Lesion count** • Significant reduction in IL in both treatment arms (SA: 1.5; JS: 2) ($P<0.001$) • Significant reduction in NIL in both treatment arms (SA:5.5; JS:6) ($P<0.001$) **Treatment success** • Significant reduction in Michaelsson Acne Score in both treatment arms (SA: 5.5; JS: 6) ($P<0.001$) • Significant reduction in PAHPI in both treatment arms (SA:6; JS:6) ($P=0.003$ [SA]), $P<0.001$ [JS])	**Local AEs** • No systemic AEs reported • Burning, stinging immediately after application reported after almost all treatments • Exfoliation 36.3% SA arm vs. 44.1% JS arms • Other commonly reported local AEs: acneiform eruption (2 mild, 3 moderate, 1 severe) • One case prolonged erythema and PIH JS arm; 5 cases post-peel erythema SA arm v.s 4 JS arm	Small sample size; short duration of follow-up; ITT and per-protocol analysis performed
Sarkar et al,[21] 2019	45	35% GA peel vs. 20% SA + 10% mandelic acid peel vs. phytic acid peel	**Lesion count** • Percent improvement comedones 56.32% GA; 62.4% SA+mandelic acid; 44.9% phytic acid • % improvement papules 69.88% GA; 70.09% SA+mandelic acid; 67.0% phytic acid • % improvement pustules 72.5%GA; 95.84% SA+mandelic acid; 68.33%phytic acid	**Local AEs** • All peels were well tolerated • 13.3% in GA & SA+mandelic acid groups reported burning vs. 0% in phytic acid group • 6.7% in SA+mandelic acid reported postprocedural erythema that subsided within 2 days **Withdrawals** • No withdrawals due to AEs	Small sample size; short duration of follow-up; evaluator bias due to subjective nature of scoring system; inconsistent reporting of *P* values; nonspecified population other than "Asian"

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CHEMICAL PEELS, continued					
Kaminaka et al,[46] 2014	25	40% GA peel vs. placebo peel	**Lesion count** • Statistically significant reduction in IL, NIL, and TLC between GA side and placebo side (P<0.01) (no raw data available) **Treatment success** • Overall therapeutic effect "excellent" or "good" for n=23 (92%) GA side; n=10 (40%) placebo side	**Local AEs** • No significant AEs (bullae, swelling, pigmentary complications, scarring) • No systemic AEs • Most patients reported transient post-treatment mild erythema that lasted a few minutes • Mild dryness (GA n=7; placebo n=25); scaling (GA n=4; placebo n=3) **Withdrawals** • No withdrawals due to AEs	Small sample size; short duration of follow-up; raw data unavailable
PHOTODYNAMIC THERAPY					
Choi et al,[22] 2018	21	ICG-PDT w/ either LED 830nm or diode laser 805nm	**Lesion count** • After avg 3.8 sessions ICG-LED group: NIL reduced 30.5±4.34 to 16.7±1.18, IL reduced 13.5±1.82 to 7±8.86 vs. after avg 3.3 sessions ICG-diode laser group: NIL reduced 31.4±5.94 to 14.7±10.58, IL reduced 14.1± 8.40 to 6.5± 6.36 **Treatment success** • After avg 3.8 sessions ICG-LED group: mean pretreatment KAGS 3.39±1.1 reduced to 2.31±1.11 vs. after avg 3.3 sessions ICG-diode laser group: mean pretreatment KAGS 3.38± 0.92 reduced to 2.13±0.99	NR	Unclear inclusion criteria on acne severity; no details on PDT parameter settings, number of passes or duration; no detail on interval length between treatment or follow-up period; no details on methods of statistical analysis
Mokhtari et al,[23] 2017	58	BPO 5% + 570nm IPL vs. BPO 5% only	**Lesion count** • Significant reduction TLC 41.86±14.17 to 6.95±6.81 BPO-IPL group vs. 44.83±25.36 to 19.65±9.11 BPO only group (P<0.0001) **Treatment success** • Significant reduction AGSS 3.34±0.67 to 0.93±0.84 BPO-IPL group vs. 3.38±0.68 to 2.17±0.83 BPO only group (P<0.0001) • Significant reduction ASI 37.47±16.67 to 5.43±6.16 BPO-IPL group vs. 42.95±41.08 to 17.98±11.02 BPO only group (P<0.0001)	**Local AEs** • BPO-IPL treatment well tolerated • After BPO-IPL, 6 patients reported erythema; 4 patients reported pain **Withdrawals**: • 2 patients withdrew due to intolerable erythema in BPO-IPL group • 4 patients withdrew in BPO only group due to erythema or skin scaling	Small sample size; nonblinding of participants and assessors; per protocol analysis; patients who were sensitive to BPO omitted several doses and recommenced at a lower dose, which introduces heterogeneity of intervention
Ma et al,[65] 2015	21	ALA 5% + LED 633nm	**Lesion count** • Significant reduction IL (papules, pustule, nodules/cysts, P<0.05 or P< 0.01) compared to NIL (comedones, P >0.05); no raw data available **Treatment success** • Total effective rates (Grades 0+1+2+3/total cases x 100%) 85.71%, 90.48%, 95.23%, respectively, after 3 PDT sessions	**Local AEs** • No serious AEs (ulceration, infection, purpura, scarring) • Pain at start of irradiation (n=19/21), post-treatment edematous erythema (n=15/21), mild desquamation (n=5/21), temporary hyperpigmentation (n=8/21) that resolved within 1–3 months without intervention	Small sample size; short follow-up period; no control group

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PHOTODYNAMIC THERAPY, continued					
Dong et al,[54] 2016	46	ALA 10%+543–548nm, and 630±6nm LED	**Lesion count** • 48.83% patients achieved ≥90% lesion clearance; 41.30% achieved 60–89% clearance; 8.70% achieved 30–59% clearance; 2.17% achieved <29% clearnace • No significant difference in therapeutic effectiveness between participants receiving 2 or 3 sessions **Patient Satisfaction** • 95% participants satisfied or very satisfied with improvement in acne • No subject reported that acne had become worse	**Local AEs** • Generally well tolerated • No new pustules, vesicles, desquamation, exfoliation, or scarring • Most patients experienced slight or moderate erythema and edema immediately following ALA-PDT, subsided within 1–2 days • 65.22% reported mild pain, 34.78% reported moderate-to-severe pain • Visible mild-to-moderate hyperpigmentation in 15.22%, but resolved within 1–2 months after last treatment session without further intervention	Small sample size and short duration of follow-up; single-blinded study; variable endpoint; unclear how patient satisfaction measured
Park et al,[49] 2015	1213	ICG-IPL-PDT	**Treatment success** • 76–100% lesion reduction achieved in 483 (39.8%) patients; 0–50% lesion reduction) achieved in 730 (60.2%) patients **Patient Satisfaction** • 16.3% highly satisfied, 73.1% somewhat satisfied, 10.6% unsatisfied	**Local AEs** • Treatment well tolerated • Reported side effects: pain, erythema, scales, pruritis (resolved without treatment within 7/7)	Subjective bias due to use of nonvalidated tools; results do not state proportion of patients who had 3, 4, or 5 sessions; no statistical analysis; inconsistent intervention
Tao et al,[52] 2015	136	ALA+LED 633±3nm	**Treatment success**: • 4/52 after final treatment: total effective rate (number of cases cured + number of cases with excellent response/total cases x 100 i.e., ≥60% clearance) of 92.65%	**Local AEs** • Erythema (n=94), edema (n=2), pain (n=53), desquamation (n=12), slight-to-moderate hyperpigmentation (n=21), exudation (n=4)	Skin was cleansed, oily crusts removed, fluctuant cysts aspirated, and comedones extracted in addition to the study intervention prior to the second and third treatment; reporter bias due to nature of study; short duration of follow-up
Song et al,[32] 2014	24	Chlorophyll-a+430±10nm & 660±10nm LED vs. LED monotherapy	**Lesion count** • Pustule count: chlorophyll-a+PDT reduced from 3.8 at baseline to 1.3 (66% improvement; $P<0.001$) vs. LED 4.2 at baseline to 3.0 (29% improvement; ($P<0.001$) • Nodules and cysts: no statistically significant difference between 2 treatments **Treatment success** • Mean acne grade on chlorophyll-a+PDT side was 1.8 vs. 2.2 on LED-only side ($P=0.02$) • Histopathology (on chlorophyll-a+PDT side only) • Decrease of dermal pilosebaceous units and perivascular inflammatory cell infiltrates; increase of normal-appearing epidermis	**Local AEs** • Tolerable in all cases—no pain, burning, itching, or PIH	Small sample size; single-blinded; histology performed on intervention side only; no chlorophyll-a–only arm

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TABLE 1 (CONTINUED). Effectiveness and tolerability outcomes (all outcomes reported pertain to those at final follow-up visit unless otherwise stated)

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PHOTODYNAMIC THERAPY, continued					
Liu et al,[24] 2014	150	ALA 5%+633nm LED vs. monotherapy w/ IPL 420nm vs. LED 415±5nm & 633±6nm	**Lesion count** • Mean number of sessions required to achieve ≥90% clearance: 3±1.52 PDT group; 6±2.15 PL group ($P<0.05$); 9±3.34 in LED group ($P<0.01$) **Treatment success** • Clearance (≥90% lesion reduction) or moderate improvements (60-89% reduction) achieved in significantly more patients in PDT group: 92% in PDT group vs. 58% in IPL group ($P<0.01$) and 44% in LED group ($P<0.01$)	**Number of patients who experienced AE** • In PDT group, 2/50 patients experienced hyperpigmentation that resolved after 1 month **Local AEs** • Mild-to-moderate pain, erythema, and edema reported after every PDT treatment by 46 out of 50 patients	Ethical approval not explicitly stated; nonblinded study; short duration of follow-up
Asayama-Kosaka et al,[55] 2014	11	5% ALA+broadband light 600–1100nm	**Treatment success** • Avg GAGS reduced from 22.1±3.8 to 19.48 after 1 month, and to 16.3 after 3 months • # patients w/ moderately severe acne decreased from 7 to 0 after 3 months • # patients w/ mild acne increased from 4 to 11 after 3 months	**Local AEs** • 10/11 experienced some local side effects during or after PDT • Erythema in 10/11 pts • No PIH • 3/11 reported minimal pain	Unclear duration of light therapy; small sample size; no SD given for GAGS scores at 1m and 3m
Ma et al,[66] 2013	397	ALA+LED 633nm for 3–4 sessions	**Treatment success** • Total effective rate 82.1% (# cases cured + # cases w/ excellent response/total cases x 100 i.e., ≥60% clearance) • No statistical significance in total effective rate between 3-session (80.2%)and 4-session (85.9%) groups ($P>0.05$)	**Local AEs** • Erythema: 23.9%, mostly mild-moderate(n=12 severe erythema); edema 11.3%; pain 6.8%; mild-to-moderate desquamation 3.3%; slight-to-moderate transient pigmentation 2.3%; transient exacerbation of acne lesions 1.5%; moderate exudation (0.5%)	Non-randomisation; short duration of study
Hong et al,[33] 2013	20	MAL+red light vs. MAL+IPL 530–750nm	**Lesion count** • Mean reduction IL: 69.5% red light side vs. 72.0% IPL side ($P<0.05$) • At 2/52, reduction IL: 26% red light side vs. 17% IPL side ($P=0.008$) • At 8/52, reduction TLC: 48.7% red light side vs. 52.5% IPL side (not significant; *p* value not reported) • No significant difference in IL or NIL counts between 2 treatments	**Local AEs** • No difference in AEs between 2 sides of face • 1 patient developed considerable erythema and inflammation on red light side after irradiation, despite dose reduction; in this patient PDT on IPL side did not show any erythema or hyperpigmentation	Single-blinding only; no placebo arm; small sample size; no ITT analysis; unclear randomisation process
Mei et al,[34] 2013	41	ALA 10%+IPL 420–950nm vs. topical placebo+IPL 420–950nm	**Lesion count** • Significant reduction mean IL count: from 31.1±3.8 to 5.0±1.3 ALA-IPL group vs. 28.2±4.1 to 8.2±1.7 placebo-IPL group ($P<0.05$) • Significant reduction mean NIL count: from 31.1±7.1 to 14.0±6.2 ALA-IPL group vs. 28.2±4.1 to 18.6±3.1 in placebo-IPL group ($P<0.05$)	**Local AEs** • No vesiculation, desquamation, crust formation, or pigmentation in IPL+ALA (study group) or IPL (control group) • All patients described a burning pain during IPL and hot flush after illumination • 3 patients in ALA+IPL group developed transient erythema and monomorphic acneiform eruptions 24h after each treatment, resolved spontaneously in 1–2 days	Blinding of participants only; limited sample size and short duration of follow-up; unclear whether other treatments coadministered during trial period

A/BPO: adapalene/benzoyl peroxide; AE: adverse event; ALA: aminolaevulinic acid; BPO: benzoyl peroxide; C/BPO: clindamycin/benzoyl peroxide; CDLQI: Children's Dermatology Life Quality Index; CI: confidence interval; DL: diode laser; DLQI: Dermatology Life Quality Index; EGSS: Evaluator's Global Severity Score; Excellent or good therapeutic effect: >50% reduction in lesion count); FMR: fractional microneedle radiofrequency; FPS: Fitzpatrick skin type; GA: glycolic acid; GAGS: Global Acne Grading System; GAI: Global Assessment of Improvement; GIS: Global Improvement Score; ICG: idocyanine green; IGA: Investigator's Global Assessment; IGA: Investigator's Global Assessment; IL: inflammatory lesion count; IPL: Intense pulsed light; ISGA: Investigator's Static Global Assessment; ITT: Intention To Treat; JS: Jessner's solution; KAGS: Korean Acne Grading System; LED: light emitting diode; LFTs: liver function tests; MAL: Methyl aminolevulinate; NIL: non-inflammatory lesion count; NR: not reported; OR: odds ratio; PIH: post-inflammatory hyperpigmentation; QoL: Quality of Life; rhGEF: topical epidermal growth factor; SA: salicylic acid; SD: standard deviation; TLC: total lesion count

TABLE 1 (CONTINUED). Effectiveness and tolerability outcomes (all outcomes reported pertain to those at final follow-up visit unless otherwise stated)

AUTHOR, YEAR	PATIENTS (N)	TREATMENT(S)	EFFECTIVENESS	SAFETY	STUDY LIMITATIONS
PHOTODYNAMIC THERAPY, continued					
Wang et al,[67] 2012	30	ALA 3, 5, or 10%+633nm-LED	**Treatment success** • Similar responses in areas receiving either 3, 5, or 10% ALA • Poisson regression analysis: no significant change in lesion count for a 1-unit increase in ALA dose 0.999 times (95% CI 0.998–1.000, *P*=0.22)	**Local AEs** • Pain during light irradiation, edema and erythema post-irradiation, epidermal exfoliation after 2–3 days requiring no intervention, mild pigmentation in 2 patients, and severity unrelated to dose of ALA **Withdrawals** • 3/55 withdrawals due to pain • Recurrence in 4 patients at 3–5 months post-intervention	55 patients recruited; results report outcomes for 30 patients only, but some AEs reported out of 55; unclear how moderate-severe acne determined; no validated tools used for primary outcomes; unclear timepoint for outcome measures
An et al,[74] 2011	13	0.5% liposome-encapsulated 5-ALA+IPL 400–720nm	**Lesion count** • Mean reduction in lesion count at 4/52: 43.2% **Treatment success** • After 2 sessions, 23.1% patients showed 1-grade improvement in KAGS severity, 38.5% showed 2-grade improvement, 7.7% showed 3-grade improvement, 30.8% showed no change	**Local AEs** • No bacterial or viral infections • No serious AEs (stinging or burning sensation, erythema, edema, hyperpigmentation, atrophy, or scarring)	No control arm; small number of patients and short duration of follow-up; inconsistent statistical analysis; no randomization
IPL					
Mohanan et al,[69] 2012	8	IPL IFL i200 system	**Treatment success** • Avg # treatment sessions per patient: 3.4 • 7 patients had good response to treatment (51–75% reduction in lesion count) and 1 patent had moderate response (25–50% reduction) **Patient Satisfaction** • 87.5% patient satisfaction with IPL	**Local AEs** • Two patients developed transient erythema after procedure, resolving spontaneously in a few hours • No other AEs	No follow-up reported; small sample size; no control arm; inconsistent reporting of statistical significance; no randomization; inconsistent #. treatments across participants
El-Latif et al,[68] 2014	50	IPL 530nm vs. 5% BPO	**Lesion count** • Mean reduction of lesions after 5th session: IPL group 61.56%±26.14 vs. BPO group 69.40%±22.35 (*P*=0.06)	**Local AEs** • All patients in BPO group, except for one, suffered from burning and irritation during study period. • In IPL group, 1 patient suffered burning sensation (increased photosensitivity) after sun exposure, lasting for 2 hours	No randomisation; no control arm; statistical significance inconsistently reported; small sample size and short duration of follow-up; unclear if ethical approval obtained
Lee GS,[70] 2012	18	IPL 420nm	**Treatment success** • All patients showed some improvement • Grade 5 (total clearance): 0 patients; Grade 4: 5/18 patients; Grade 3: 8/18 patients; Grade 2: 4/18; and Grade 1: 1/18 • 14/18 subjects (78%) had clearance ≥60%	**Local AEs** • No serious AEs (including secondary hyperpigmentation) • Very mild erythema in all patients, resolved spontaneously within 24–48 hours	Results for 1 vs. 2 sessions not reported separately; range of follow-up times; no control arm; no measures of statistical significance

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TABLE 1 (CONTINUED). Effectiveness and tolerability outcomes (all outcomes reported pertain to those at final follow-up visit unless otherwise stated)

AUTHOR, YEAR	PATIENTS (N)	TREATMENT(S)	EFFECTIVENESS	SAFETY	STUDY LIMITATIONS
LED					
Kwon et al,[47] 2013	35	LED 420nm blue light and 660nm red light vs. sham device	**Lesion count** • Decrease in IL and NIL counts by 76.8% (22.8–5.3, $P<0.01$) and 54% (51.2–23.7, $P<0.01$), respectively, in IPL group • No significant difference in control group in IL and NIL counts ($P>0.05$) **Treatment success** • No patients with IGA Grade 0 or 1 at baseline for both groups, 9 patients improved to Grade 1 and 5 patients to Grade 0 in treatment group (n=18); 2 patients improved to Grade 1 in control group (n=17)	**Local AEs** • Mild dryness (n=2), mild erythema and desquamation (n=1) in LED group	Unclear enrollment process and inclusion criteria; variable duration of LED use/day per patient despite regular adherence checks; small sample size; short duration of follow-up
LASERS					
Kang et al,[35] 2019	9	Laser one pass 1319nm and one pass 589nm	**Lesion count** • 85.7% patients achieved reduction in TLC • Final follow-up 5.4 weeks after final treatment: IL reduced by 2.5 (-23.1%) on treatment side and increased 1.1 (+11.1%) on control side • Increased acne counts on both sides of face in 2 patients	**Local AEs** • Mild discomfort (n=5) and moderate discomfort (n=3) during treatment	Small sample size; short follow-up, unable to assess sustainability of results; no reporting on number of acne lesions; no statistical significance reported; single-blinded
Kwon et al,[29] 2018	25	1450nm diode laser in dual mode vs. 1450nm diode laser in high energy mode	**Lesion count** • Mean IL count decreased by 63.5% (13.6 to 5) on dual-mode side and 39.3% (12.3 to 7.5) on stamp mode-only side ($P<0.05$) **Treatment success** • Mean Leeds Revised Scale from 3.9±0.9 to 1.9 for dual-mode side vs. to 2.7 for stamp-only side ($P<0.05$)	**Local AEs** • Less erythema and edema with dual mode ($P<0.05$) • Localized pigmentation in 4 cases of stamp-only mode • No PIH in dual-mode regimen group • Lower pain score in dual mode than stamp-only mode groups (3.2±1.5 vs. 6.5±2.3, $P<0.05$)	Single blind; small study group; short follow-up period
LASERS AND SYSTEMIC TREATMENT					
Li et al,[36] 2021	47	IPL 420nm +isotretinoin 0.5–0.75mg/kg/day	**Lesion count** • Significant reduction in TLC: 51%±34.3 in isotretinoin+IPL group vs. 27.4%±12.7 in isotretinoin-only group ($P<0.01$) **Treatment success** • Significant GEA reduction from 2.8±0.7 to 1.8±0.8 in isotretinoin+IPL group vs. 2.7±0.7 to 2.3±0.4 in isotretinoin-only group ($P<0.05$) **QoL** • Significantly lower average DLQI in isotretinoin+IPL group (4.7±2.2), compared to isotretinoin-only group (6.3±1.9) ($P<0.05$)	**Local AEs** • No severe AEs (ulceration, infection, depigmentation, atrophy, or scarring) • Isotretinoin+IPL group: mild erythema post-IPL, 1 patient with 1cm blister • Both groups: skin dryness, peeling lips, reaction to coadministered adapalene 0.1% gel	Other topical agents also used in both groups (adapalene 0.1% gel and fusidic acid 2% cream); limited sample size and short duration of follow-up; single-blinded study

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TABLE 1 (CONTINUED). Effectiveness and tolerability outcomes (all outcomes reported pertain to those at final follow-up visit unless otherwise stated)

AUTHOR, YEAR	PATIENTS (N)	TREATMENT(S)	EFFECTIVENESS	SAFETY	STUDY LIMITATIONS
FMR					
Kwon et al,[37] 2018	26	FMR w/ 0.8mm and 2.0mm penetration depth and 20–50 intensity vs. 1450nm diode laser	**Lesion count** • Decrease in IL count by 39.3% (from 14.5 to 9.5) on DL side, and 58.2% (from 15.6 to 6.0) on FMR side ($P<0.05$) • Decrease in NIL count by 27.5% (22.8 to 16.5) on DL side and 33.2% (23.1 to 15.4) on FMR side ($P<0.05$) **Treatment success** • Leeds Revised Acne Grade decreased to 3.1 on DL side and 2.0 on FMR side	**Local AEs** • No significant difference in post-treatment erythema and edema ($P>0.05$) between treatment groups • No PIH on FMR side, but 2 cases of mild, localized PIH on DL side	Single blinded; short follow-up time; no control arm
Lee et al,[71] 2013	20	FMR w/ 1.0mm or 1.5mm penetration depth for 50ms, or 100ms	**Lesion count** • Mean TLC reduced from 18 at baseline to 14.1 at Week 2, but subsequently increased to 19.6 (Week 4) and 17 (Week 8) • # IL not significantly different between right and left cheeks **Treatment success** • Acne severity mean scores: 1.8, 1.3, and 0.6 at Weeks 2, 4, and 8, respectively • Facial oiliness mean scores: 2.2, 1.9, and 1.7 at Weeks 2, 4 ,and 8 respectively	**Local AEs** • No serious AEs, including secondary infection, scarring, or hyper/hypo-pigmentation • More pain and post-treatment crusting on right cheek associated with longer RF exposure time • Mild pain during treatment • Post-therapy bleeding, erythema, and edema improved within 1 week • 2 patients experienced mild multiple pin-head sized pustular eruptions (self-resolved)	No control group; small sample size; no histological assessment of sebaceous gland; only one session of treatment
Lee et al,[50] 2012	18	FMR w/ 3.0mm penetration depth and 7 intensity	**Treatment success** • GIS for active inflammatory lesions—18 patients: Grade 4 (>75% improvement); 8 patients: Grade 3 (51–75% improvement); 6 patients: Grade 2 (26–50% improvement); 2 patients: Grade 1 (0–25% improvement)	**Local AEs** • Pain during treatment, post-treatment crusting and scaling, edema, post-therapy edema, and oozing • Post-treatment bleeding, crusting, and scaling improved in 5 out of 7 patients without treatment.	Single blinded; no statistical analysis to determine significance; retrospective assessment from photographs: subjective bias and difficult to assess true skin pattern
Suh et al,[72] 2021	12	Topical gold nanoparticles plus 400nm tip photopneumatic device	**Lesion count** • Avg # pustules decreased from 6.50 (assessor A) and 8.00 (Assessor B) to 2.17 (A) and 2.50 (B) after treatment ($P=0.001$) • Avg # papules decreased from 12.42 (Assessor A) and 13.33 (Assessor B) to 6.42 (A) and 6.50 (B) ($P<0.001$) • Avg # comedones decreased from 29.75 (Assessor A) and 27.33 (Assessor B) to 10.33 (A) and 11.58 (B) ($P= 0.001$) **Histopathology**: • Decrease in inflammatory cell infiltration and fibrotic changes of the dermis	**Local AEs** • No serious AEs	No control arm; No objectively measured values; Small population size; Short duration of follow-up; Variation of assessment parameters between assessors

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TABLE 1 (CONTINUED). Effectiveness and tolerability outcomes (all outcomes reported pertain to those at final follow-up visit unless otherwise stated)

AUTHOR, YEAR	PATIENTS (N)	TREATMENT(S)	EFFECTIVENESS	SAFETY	STUDY LIMITATIONS
SYSTEMIC THERAPIES					
Gan et al,[51] 2012	2,255	Oral isotretinoin	**Treatment success** • Majority (93.9%) of patients achieved complete remission or substantial improvement (not defined); OR for achieving complete remission 3.85 (95% CI: 2.68–5.55) for those who took ≥100 mg/kg of isotretinoin compared to those who took less • On average, patients received 7.8 months of treatment at a mean dose of 0.5mg/kg (SD±0.2) and mean total cumulative dose was 95.6mg/kg (SD±40.0)	**Local AEs** • Isotretinoin generally well-tolerated • Among documented side-effects, cheilitis was the most common (64.8%, n=1,461), followed by headache (1.8%, n=41), mood change (1.6%, n=37), and photosensitivity (1.5%, n=33) **Withdrawals** • 6.4% (n=145) discontinued treatment due to cheilitis, dyslipidaemia, deranged LFTs, mood changes, arthralgia/myalgia, and headache	Complete remission and substantial improvement not defined; GAGS used at baseline but not at point of outcome measurement; data on long-term follow-up not available; retrospective study: incomplete documentation; missing data
Kim et al,[48] 2014	20	Topical epidermal growth factor vs. vehicle cream	**Lesion count** • IL count reduced by 33.5% ($P<0.05$) on rhGEF side; no significant reduction on control side • NIL count reduced by 25.2% ($P<0.05$) on rhGEF side vs. increased mean count on control side **Treatment success** • Mean baseline IGA reduced from 2.9 to 1.85 on rhGEF side vs .no significant changes on control side ($P<0.05$)	**Local AEs** • No significant AEs including skin irritation or allergic reactions	Unclear process of randomization; small sample size; short duration of follow up
OTHER THERAPIES					
Brownell et al,[56] 2021	13	Topical bakuchiol (UP256)	**Lesion count** • Mean % decrease in IL counts 26.9% (P=0.017) and 28.4% (P=0.013) at 8 weeks and 12 weeks, respectively	**Local AEs** • Investigator-reported AEs included erythema, dryness, scaling, oiliness **Withdrawals** • No participants discontinued due to AEs	No control arm; no blinding; small sample size; short duration of follow-up
Isoda et al,[73] 2015	18	Mild facial cleanser formulated w/ sodium laureth carboxylate and alkyl carboxylates (AEC/soap)	**Lesion count** • 5 subjects had no acne lesions, 2 subjects had mild acne, and 11 had modest acne, compared to 7 patients with modest acne, 9 with mild acne, and 2 with moderate acne at baseline • Acne lesions were not detectable in 25% subjects	**Local AEs** • No complaints of dryness or irritation	20 patients recruited but only 18 analysed; self-reported as controlled trial, but no method of control identified; limitations of study not explored; inconsistent reporting of statistical significance

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radiofrequency and microneedling,[37,50,71] and four studies[48,56,72,73] evaluated other therapies.

Outcomes relating to reduction in lesion count were reported in all but 12 studies.[24,34,49–52,55,64,66,67,69,70] AEs were reported in most studies. However, no studies reported AEs as per data standards (e.g. the Common Terminology Criteria for Adverse Events (CTCAE) classification[75]). The main outcomes regarding effectiveness and tolerability are summarized in Table 1. Appendices 4 and 5 summarize study characteristics and participant demographic data, respectively.

Topical retinoids. Retinoids are a class of compounds with a basic core structure of vitamin A and its oxidized metabolites. They are of particular use in skin of color due to their dual action to treat acne and PIH. Three of the included studies[25,57,58] explored topical retinoids as monotherapy in skin of color. One post-hoc analysis of two multicenter RCTs[7] evaluated lesion count change and reduction in EGSS with tretinoin 0.05%, reporting 60.1-percent reduction

in IL count and 53-percent reduction in noninflammatory lesion (NIL) count versus 51.1 percent and 38.7 percent, respectively, with vehicle. Common side effects of topical tretinoin 0.05% lotion included pain, dryness, erythema, scaling, and burning. Another post-hoc analysis by Lain et al[58] reported that tretinoin 0.05% lotion resulted in greater mean percent reduction in NIL counts in female patients, compared to baseline data in active treatment and vehicle-only groups. Treatment was significantly more effective in female patients than male patients. Tretinoin 0.05% lotion was well tolerated by both sexes, although there was a higher incidence of treatment-related AEs, especially skin dryness, in female patients. Kubota et al[25] evaluated adapalene 0.01% efficacy and safety in 66 Japanese subjects and concluded that twice-weekly application produced similar efficacy results as once-daily application, which may reduce likelihood of AEs in patients with skin of color.

Topical antibiotics. Topical antibiotics provide both antibacterial and anti-inflammatory properties and are typically used concurrently with benzoyl peroxide (BPO) to reduce bacterial resistance. This systematic review yielded 10 studies[20,26,27,38–40,59–61,63] that explored antibiotics as a monotherapy in patients with skin of color. Cook-Bolden et al[60] reported that, at Week 12, there was a median reduction in IL count of 71.6 percent with clindamycin 1.2%/benzoyl peroxide 3.75% compared to 57.1-percent reduction in the clindamycin-only group, 58.4-percent reduction in benzoyl peroxide-only group, and 47.6-percent reduction in the vehicle group, with excellent tolerability. No patient withdrew due to AEs. Callender et al[61] reported that clindamycin 1.2%/BPO 2.5% gel was similarly effective between patients with FPS I to III and those with FPS IV to VI. Similar to the previous study, almost a third of patients reported an IGA of "clear" or "almost clear." In contrast, Amar et al[63] presented an open-label, non-RCT study with a small number of patients and nonvalidated definitions of treatment success, reporting a much higher percentage of improvement in LC and IGA scores in patients using clindamycin 1.2%/BPO 3.75%. In a much larger cohort (N=800) of Japanese patients, Kawashima et al[27] reported that clindamycin 1.2%/BPO 3.0% once daily was more effective than clindamycin monotherapy in reducing total LC, but was less effective than clindamycin 1.2%/BPO 3.0% twice-daily application. Contact dermatitis was the leading reason for study withdrawal, which was most frequent in the twice-daily clindamycin 1.2%/BPO 3.0% group. Xu et al[26] reported significant improvement in LC using clindamycin 1%/BPO 5% once daily, compared to twice-daily application, among Chinese patients with AV. Main adverse events included application site reaction. Alexis et al[59] reported clindamycin 1.2%/BPO 3.75% to be superior to vehicle in terms of LC and improvement in EGSS across all FPS types, with infrequent AEs. Hayashi et al[28] reported similar efficacy of clindamycin 1.2%/BPO 3% in terms of LC compared to clindamycin 1.2%/adapalene 0.1%, but clindamycin 1.2%/BPO 3% was superior in terms of ISGA score. A study by Kawashima et al,[20] which evaluated BPO 2.5% monotherapy in Japanese patients, had the longest follow-up period of 52 weeks. Investigators found BPO 2.5% monotherapy to be effective, with comparable results to BPO 5%, in reducing IL and TL counts, but BPO 2.5% monotherapy was less superior in reducing NIL. In a separate study, Kawashima et al[39] reported BPO 3% was effective but was associated with more AEs (58%), compared to vehicle, with contact dermatitis being the most commonly reported. Only one study explored the use of nadifloxacin 1% as monotherapy. Jung et al[40] found that IL counts were reduced by 70 percent on nadifloxacin-treated skin and increased by 13.5 percent on vehicle-treated skin; NIL showed reductions of 48.1 and 10.1%, respectively. AEs included mild erythema and dryness, which resolved spontaneously. Treatment duration of eight weeks was chosen to avoid antibiotic resistance; thus, long-term data from this study are not available.

Combination retinoids and antibiotics. Seven studies[28,30,31,41,42,62,64] examined combination retinoid and antibiotic treatment, and all authors reported an improvement in LCs. DuBois et al[64] reported results from a split-faced, observer-blinded study in Korean subjects, in which a topical combination of adapalene and benzoyl peroxide (A/BPO) was found to be superior to monotherapy. Kim et al[30] also reported A/BPO to be superior to monotherapy in Korean patients, and Alexis et al[62] reported similar improvements in LCs between patients with lighter skin types and those with darker skin types, all of whom were treated with A/BPO. AEs included erythema and scaling, which were also similar between the FPS I to III and FPS IV to VI groups. Interestingly, 9.7 percent of participants adopted a regimen of alternate-day application due to side effects.

Studies by Callender[41] and Schmidt et al[42] evaluated clindamycin/tretinoin combination in skin of color patients, reporting excellent responses and minimal side effects. However, it was noted that one patient in Callender's study withdrew due to periorbital edema.

Takigawa et al[31] demonstrated that combination of adapalene 0.1% and nadifloxacin 1% cream had significantly greater efficacy than adapalene monotherapy in reducing IL in patients with moderate or severe AV. Combination use of topical adapalene and nadifloxacin may have additive and complementary effects, resulting in clinical superiority of combination therapy to monotherapy. Furthermore, bacterial examination revealed that no resistance to nadifloxacin was demonstrated among 76 strains of *P. acnes* isolated from 87 patients.

Dapsone. Taylor et al[43] found that dapsone 7.5% gel significantly reduced inflammatory, comedonal, and total lesions in FPS I to III ($P<0.001$) and IV to VI ($P<0.01$) groups versus vehicle. ILs responded to treatment first, compared to other lesion types. However, similar to the Alexis et al[53] study, evaluation between skin types was not the primary outcome. Draelos et al[44] concluded that dapsone 7.5% resulted in similar improvement in LC between skin types compared to vehicle but was superior in terms of GAAS and PIH improvement compared to vehicle. The use of oral dapsone in patients with skin of color has not been practiced widely due to higher incidence of G6PD deficiency in certain ethnic groups, such as African, South Asian, Middle Eastern, and Mediterranean.[3]

Peels. Chemical peels, similar to retinoids, have dual action against acne and PIH. Sarkar et al[21] reported that LCs and PIH improved in all three study groups (5% glycolic acid, 20% salicylic–10% mandelic acid, and phytic acid

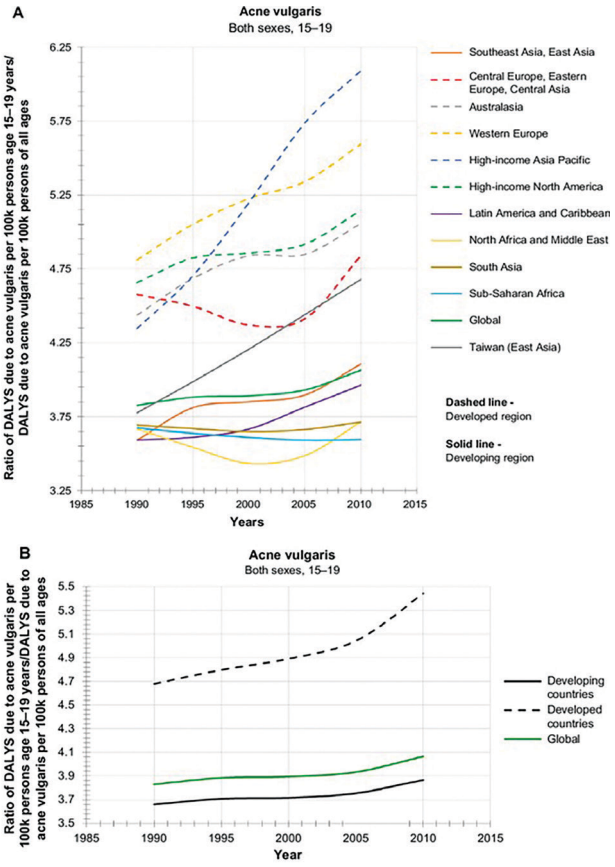

FIGURE 1. Global burden of acne vulgaris in adolescents 15 to19-year-olds stratified to developing and developed countries (adapted from Lynn et al[5])

combination peels) in patients with FPS IV to VI. Data indicate that 20% salicylic–10% mandelic acid had greatest effect in reducing PIH, while glycolic acid was more effective in reducing NIL than IL, according to Kaminaka et al.[46] How et al[45] reported that Jessner's and salicylic acid were both equally effective across all outcome measures studied.

Photodynamic therapy (PDT). A range of PDT combinations have been evaluated. Two studies included Korean patients: Choi et al[22] (N=21) and Park et al[49] (N=1,213). Choi et al evaluated the use of idocyanine green (ICG)-based PDT versus methyl aminolevulinate (MAL)-based PDT in combination with 630nm light-emitting diode (LED), 805nm diode laser, or 830nm (LED).[22] Choi et al[22] reported no bactericidal effects of MAL-PDT; however, cultured *P. acnes* were killed using the 805nm diode and 830nm LED lasers in combination with ICG-PDT, though the difference in the efficacy of the 805nm diode laser and 830nm LED was not statistically significant. Park et al[49] reported that 39.8 percent of study participants who had received 3 to 5 sessions of ICG-PDT demonstrated excellent improvement in acne lesions (qualified as 76–100% improvement). ICG-based PDT was generally well-tolerated with reports of pain, erythema, scaling and pruritus, which resolved within seven days without further intervention. These studies suggest that ICG-based PDT is an effective treatment option for AV in Korean patients; however, the optimal light source remains equivocal.

Aminolevulinic ccid (ALA)-based PDT was evaluated in nine studies.[24,34,52,54,55,65–67,74] Two studies[34,74] evaluated 10% ALA, four studies[24,55,65,66] evaluated 5% ALA, one study evaluated 3.6% ALA,[52] one study evaluated 0.5% ALA,[74] and one study[67] evaluated three different concentrations (3%, 5% and 10%). The light source in these studies included LED in five studies,[52,54,65–67] intense pulsed light (IPL) in two studies,[34,74] and broadband light in one study.[55] One study[24] compared the effectiveness of PDT, IPL, or blue-red LED phototherapy . Three studies[52,54,66] reported clearance rates (≥90% reduction in lesion count) of 47.06 percent,[52] 32.5 percent,[66] and 47.83 percent[54] with ALA-LED-PDT. An et al[74] reported a mean reduction in lesion count of 43.2 poercent with ALA-IPL-PDT. Similarly, Mei et al[34] found that ALA-IPL-PDT was more effective than monotherapy with IPL with global lesion count reductions of 75.2 percent and 51.0 percent, respectively. Similarly, Liu et al[24] found that 92 percent of participants achieved clearance and moderate improvements (≥60% reduction in lesion count) in the ALA-PDT group versus 58 percent in the IPL only group and 44 percent in the LED only group. Finally, Asayama-Kosaka et al[55] found that ALA-PDT with broadband light reduced the Global Acne Grading Scale (GAGS) from 22.1 (standard deviation [SD]±3.8) to 16.3 after one treatment only. Despite the heterogeneity of ALA concentrations and light sources used, it appears that ALA-PDT is an effective treatment for AV in patients with skin of color. However, most patients reported a combination of pain, erythema, and/or oedema after ALA-PDT, which may adversely affect patient adherence. Similarly, the ideal regimen (dose, light source, duration, frequency) requires considerable optimization. However, it should be noted that Wang et al[67] reported no significant change in lesion count for a one-unit increase in ALA concentration.

Other PDT regimens included BPO 5% with IPL therapy versus BPO alone, chlorophyll-a-PDT with LED versus LED alone, and MAL-PDT with IPL versus red light.[23,32,33] Mokhtari et al[23] reported a reduction in total LC from 41.86 (SD±14.17) to 6.95 (SD±6.81) in the BPO-IPL group versus 44.82 (SD±25.36) to 19.65 (SD±9.11) in the topical BPO-only group. Interestingly, Song et al[32] reported that chlorophyll-a PDT resulted in a statistically significant reduction in pustule count of 66 percent versus 29 percent in the LED-only group. Hong et al[33] reported a 48.7-percent reduction in IL among patients treated with MAL-PDT using red light versus 52.5 percent in the IPL-only group, though these results were not statistically significant. Notably, this study necessitated a reduction of red

light dose from 37J/cm^2 to 22 J/cm^2 due to reports of pain, erythema, and edema. The MAL-PDT and BPO-PDT studies both reported significant numbers of patients experiencing pain, erythema, and edema post-treatment with PDT. Likewise, two[33] and six[23] patients withdrew from these studies due to the intolerability of these side effects. By contrast, Song et al[32] showed that a chlorophyll-a-PDT was well-tolerated, reporting no pain, erythema, or edema.

IPL. The effectiveness of IPL therapy was assessed in two nonrandomized interventional trials[68,69] and one preliminary trial.[70] El-Latif et al[68] compared the efficacy of topical 5% BPO gel applied once nightly for 5/52 with five once-weekly sessions of IPL (530nm) among Egyptian (FPS IV) participants; Lee et al[70] and Mohanan et al[69] conducted interventional trials evaluating Korean and Indian participants' responses, respectively, to IPL without a comparator group. El-Latif et al[68] reported that BPO and IPL resulted in considerable improvement of acne after 5/52, with a mean 69.40-percent (SD±22.35) reduction of lesions in the BPO group versus 61.56 percent (SD±26.14) in the IPL group, though the difference between the two treatment arms was not considered significant. Lee[70] and Mohanan et al[69] trials reported 78 percent and 87.5 percent (respectively) of participants achieved an LC rate of at least 50 percent. In all three studies, there were no serious AEs were reported, three reported instances of self-resolving erythema (one in Lee,[70] two in Mohanan et al),[69] and one report of a "burning sensation" for two hours after sun exposure.[68] All studies concluded that IPL is a useful and well-tolerated treatment modality for AV in these patient populations.

LED. One double-blind RCT[47] evaluated the efficacy of LED (420nm blue light and 660nm red light) versus a sham device over four weeks. The authors reported a statistically significant reduction in IL and NIL counts of 76.8 percent (from 22.8 to 5.3) and 54 percent (51.2 to 23.7) respectively in the study group. This study also reported histopathological and immunohistochemical changes and noted that LED treatment resulted in reduced sebum output, attenuated inflammatory cell infiltrations and reduced the size of sebaceous glands; these changes were not noted in the control group. The treatment was well-tolerated, with mild erythema and dryness noted in three participants, but no severe AEs reported. Overall, LED appears to be tolerable and effective therapy for acne vulgaris in skin of color patients.

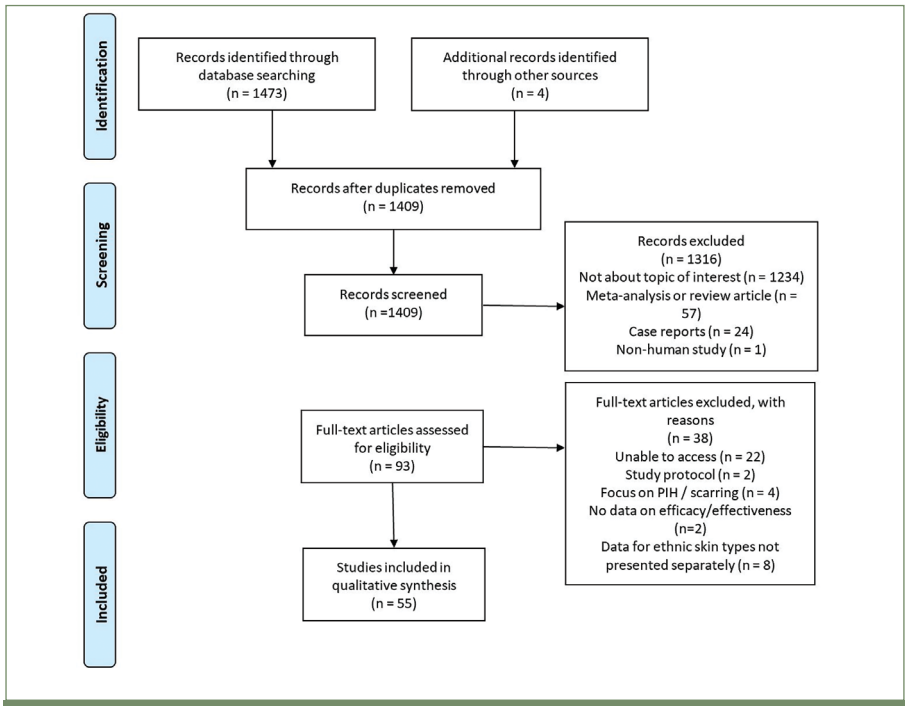

FIGURE 2. PRISMA flow chart

Laser. Two single-blinded, split-face RCTs[29,35] evaluated the efficacy of laser therapy. Kang et al[35] included nine participants (one of which was White) who were treated with a regimen of one pass with a 1319nm laser followed by one pass with 589nm laser for four sessions at 2 to 3 week intervals to one side of the face, with no intervention on the control side. At the final follow-up (5.4 weeks after the final treatment), IL counts had reduced by 23.1 percent on the treatment side versus an increase of 11.1 percent on the control side. In a study by Kwon et al,[29] participants received treatment using a 1450nm diode laser with low-energy stamp mode targeting ILs, followed by moving mode for 4 to 5 passes on the intervention side versus one pass of 1450nm diode laser with conventional high-energy stamp mode on the control side for three sessions at four-week intervals. Twelve weeks after the final treatment, the number of ILs had reduced by 63.5 percent on the dual-mode side versus 39.3 percent on the stamp mode-only side ($P<0.05$). In both studies, treatment was well-tolerated with no severe AEs reported and a few reports of discomfort during treatment. These studies suggest that laser treatment is a useful monotherapy or adjunct therapy for the treatment of AV in skin of color patients. However, the optimal frequency and mode (dual-mode vs stamp mode) remains undetermined.

Combined IPL and systemic therapy. One RCT[36] reported treatment efficacy in Chinese patients (FPS III–IV) with AV using a combined regimen of oral isotretinoin (0.5–0.75mg/kg/day) and biweekly IPL (420nm) versus oral isotretinoin alone. At Week 12, investigators reported a statistically significant ($P<0.01$) reduction (53%) in the total number of lesions (SD±33.5) in the study group (combined oral isotretinoin plus IPL) compared to 27.2 percent (SD±14.7) in the control (oral isotretinoin only) group. Similarly, the GEA grade reduced from 2.8 at baseline (SD±0.7) to 1.8 (SD±0.8) in the study group vs 2.7 at baseline (SD±0.7) to 2.3 (SD±0.4) in the control group ($p< 0.05$). No severe AEs were reported; however ,62.5 percent of the participants reported mild-to-moderate pain during the IPL treatment. Other mild AEs included mild erythema

immediately post-IPL reported by most participants; one participant developed a 1cm blister post-IPL, which resolved within one week without further intervention. Both groups reported skin dryness, peeling lips, and allergic reactions to coadministered adapalene 0.1% gel without a statistically significant difference observed between the groups. There is little evidence to support the use of combined oral isotretinoin plus IPL (420-nm) for the treatment of AV in Chinese patients (FPS III–IV). However, this single-blind RCT suggests that this treatment regimen might be useful and well-tolerated.

Fractional radiofrequency and microneedling (FRM). FRM was evaluated in three studies.[37,50,71] In a prospective interventional study by Lee et al,[71] participants received one pass of treatment, whereas participants in Lee et al's[50] retrospective cohort study received two FMR passes in each of two sessions, one month apart. Kwon et al[37] reported that in a single-blind, split-face RCT, participants received 2 to 3 passes of FMR on one side of the face versus two passes of 1450nm diode laser on the other side. Unfortunately, all three of these studies reported heterogenous outcomes. Lee et al[71] reported a reduction in mean total IL from 18 at baseline to 14.1, 19.6, and 17 at Week 2, 4, and 8 respectively, demonstrating an improvement in lesion count after a single treatment and at Week 2, but worsening thereafter. In the retrospective cohort study,[50] the mean clinical improvement scores for active lesions and for severity of lesions were Grade 2.6 and Grade 2.4, respectively (Grade 2=26–50% improvement, Grade 3=51–75% improvement). Kwon et al[37] reported a statistically significant reduction in total IL count of 39.3 percent on the diode laser side versus 58.2 percent in the FMR side. There were no severe AEs reported among these three studies; however, there were several reports of pain during treatment plus post-treatment bleeding, pain, crusting, and scaling. Kwon et al[37] reported no statistically significant difference between the DL and FMR group in terms of AEs. These studies suggest that FMR is an effective treatment option for AV in skin of color patients. However, there remains a need to determine the optimal power settings, number of sessions and interval between sessions.

Systemic therapies. This search found only one study that evaluated the use of systemic treatment for AV in patients with skin of color. Gan et al[51] evaluated the effectiveness of oral isotretinoin in a multiracial Asian cohort. This study reported that 93.9 percent of the patients achieved complete remission or substantial improvement; however, these terms were not quantified within the study. The odds ratio for achieving complete remission for patients receiving at least 100mg/kg of isotretinoin was increased to 3.85 when compared to patients receiving a lower dose. Overall, isotretinoin was well-tolerated; however, side effects included cheilitis (64.7%), headache (1.8%), mood change (1.6%), and photosensitivity (1.5%). Importantly, less than five percent of the patients developed abnormal liver function tests and/or raised serum triglycerides. Oral isotretinoin is a well-established treatment for AV; however, there is a paucity of evidence supporting its use in skin of color patients.

Other therapies. Kim et al[48] reported that topical recombinant human epidermal growth factor (rhEGF) was effective in reducing IL and NIL in 20 Korean adults with mild-to-moderate AV, with minimal AEs. Topical EGF likely reduces the level of sebum due to its ability to suppress lipogenesis. Possible anti-inflammatory effects include rhEGF's interference with arachidonic acid metabolism, regulating chemokine expression in keratinocytes, and reduction of keratin plugs in follicles.

Isoda et al[73] reported that a sodium laureth carboxylate and alkyl carboxylates (AEC) based-soap was effective and well tolerated in 20 Japanese male patients with mild-to-moderate acne. At Week 4, 25 percent of the patients reported no acne lesions. However, although 20 patients were recruited, only 18 were analyzed with no intention-to-treat analysis, and there was inconsistent reporting of statistical significance.

Brownell et al[56] reported that bakuchiol, an ingredient found in the leaves and seeds of the *Psoralea corylifolia* plant, decreased IL count by 26.9 percent and 28.4 percent at Week 8 and Week 12, respectively, in a single center, open-label pilot study. Thirteen subjects with FPS III to VI and mild or moderate acne received treatment twice daily for 12 weeks. AEs included erythema, dryness, scaling, and oiliness, with no reported discontinuation. However, the lack of control arm, small sample size, and short follow-up duration limit this study's findings.

One nonrandomized interventional trial[72] assessed the efficacy of a novel treatment: topical application of gold nanoparticles followed by treatment with a pneumatic device (Isolaz™, Aesthera Corporation, Pleasanton, California) with a flashlamp and vacuum for applying negative pressure. In this trial, Korean patients with moderate-to-severe AV received three successive treatments at 1 to 2 week intervals. According to Assessor A, the average number of pustules decreased from 6.50 to 2.17 after treatment, and the average number of papules decreased from 12.42 to 6.42. Similar results were observed by Assessor B—the average number of pustules decreased from 8.00 to 2.50 after treatment and the average number of papules decreased from 13.33 to 6.50. Histopathological findings reported a decrease in inflammatory cell infiltration and fibrotic changes of the dermis. No serious AEs were reported. In this preliminary trial, gold photothermal therapy showed significant clinical and histological improvements in AV in Asians without serious AEs; however, the very small sample size limit these findings. Randomized, controlled studies with larger patient populations are necessary before firm conclusions can be drawn.

DISCUSSION

This systematic review, based on 55 studies, assesses the effectiveness and tolerability of four main therapies in the treatment of AV in skin of color patients: topical therapies, laser- and light-based therapies, systemic therapies, and miscellaneous therapies. To our knowledge, no previous systematic review or meta-analyses have been performed that specifically evaluate the effectiveness and tolerability of treatments used in patients with AV and skin of color. Previous evidence-based reviews[2,76] have collated some data on pharmacological and nonpharmacological therapies when managing AV in skin of color patients. These reviews also noted the paucity of clinical studies that evaluate the tolerability and efficacy of acne treatments specifically among patients with skin of color.

Topical therapies. Retinoids have been

the mainstay treatment for AV. Cook Bolden et al[57] reported tretinoin 0.05% lotion to be well tolerated and efficacious in Hispanic patients. The investigators interestingly chose to compare tretinoin and vehicle to baseline data, although results would have been more robust if tretinoin was compared directly to vehicle. Furthermore, there was a relatively large discontinuation rate, and a significant side effect profile was reported for tretinoin, which included application site pain, dryness, erythema, scaling, and burning. Almost three quarters of patients expected to see results overnight or in 1 to 2 weeks (81% Hispanics, 68% White); treatment adherence was lower among Hispanic participants. This reinforces the need to manage unrealistic expectations, which may be higher among Hispanics for unexplained reasons. The concern with using retinoids in skin of color is partly due to the fear of an exaggerated PIH response, an element of irritant contact dermatitis. However, more studies recently have concluded that retinoids are better tolerated and efficacious in skin of color when used at lower concentrations.

Adapalene is a third-generation topical retinoid used in the treatment of mild-to-moderate acne. Kawashima et al[20] reported a significant incidence of adapalene-related side effects. Tu et al[77] compared adapalene 0.1% to tretinoin 0.025% in Chinese patients and found equivalent efficacy but reported higher incidence of local irritation with tretinoin, which was echoed by Goh et al,[78] based on data from Chinese, Indian, Malay and Caucasian subjects, although a report on efficacy was not provided. Tazarotene was found to be effective in reducing lesion count among Indian subjects, as reported by Saple et al,[79] however as this study had a short follow-up period; hence, long-term conclusions cannot be safely drawn.

The use of topical antibiotics in the treatment of AV is a common practice in all skin types. Cook-Bolden et al[60] reported clindamycin phosphate 1.2% in combination with BPO 3.75% to be superior to vehicle, with differences becoming evident at Week 4. Study weaknesses include the short follow-up period and the failure to report results in relation to FPS rather than ethnic group, as even within the Hispanic population, FPS can vary considerably. Amar et al[63] echoed the findings of Cook-Bolden et al[60] when trialing clindamycin/BPO combination in patients with FPS V to VI with moderate facial acne. The author reported at least 1-grade improvement in IGA in 100 percent of the participants. However, critics may question whether a 1-grade reduction on IGA/PIH scale, is a meaningful outcome in clinical practice. Many authors use at least a 2-grade reduction in the scale as a primary or secondary outcome. Callender et al[61] reported clindamycin phosphate 1.2 %/BPO 2.5% to be well tolerated and to have similar efficacy in reducing IL and NIL in patients with FPS I to III, compared to those with FPS IV to VI, at Week 12 (40%, 25.6%, 28.8% vs 40%, 25.7%, 29.4% respectively). Xu et al[26] reported that, among 1,020 Chinese subjects with mild-to-moderate acne, more patients achieved a 2-grade or greater improvement in ISGA scores at Week 12 using clindamycin 1%/BPO 5% once daily gel, compared to clindamycin 1% twice-daily gel, though it is not clear why study investigators compared twice daily combination therapy to once daily monotherapy.

Dubois et al[64] evaluated adapalene 0.3% in combination with BPO and noted that 56 percent of study participants had IGA 0/1 and 87 percent reported excellent improvement in GAIS. Hyperpigmentation was reduced by 27 percent compared to baseline over a period of 16 weeks. Tolerability of A/BPO 0.1% was similar to A/BPO 0.3%, with no observed increased risk of PIH. Hence, one can argue that adapalene 0.3% is an effective treatment for AV in skin of color and is more tolerable when combined with BPO.

Similarly, in a study by Kim et al[30] topical A/BPO was superior to monotherapy in Korean subjects in a split-face model. Lesion count improved but more patients complained of local irritation. However, these findings are limited by the study's single-blinded design. Alexis et al[62] performed a randomized, controlled, post-hoc analysis and reported that adapalene 0.3%/BPO 2.5% gel was equally effective among light- and dark-skinned patients (63.6% change in NIL count in lighter skin type vs 61.1% in darker skin typ; similar results in IL count). However, the purpose of the study was to compare differences compared to baseline. The study was insufficiently powered to compare differences between skin types. Callender et al[41] found that the clindamycin/tretinoin topical gel combination was well tolerated, causing little to no irritation. However, results cannot be extrapolated to more severe stages of acne as the patient group studied had mild-to-moderate acne. It is, however, commendable that the washout period was mandatory for oral corticosteroids and antibiotics, which was not been explicitly mentioned in many of the other studies. Clindamycin appears to enhance comedolytic activity of tretinoin via its ability to loosen and prevent follicular impactions, and tretinoin may provide greater accessibility and penetration of clindamycin into follicular environment. In terms of AEs, the topical antibiotic was well tolerated but there appeared to be a disproportionally higher incidence of contact dermatitis than with other treatment modalities. Topical dapsone was reported to be efficacious and well tolerated; however, overall recommendations are not possible based on only three studies evaluating distinct formulations. Chemical peels appear to be effective but are likely used in combination with other agents. Large dropout rates seen in chemical peel trials, possibily in part due to the number of treatment sessions required, can be problematic in patients with skin of color, a patient group in which treatment adherence is already known to be low.[21] Salicylic acid 20% to 30% seemed to be particularly effective in active LC and PIH in Asian subjects.[22,80-81]

Light and laser therapies. Regarding ALA-PDT and light-based therapies, most treatments were well-tolerated, and the most frequently reported side-effects included erythema, pain, edema, and hyperpigmentation. However, our most significant finding is the paucity of evidence available to facilitate effective and safe decision-making for the treatment of AV in skin of color patients.

Several studies in this review evaluated the use of light-based therapies in patients with skin of color; however, the quality of these studies was highly variable. Likewise, there was significant variation in the interventions evaluated, such as different photosensitizers, wavelengths, fluences, numbers of sessions, and frequencies of application.

The current systematic review revealed that the number of light-based sessions varied from 1 to 8, with 2 to 4 sessions being the most common. Our analysis indicates that PDT using topical ALA has been the most investigated light-based therapy. Topical ALA's mechanism of action in PDT is via penetration of the stratum corneum and preferential accumulation in the sebaceous glands where it is metabolized to PpIX, a potent photosensitizer, in sebocytes.[55,74] This enhances phototoxicity in preparation for light-based therapies, which leads to the destruction of affected sebaceous glands.[55] Eight studies reporting on this treatment showed that ALA-PDT can be successfully used to treat AV in ethnic skin. Three studies[52,54,66] reported clearance rates (≥90% reduction in lesion count) of greater than 35 percent, and two studies[34,74] reported lesion count reductions greater than 40 percent. However, the ideal regimen (ALA strength, light source, duration, frequency) requires considerable optimization. Higher strengths of ALA may result in increased rates of PIH,[66] a particular concern among darker skinned individuals. Notably, Wang et al[67] reported that three different ALA concentrations (3%, 5%, 10%) generated similar responses, and Tao et al[52] reported that a 3.6% ALA strength with 1.5 hour occlusion may increase patient acceptability of treatment by reducing overall treatment time and side effects. It may, therefore, follow that lower strength ALA preparations would offer maximal therapeutic benefits while attenuating post-treatment side effects in patients with skin of color.

Other photosensitizers evaluated for use in skin of color patients include ICG, MAL, BPO, and chlorophyll-a. ICG-based PDT using 685nm IPL, 830nm LED, and 805nm diode laser had significant clinical effects on reducing acne severity. BPO-PDT was reported to produce a statistically significant reduction in total lesion count compared to BPO monotherapy, and chlorophyll-a PDT was reported to achieve a statistically significant reduction in pustule count compared to LED monotherapy. However, MAL was found to produce no statistically significant reduction in ILs compared to red-light monotherapy. Again, the quality of evidence supporting the effectiveness of these regimens in patients with skin of color is poor. Likewise, the small, single study evaluating photopneumatic therapy with gold particles that combined physical extraction of comedones with that of traditional PDT, cannot reliably be used to inform decision-making for skin of color patients with AV, despite results demonstrating significant clinical and histological improvements.

The light source for PDT remains equivocal. Studies included in this review included IPL, LED, and diode laser as the light source during PDT. Unfortunately, only two studies directly compared a photosensitizer with different light sources—Hong et al[33] compared IPL-based MAL-PDT with red light MAL-PDT, and Choi et al[22] compared LED-based ICG-PDT with diode laser ICG-PDT. These studies found no statistically significant difference between the two treatment groups.

Dong et al[54] concluded that IPL is a useful type of light for PDT due to its ability to increase temperatures in inflamed acne lesions and at the dermal-epidermal junction; and to cause photoactivation and induction of singlet oxygen production—evidenced by the presence of absorption peaks for endogenous porphyrins after IPL-PDT.[54] However, Hong et al[33] reported that red light was preferable due to the longer wavelength, when compared to IPL, which results in deeper penetration into the dermis to activate porphyrin in deeply-situated sebaceous glands. A similar argument was made by Choi et al[82] who suggested that red-light LED is a better treatment option than diode lasers due to its ability to penetrate deeper into the skin and irradiate the entire face and lesions simultaneously. Importantly, in the Hong et al[33] study, the red light LED dose was reduced from 37J/cm^2 (a protocol accepted in Caucasian patients) to 22J/cm^2 because two patients withdrew from the study due to intolerable pain, erythema, and edema. This suggests that smaller doses of red light LED might be preferable in skin of color patients.

Five studies evaluated light-based therapies as monotherapy in skin of color patients. IPL, LED, and laser therapies were found to be effective and well-tolerated treatment options for the treatment of AV. The use of these modalities may offer comparable clinical efficacy to pharmacological therapies, with fewer local AEs and systemic side effects that may complicate oral treatment.[47] However, as previously stated, there is an urgent need to optimize treatment protocols in patients with skin of color to determine which therapies offer superior clinical efficacy in this population.

Other therapies. FRM uses insulated needles to target dermal structures using electrothermal energy.[71] This may lead to therapeutic effect via thermal damage to sebaceous glands or physical disruption of hyperkeratotic plugs by microneedles.[71] FRM led to statistically significant reductions in lesion counts in the three studies in which this treatment was evaluated. FRM may also offer a more tolerated delivery of thermal energy to dermal tissues via microneedles when compared to nonablative radiofrequency devices or ablative fractional lasers.[50] Similarly, there is a reduced risk of hyperpigmentation following treatment with FRM due to the reduced energy absorption of melanin pigment.[50] Although these studies reported significant results, an overall conclusion based on three studies must be interpreted with caution.

Our search found only one study[51] that evaluated the use of systemic therapies for the treatment of AV in skin of color patients. Oral isotretinoin was evaluated in a large cohort study and was found to be effective and well-tolerated, despite the known potential for hepatotoxicity and iatrogenic hypertriglyceridaemia. No studies were found that evaluated the efficacy of other commonly used oral therapies, including oral antibiotics and hormonal therapies. This may be due to our inclusion/exclusion criteria, specifically our exclusion of studies pre-2011; however, despite the widespread use of these agents, their use in skin of color patients is most likely derived from studies evaluating efficacy in Caucasian patients.

One of the most important findings in our review was the lack of studies that evaluated the efficacy and tolerability of treatments among Black, African-American, and Afro-Carribean patients. Out of 55 included studies, only four papers[45,53,63,64] exclusively evaluated our primary outcome in patients with FPS IV to VI. The paucity of data pertinent to this population demonstrates the tendency for Black, African American, and Afro-Caribbean patients to be underrepresented in clinical trials.[83,84] Participants in clinical trials should

reflect the diversity of the population, with a particular focus on those most affected by the disease. The lack of representation of this group in clinical trials has resulted in the adoption of treatment regimens that potentially are less efficacious in this population.

Limitations. An important limitation of our review is the high level of heterogeneity among included studies. There was wide variability in treatment modality, outcome measurement tools, different study characteristics (e.g. parameters, concentrations, number of treatments, follow-up periods) and differences in reporting results (e.g. absolute values, percentages, graphs, and figures). Similarly, the studies we included in our evaluation were performed in different geographical and cultural settings, which may prevent generalization of any results due to factors such as differences in exposure to natural sunlight and baseline variations in FPS. These factors must be taken into account when interpreting our findings.

We also experienced limitations in the inclusion of studies, in particular the inclusion of non-RCT studies. However, this was necessary in order to ensure sufficient data were available for adequate exploration of our primary aim: to assess the effectiveness and tolerability of pharmacological and nonpharmacological therapies in skin of color patients with AV. Several studies had a split-face design; however, it is unclear whether there are systemic effects that light and other therapies may exert on the control side of the face, even if it is not treated directly. Therefore, this review has highlighted the necessity for high-quality RCTs, with inclusion of a control arm in the study design, in order to determine the efficacy of an intervention in patients with skin of color.

The majority of the included studies demonstrated low levels of evidence. The small numbers of participants in most interventional trials indicates that most of the included studies were likely underpowered, which may have resulted in nonstatistically significant results. Secondly, most studies used short follow-up periods, which means that our findings may not be representative of long-term effects. Furthermore, the moderate-to-high risk of bias among the majority of the studies possibly affected the study results. The most common risk of bias was performance bias. In some studies, participants and/or assessing clinicians were not blinded, meaning that participants and/or clinicians were most likely aware of the treatment side. Only a small number of studies ensured blinding integrity by exposing the control arm to a sham or placebo treatment. Furthermore, in most studies, the research integrity was questionable, such as unclear ethical approval or possible conflicts of interest. Finally, many studies did not adequately describe the use of concomitant interventions, which made it difficult to solely evaluate the effectiveness of the investigated therapy.

The authors also acknowledge that this review is likely to have included a biased selection of the evidence, due to exclusion of gray literature and articles without full texts.

Furthermore, to date there is no acne severity assessment tools that have been validated for different ethnic skin types. The lack of standardized assessment tool also presents problems in that data cannot be reliably compared across the literature as these systems are not interchangeable. Development of a universal system is difficult due to the way in which acne can be defined by the multiple lesion types, the changing nature of the lesions, and involvement of multiple body sites other than the face.[91] Similarly, lower rates of post-treatment erythema and inflammation as a cause of this erythema are likely due to poor detection with no official assessment tool available for darker skin types.

CONCLUSION

AV seems to share the same pathogenesis regardless of race or ethnicity but has different clinical presentations. In darker skin types, there seems to be a heightened subclinical inflammatory response, even in noninflammatory lesions, which is thought to trigger an exaggerated PIH response and keloid scarring. Our findings are in line with previous reviews regarding the general direction of evidence for the use of current available treatments in AV specific to skin of color.

Our results reinforce the need for standardized outcome measures, larger studies of better quality, and adequate reporting, raised by previous studies on acne in skin of color patients. Due to limited evidence, we are unable to draw firm conclusions from the results of this review to guide decisions in practice, especially those pertaining to long-term outcomes. Our systematic review found a paucity of high-quality clinical trials evaluating the effectiveness and tolerability of therapies for the treatment of AV in darker-skinned patients. Certainly, there is the unmet need for more trial and real-life clinical data on ethnic skin in all areas of dermatology. We would welcome future research, using double-blinded, placebo-controlled study designs with homogeneous data collection and processing to optimize treatment outcomes in this frequently neglected patient group.

APPENDICES

Appendices to this article can be accesed here: https://jcadonline.com/wp-content/uploads/Peterknecht-Appendices.pdf

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