doi:10.36849/JDD.8148

 ORIGINAL ARTICLE

Treatments for Moderate-to-Severe Acne Vulgaris: A Systematic Review and Network Meta-Analysis

Julie C. Harper MD,[a] Hilary Baldwin MD,[b,c] Saswata Paul Choudhury MS,[d] Deepti Rai MS,[d] Bikramaditya Ghosh MPH,[d] Md Sohail Aman MS,[d] Abhra R. Choudhury MDS,[d] Sekhar Kumar Dutta MS,[d] Debalina Dey MS,[d] Subrata Bhattacharyya MS,[d] Tina Lin PharmD,[e] George Joseph PhD,[e*] Ankur A. Dashputre PhD MS,[e] Jerry K.L. Tan MD FRCPC[f,g]

[a]The Dermatology and Skin Care Center of Birmingham, AL
[b]Robert Wood Johnson Medical Center, New Brunswick, NJ
[c]The Acne Treatment and Research Center, Brooklyn, NY
[d]PharmaQuant, Kolkata, West Bengal, India
[e]Bausch Health US, LLC, Bridgewater, NJ
[f]Windsor Clinical Research Inc, Windsor, ON, Canada
[g]Department of Medicine, University of Western Ontario, Windsor, ON, Canada
[*]Current affiliation: BioNTech US Inc, Cambridge, MA

ABSTRACT

Background: Multiple treatment options exist for the management of moderate-to-severe acne. However, the comparative effectiveness (efficacy/safety) of moderate-to-severe acne treatments has not been systematically examined.

Methods: A systematic literature review (SLR) was conducted to identify randomized controlled trials of ≥4 weeks of treatment (topical, oral, physical, or combinations) for moderate-to-severe facial acne in patients aged ≥9 years. Efficacy outcomes included: percentage of patients achieving ≥2-grade reduction from baseline and "clear" or "almost clear" for global severity score (treatment success); absolute change in inflammatory (ILs reduction); and noninflammatory lesion counts (NILs reduction). A random-effects network meta-analysis (NMA) was conducted for the efficacy outcomes. Treatments were ranked with posterior rank plots and surface under cumulative ranking values.

Results: Eighty-five studies were included in the SLR/NMA. Topical triple-agent fixed-dose combination (FDC) gel (clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1%) and combinations of double-agent fixed-dose topical treatments with oral antibiotics (TOA3) consistently ranked in the top 3 treatments. Topical triple-agent FDC gel was numerically superior to TOA3 for treatment success (log-odds ratios: 1.84 [95% credible interval (CrI) 1.36 to 2.29]) and 1.69 (95% CrI: 1.01 to 2.32) vs placebo/vehicle). TOA3 was numerically superior to topical triple-agent FDC gel for reduction of ILs (mean difference: -8.21 [-10.33 to -6.13]) and -10.40 [-13.44 to -7.14] vs placebo/vehicle) and NILs (mean difference: -13.41 [-16.69 to -10.32] and -17.74 [-22.56 to -12.85] vs placebo/vehicle).

Conclusions: Based on this SLR/NMA, topical triple-agent FDC gel was the most efficacious and safe treatment for moderate-to-severe acne.

J Drugs Dermatol. 2024;23(4):216-226. doi:10.36849/JDD.8148

INTRODUCTION

Acne vulgaris (acne) is an inflammatory cutaneous disorder of the pilosebaceous unit of the skin that leads to the development of whiteheads, blackheads, papules, pustules, nodules, and cystic lesions.[1] It is the most commonly diagnosed skin condition in the United States (US), predominantly among adolescents and young adults in their twenties.[1,2] The estimated prevalence in the US is 30.2 per 1,000 people, with more than 8 million cases.[3] Annual direct medical costs of acne in the US in 2013 were $846 million and the opportunity costs were $398 million.[4]

Guidelines from the US, Canada, and Europe recommend topical combination treatments, with consideration of oral drugs, as the first-line approach in moderate-to-severe acne.[5-8] Topical benzoyl peroxide (BPO), topical retinoids, topical antibiotics, and systemic drugs are all effective, but there is a lack of clarity about the most efficacious acne treatment.[9] Four systematic literature reviews (SLRs) and network meta-analyses (NMAs) have examined the relative efficacy of the numerous acne treatments.[8,10-12] Two were specific to patients with mild-to-moderate acne,[10,11] and the other 2 included patients with any severity of acne.[8,12] No SLR/NMA has specifically addressed

patients with moderate-to-severe acne, despite this subgroup bearing a greater disease and economic burden.[8,13] The purpose of this SLR/NMA was to evaluate the relative efficacy of available treatments for moderate-to-severe acne.

MATERIALS AND METHODS

Search Strategy

We searched the following literature databases (Figure 1): Ovid (MEDLINE), Ovid (EMBASE), Cochrane Central, PubMed, the National Health Service Economic Evaluation Database (NHSEED), and the Pediatric Economic Database Evaluation (PEDE). We searched the following health technology assessment databases: National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), the Pharmaceutical Benefits Advisory Committee (PBAC), Scottish Medicines Consortium (SMC), and the International Network of Agencies for Health Technology Assessment (INAHTA). We also searched trial registries (clinicaltrials.gov and EU Clinical Trials Register) and conference abstracts (American Academy of Dermatology [AAD], International Society of Dermatology [ISD], International Society for Pharmacoeconomics and Outcomes Research [ISPOR], and Northern Light Life Sciences). All searches spanned from inception until February 2023. We also screened citations in previously published SLRs and NMAs and cross-verified using Retraction Watch Database Version 1.0.6.0 for studies retracted due to compromised methodology.[14] The MeSH and EMTREE terms used for conducting the search, along with the search strategy, are provided in Appendix S1. (All appendices are available at: https://jddonline.com/wp-content/uploads/2024/03/M8148_Supplementary-data_JDD.pdf.)

Study Selection

Population

The SLR/NMA included studies based on a quantitative and qualitative approach to lesion counts and global assessment of acne severity. The US Food and Drug Administration (FDA) guidance[15] recommends using diagnostic scales for new drug approvals that encompass numbers and types of acne lesions as well as disease severity, such as Investigator's Global Assessment (IGA) and equivalent scales like Evaluator's Global Severity Scale (EGSS) and Investigator's Static Global Assessment (ISGA).[16] As the first scale, (IGA) was described by the FDA in 2005[17]; studies published prior to 2005 did not use these scales and hence were excluded. We included studies with male and female patients aged ≥9 years, diagnosed with moderate-to-severe facial acne (IGA/EGSS/ISGA: 3 [moderate] or 4 [severe]) at baseline. We excluded treatments with only a single randomized, controlled trial (RCT) because drug development for acne typically uses at least 2 RCTs.[18] The SLR/NMA included RCTs (phase 2, phase 3, parallel, or cross-over) and pooled studies (if the primary publication was not available). We included English-language RCTs with ≥50 patients in each arm, to minimize small sample bias and uncertainty in estimates.[8] The full inclusion/exclusion criteria are provided in the Appendix S2.

Treatments

We considered the following treatments based on AAD guidelines[19]:

- Monotherapy:
  - Topical (BPO, antibiotic, or retinoid)
  - Oral (antibiotic, retinoid, spironolactone, or contraceptive)
- Combination treatment:
  - Topical combinations
  - Topical triple-agent fixed-dose combination (FDC) gel
  - Topical double-agent FDCs
  - Pharmacologic + physical treatment
  - Topical + oral treatment
  - Other combinations
- Physical treatment:
  - Chemical peels
  - Comedone extraction
  - Photothermal therapy
  - Photochemical therapy
  - Photothermal + photochemical therapy
  - Photodynamic therapy
  - Photopneumatic therapy
  - Radiofrequency therapy
- Other treatments
  - Combined oral contraceptives
  - Metformin[20]

Outcomes

As per regulatory guidance,[15,16] efficacy outcomes were based on both quantitative and qualitative evaluation of acne. Hence, we included 3 outcomes: percentage of patients who achieved ≥2-grade reduction from baseline and "clear" or "almost clear" in IGA/EGSS/ISGA ("treatment success"); absolute change from baseline in inflammatory lesion counts ("ILs reduction"); and absolute change from baseline in noninflammatory lesion counts ("NILs reduction").

Citation Screening Process

We double-screened publications against eligibility criteria at 2 stages: title/abstract screening and full-text screening. A senior author resolved any disagreements. We used EndNote 20 (Clarivate, London, UK) to manage citations from search results, DistillerSR (DistillerSR Inc, Ottawa ON) for removing duplicates and screening citations, and MS-Excel (Microsoft Corporation, Redwood WA) for data extraction.

Data Extraction

We structured the data extraction form based on the format and guidelines used in Cochrane treatment reviews.[21-23] We extracted intention-to-treat data, or completer data only if intention-to-

treat data were not available. We extracted data based on study characteristics, outcomes, adverse events, tolerability, and acceptability.

Base-Case Model

We conducted feasibility assessments for each outcome (Appendix S3).[24-26] Under the assumption that treatments within a group exhibit equivalent efficacy, we considered 2 models: one with random study effects and fixed class effects (RSFC), and another with fixed study effects and fixed class effects (FSFC). Treatment duration was considered as a covariate in this analysis, and the Deviance Information Criterion (DIC) and posterior residual deviance were used to identify the best-fitted model.[27] We ranked treatments with posterior rank plots and surface under cumulative ranking (SUCRA) values. We presented relative treatment effects in pairwise analyses as a log-odds ratio with a 95% credible interval (95% CrI) for binary outcomes and mean difference (95% CrI) for continuous outcomes (Appendix S4).

Inconsistency

We compared a base-case model that assumed consistency and a global inconsistency model that assumed unrelated mean effects (UME)[28] (Appendix S5). This comprehensive approach allowed us to identify data points that might drive inconsistencies.[28]

Bias Adjustment Model

We used bias adjustment models to account for bias in each domain of the Cochrane Risk of Bias Tool (V2.0).[29] We down-weighted studies with high or unclear risk of bias to mitigate the impact on overall results (Appendix S6 and S7).

Threshold Analysis

We conducted study-level threshold analysis[30] as an alternative to the GRADE system to assess the influence of the study biases and sampling variation on the NMA results. The analysis addressed the question, "To what extent would the evidence need to be altered for the recommendation to change?" (Appendix S8). Threshold analysis determines the amount of evidence necessary to change the confidence in the efficacy estimate, accounting for biases and sampling variation. This analysis also provides insights into the robustness, stability, and reliability of efficacy estimates when facing data changes that could impact threshold values.

Protocol

We registered the study protocol in the International Prospective Register of Systematic Reviews (PROSPERO) (Registration id CRD42023430668). This report follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline[31] and its extensions for reporting SLRs (PRISMA-S)[32] and NMAs (PRISMA-NMA).[33]

RESULTS

We screened 3417 records, assessed 1022 reports, and included 104 publications in the SLR. The reasons for exclusion are shown in Figure 1. We also identified 333 reports from other methods and included 2 non-duplicate publications from these methods in the SLR. From these publications, 85 RCTs met the inclusion criteria for the NMA.

Feasibility Assessment

The NMA included RCTs that used IGA/ISGA/EGSS scales, based on the assumption that the efficacy measured using these scales would be similar (refer to Appendix S9 and S10 for a list of included/excluded trials). Random-effects meta-analysis confirmed there was no statistically significant variability for treatment success across IGA/EGSS/ISGA scales (Appendix S3), justifying this approach. There was no statistically significant difference in effect sizes between vehicle and placebo groups, supporting the use of a single placebo/vehicle group in the NMA.

We observed significant differences in the baseline characteristics, especially in terms of gender and the percentage of patients with moderate severity. These variations were apparent both among different studies (Appendix S11) and within and between the treatment groups (Appendix S12). The mean age was approximately 20 years in most studies (Appendix S13) and exhibited minimal variation across studies.

We conducted a rapid review and meta-regression to find potential effect modifiers. A rapid review found conflicting evidence regarding the potential effects of age and sex as modifiers (Appendix S14). Body mass index, severity of disease, and family history were identified as potential treatment effect modifiers (Appendix S15). Meta-regression revealed statistically significant effects (*P* value $P<0.05$) of acne severity and duration of treatment for all 3 outcomes.

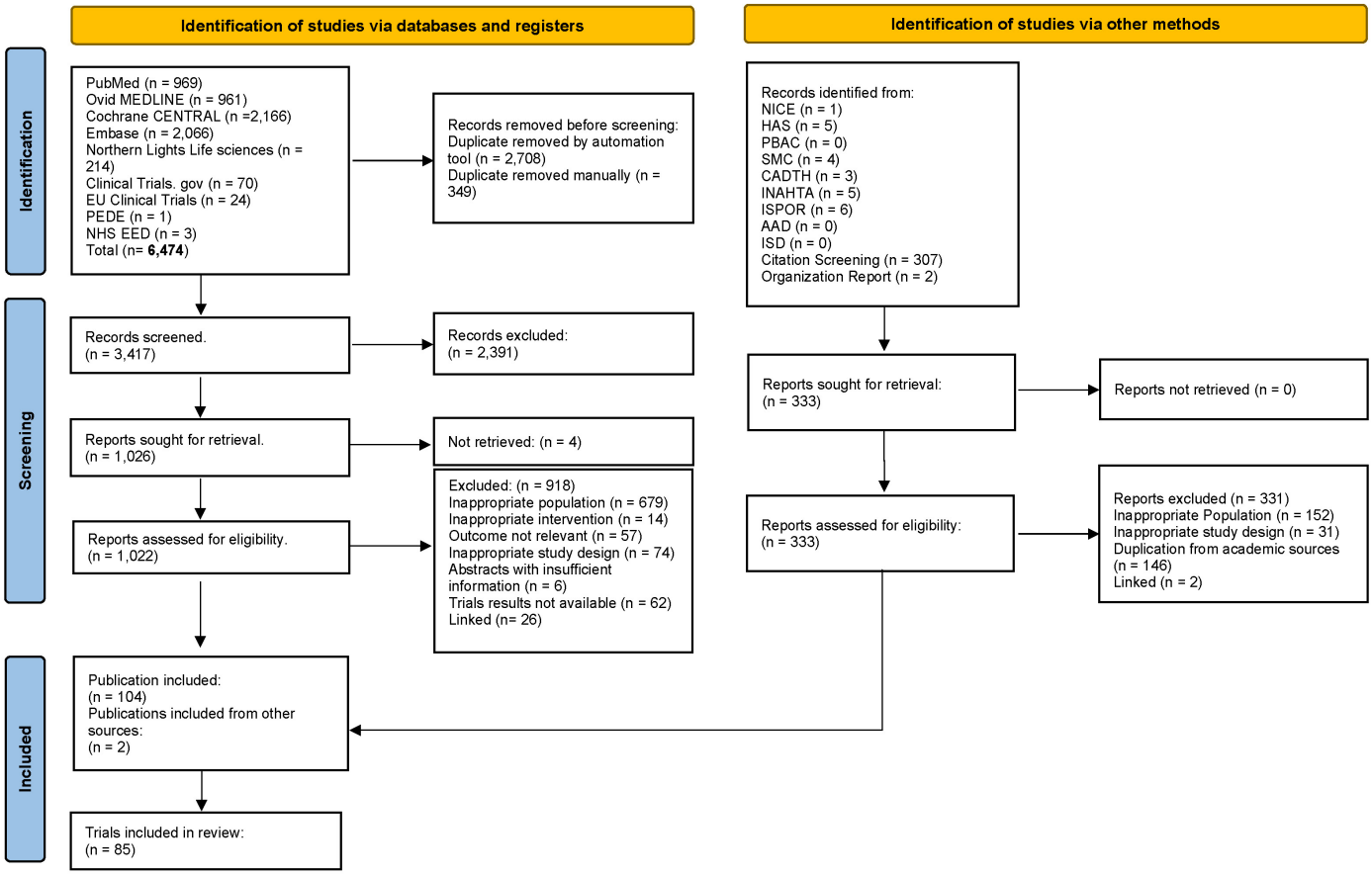
Model Fit

We chose the RSFC for each outcome based on the adequate fit of the posterior residual deviance and DIC (Appendix S16).

Treatment Success

Across 48 RCTs reporting treatment success (Appendix S17), 46 were multicenter studies and 28 were phase 3 trials (Appendix S13). The network diagram had 12 treatments (Figure 2A) and the number of patients ranged from 108 to 2,813 per study. Treatment characteristics and treatment success for included RCTs are listed in Appendix S17. The top 3 treatments for treatment success were: (1) topical triple-agent FDC gel (clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1%[34]); (2) combinations of double-agent FDC topical treatments with oral antibiotic (TOA3); and (3) topical retinoid/BPO FDC (TFDCRB2). For these 3 treatments, log-odds ratios (95% CrI) compared with vehicle/placebo were 1.84 (1.36–2.29), 1.69 (1.01–2.32), and 1.36

FIGURE 1. Study selection process (PRISMA flowchart).



AAD, American Academy of Dermatology; CADTH, Canadian Agency for Drugs and Technologies in Health; HAS, Haute Autorité de Santé; INAHTA, International Network of Agencies for Health Technology Assessment; ISD, International Society of Dermatology; ISPOR, International Society for Pharmacoeconomics and Outcomes Research; NHS EED, National Health Services Economic Evaluation Database; NICE, National Institute for Health and Care Excellence; PBAC, Pharmaceutical Benefits Advisory Committee; PEDE, Pediatric Economic Database Evaluation; SMC, Scottish Medicines Consortium.

(1.12–1.58), respectively (Figure 3A). Posterior ranks (95% CrI) were 1.49 (1–3), 2.28 (1–6), and 3.82 (2–6), respectively (Figure 4A) (Appendix S18). SUCRA probabilities were 96%, 88%, and 74%, respectively (Figure 5A).

Inflammatory Lesions Reduction

Across 50 RCTs reporting ILs reduction (Appendix S17), 47 were multicenter studies and 27 were phase 3 trials (Appendix S13). The network diagram had 12 treatments (Figure 2B), and the number of patients ranged from 107 to 2,813 per study. The top 3 treatments for ILs reduction were: (1) TOA3; (2) topical triple-agent FDC gel; and (3) topical antibiotic/BPO FDC (TFDCAB2). For these 3 treatments, mean (95% CrI) differences vs placebo/vehicle were –10.40 (–13.44 to –7.41), –8.21 (–10.33 to –6.13), and –6.62 (–8.27 to –4.95), respectively (Figure 3B). Posterior ranks (95% CrI) were 1.17 (1–2), 2.11 (1–3), and 3.32 (2–5), respectively (Figure 4B) (Appendix S18). SUCRA values were 98%, 90%, and 79%, respectively (Figure 5B).

Noninflammatory Lesions Reduction

Across 46 RCTs reporting NILs reduction (Appendix S17), 43 were multicenter studies and 27 were phase 3 trials (Appendix S13). The network diagram had 12 treatments (Figure 2C), and the number of patients ranged from 107 to 2,813 per study. The top 3 treatments for NILs reduction were: (1) TOA3; (2) topical triple-agent FDC gel; and (3) TFDCRB2. For these 3 treatments, mean (95% CrI) differences vs placebo/vehicle were –17.74 (–22.56 to –12.85), –13.41 (–16.69 to –10.32), and –9.79 (–11.97 to –7.65), respectively (Figure 3C). Posterior ranks (95% CrI) were 1.08 (1–2), 1.96 (1–3), and 3.34 (3–5), respectively (Figure

4C) (Appendix S18). SUCRA values were 99%, 91%, and 79%, respectively (Figure 5C).

Inconsistency and Bias-adjustment Model

The UME model demonstrated no meaningful differences between estimates of RSFC consistency and inconsistency models (Appendix S19). There were no meaningful differences in estimates of RSFC and bias adjustment models (Appendix S20), indicating the robustness of estimates in base-case models.

Threshold Analysis

Threshold analysis for all 3 efficacy outcomes indicated that, in most instances, uncertainty surrounding results (illustrated by 95% CrI) was contained within the range where efficacy estimates were expected to remain consistent (Appendix S21). This supported the robustness and stability of the results of the efficacy analyses and treatment rankings, as most of the observed data fell within the predetermined acceptable range for decision-making. Threshold analysis highlighted that the decision was sensitive to bias adjustments for treatment success in only 2 studies[35,36] and for ILs reduction in only 4 studies.[37-40] Threshold analysis also demonstrated robustness to bias adjustments in most of the studies with wide, invariant intervals.

Safety and Tolerability

SLR showed that the topical triple-agent FDC gel was tolerated well (Appendix S22), with low rates of discontinuation due to treatment-emergent adverse events (2.8%). Double-agent FDCs had a higher proportion of patients with treatment-related adverse events (nearly 32%). Topical triple-agent FDC gel had a better safety and tolerability profile with lower burning (4.4%) and stinging cases (2.1%) than topical double-agent FDC (adapalene/BPO) FDC, which had a greater incidence of burning (5.5%) and stinging (4.1%). Furthermore, no scaling, itching, and erythema were reported in patients applying topical triple-agent FDC gel. Although combinations of topical double-agent FDCs with oral antibiotics had less frequent adverse events (26.3%), the side effects were more systemic in nature.

DISCUSSION

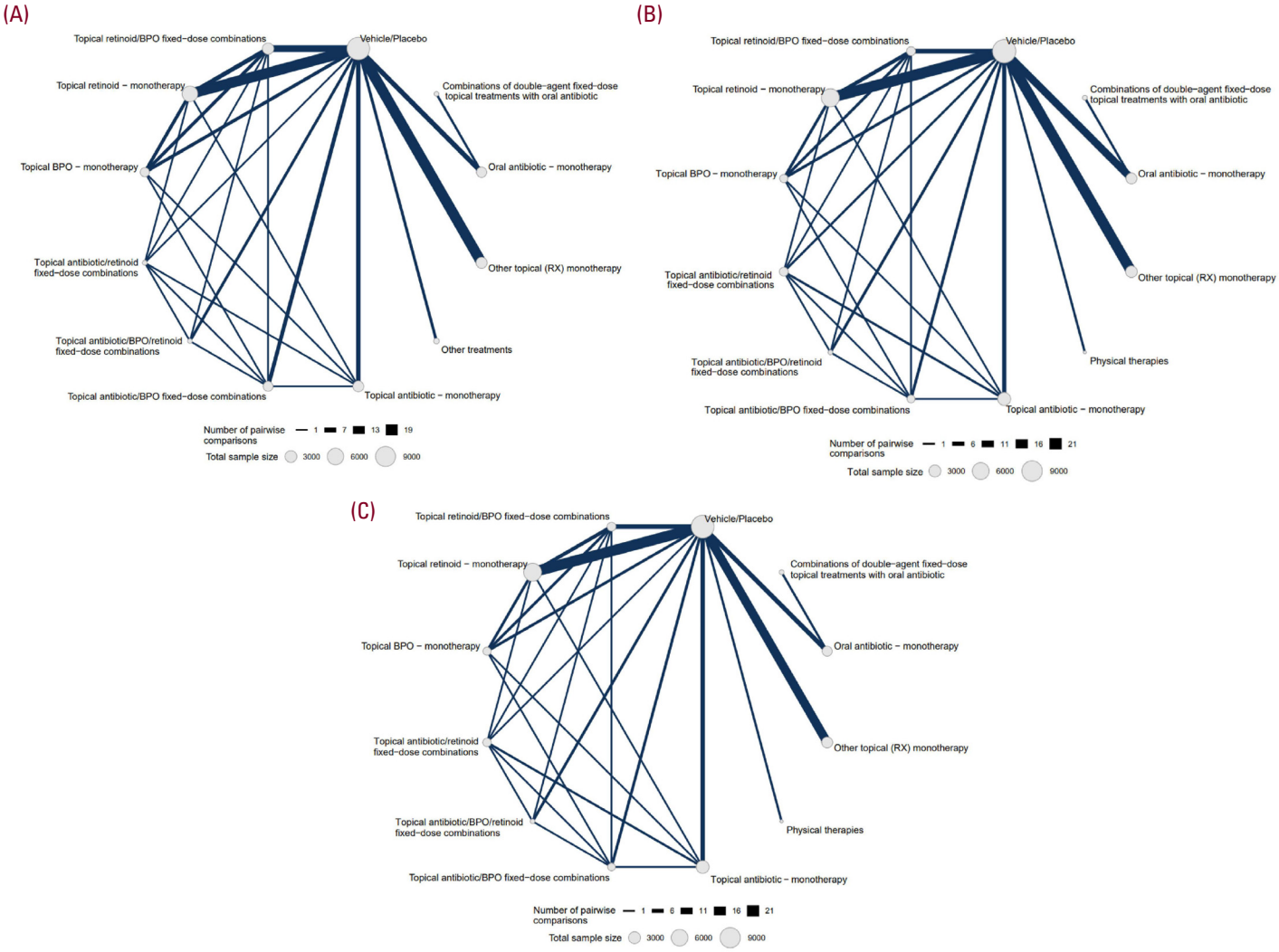
Our analysis showed that for treatment success outcomes, topical triple-agent FDC gel was superior to all treatments. TOA3 was numerically superior to topical triple-agent FDC gel in reducing ILs and NILs. There was a 90% or greater likelihood that topical triple-agent FDC gel was the most efficacious treatment for each outcome. Collectively, these findings suggest that adding an oral antibiotic to topical double-agent FDC gel does not offer significant benefits compared with topical triple-agent FDC gel. The use of the topical triple-agent FDC gel makes it possible to reduce the need for oral antibiotics, thereby minimizing the risk of antibiotic resistance.[41]

Oral antibiotics, topical antibiotics, topical retinoids, and topical BPO as monotherapies had similar efficacy in reducing ILs. Oral antibiotics as monotherapy appeared efficacious compared with topical monotherapies in reducing ILs. However, topical retinoids demonstrated significantly greater efficacy for NILs, while oral antibiotics alone were deemed inadequate. Topical and oral antibiotics were less efficacious than other topical monotherapies, while oral contraceptives were comparable to topical double-agent FDC for treatment success outcomes. Overall, monotherapies of oral antibiotic or topical treatments ranked lower than combined treatments in terms of efficacy. Physical therapies appeared more successful in reducing ILs compared with NILs.

Across all outcomes, an oral antibiotic was more efficacious when given with topical treatment rather than as monotherapy; but adding an oral antibiotic to topical therapy introduces safety and tolerability concerns. Our SLR found that when treatments are combined, major adverse events are generally due to the oral antibiotic, not the topical therapy. Systemic antibiotics for the treatment of moderate-to-severe acne, such as tetracyclines or macrolides, have contraindications, adverse events, and the potential for increased antibiotic resistance.[5-8] These adverse consequences are bypassed when the antibiotic is administered topically. The anti-inflammatory properties of topical clindamycin can also provide a moderating effect on the cutaneous safety and tolerability of adapalene and BPO,[42] which may explain why our SLR found a lower incidence of adverse events/tolerability issues such as burning and stinging for topical triple-agent FDC gel compared with double-agent FDC gel. The efficacy and safety of topical triple-agent FDC gel may also be attributed to a polymeric gel formulation of the vehicle that provides a uniform distribution of ingredients, a combination of active ingredients, or both.[42]

Shi et al reported that combining topical retinoids with BPO was the best option, followed by topical antibiotics and BPO, for mild-to-moderate acne.[11] Stuart et al found that adapalene with BPO was the most efficacious for mild-to-moderate acne;[10] but their study did not consider several treatments, such as tazarotene, trifarotene, and clascoterone. Mavranezouli et al measured efficacy based on the percentage change in total lesion counts for moderate-to-severe acne.[43] Consistent with our findings, that study demonstrated that topical FDCs and combinations of oral antibiotics with topical double-agent FDC are efficacious for moderate-to-severe acne. Also in line with our findings, Huang et al concluded that topical triple-agent FDC gel and TOA3 were efficacious, but they did not focus on moderate-to-severe acne and they included only pharmacological treatments.[12] That study also used the frequentist method, whereas our study used the more robust Bayesian framework. Both Huang et al and Mavranezouli et al found that oral retinoids are the most efficacious treatment for reducing ILs and NILs.

FIGURE 2. Network plots of included studies. (A) Proportion of patients with ≥2 grade reduction from baseline and "clear" or "almost clear" skin. (B) Absolute change in inflammatory lesions. (C) Absolute change in noninflammatory lesions.



The width of each line connecting 2 treatments (nodes) is proportional to the number of head-to-head studies for that comparison.
BPO, benzoyl peroxide.

Oral isotretinoin is efficacious for severe acne with scarring,[44] but its adverse event profile and teratogenicity require specially trained prescribers and close monitoring.[5-8] No RCTs of oral retinoids met the inclusion criteria for our study, which included RCTs published through February 2023 with both quantitative and qualitative clinician assessments of efficacy, per the FDA guidance.[15] We also included studies of both pharmacological and non-pharmacological treatments for the treatment of moderate-to-severe facial acne.

A primary advantage of our study was the study-level threshold analysis for all 3 outcomes, representing an approach that had not been explored previously in the field. We also conducted an end-to-end feasibility analysis of the depth and rigor of our research. The NMA included a broad range of acne treatments and a larger number of RCTs, which is expected to bring significant heterogeneity. We conducted a comprehensive feasibility assessment to identify variability in trial and baseline characteristics within and between treatment groups. We

FIGURE 3. League tables for indirect pairwise comparisons. (A) Proportion of patients with ≥2 grade reduction from baseline and "clear" or "almost clear" skin; log-odds ratios (95% CrI). (B) Absolute change in inflammatory lesions; mean (95% CrI) differences. (C) Absolute change in noninflammatory lesions; mean (95% CrI) differences.

(A)

	Vehicle/ Placebo	Oral antibiotic - monotherapy	Other treatments	Topical antibiotic/BPO fixed-dose combinations	Topical antibiotic/BPO /retinoid fixed-dose combinations	Topical antibiotic/retinoid fixed-dose combinations	Topical retinoid/BPO fixed-dose combinations	Topical antibiotic - monotherapy	Topical BPO - monotherapy	Other topical (RX) monotherapy	Topical retinoid – monotherapy
Oral antibiotic- monotherapy	**0.67 (0.29, 1.05)**										
Other treatments	**1.28 (0.79, 1.79)**	**0.61 (0.01, 1.30)**									
Topical antibiotic/BPO fixed-dose combinations	**1.27 (0.95, 1.59)**	**0.60 (0.13, 1.13)**	-0.01 (-0.62, 0.58)								
Topical antibiotic/BPO/ retinoid fixed-dose combinations	**1.84 (1.36, 2.29)**	**1.17 (0.57, 1.77)**	0.56 (-0.18, 1.24)	**0.57 (0.03, 1.05)**							
Topical antibiotic/retinoid fixed-dose combinations	**1.23 (0.77, 1.71)**	0.56 (-0.04, 1.18)	-0.05 (-0.74, 0.62)	-0.04 (-0.54, 0.47)	**-0.61 (-1.17, -0.03)**						
Topical retinoid/BPO fixed-dose combinations	**1.36 (1.12, 1.58)**	**0.69 (0.25, 1.12)**	0.08 (-0.48, 0.63)	0.08 (-0.29, 0.45)	-0.49 (-0.98, 0.04)	0.13 (-0.38, 0.64)					
Topical antibiotic- monotherapy	**0.64 (0.32, 0.95)**	-0.02 (-0.51, 0.48)	**-0.64 (-1.22, -0.05)**	**-0.63 (-1.01, -0.25)**	**-1.20 (-1.71, -0.66)**	**-0.58 (-1.11, -0.09)**	**-0.71 (-1.08, -0.33)**				
Topical BPO - monotherapy	**0.73 (0.43, 1.05)**	0.06 (-0.42, 0.54)	-0.55 (-1.17, 0.05)	**-0.54 (-0.92, -0.14)**	**-1.11 (-1.63, -0.58)**	**-0.50 (-0.88, -0.11)**	**-0.62 (-0.99, -0.31)**	0.09 (-0.32, 0.49)			
Other topical (RX) monotherapy	**0.85 (0.56, 1.17)**	0.18 (-0.29, 0.68)	-0.43 (-1.01, 0.15)	-0.42 (-0.87, 0.05)	**-0.99 (-1.54, -0.38)**	-0.38 (-0.95, 0.21)	**-0.50 (-0.88, -0.11)**	0.21 (-0.24, 0.67)	0.12 (-0.33, 0.56)		
Topical retinoid - monotherapy	**0.74 (0.53, 0.93)**	0.07 (-0.34, 0.48)	**-0.54 (-1.11, -0.01)**	**-0.53 (-0.89, -0.19)**	**-1.10 (-1.57, -0.58)**	**-0.49 (-0.98, -0.04)**	**-0.62 (-0.88, -0.34)**	0.10 (-0.28, 0.44)	0.01 (-0.33, 0.34)	-0.11 (-0.49, 0.26)	
Combinations of double-agent fixed-dose topical treatments with oral antibiotic	**1.69 (1.01, 2.32)**	**1.02 (0.46, 1.54)**	0.41 (-0.43,1.22)	0.42 (-0.36, 1.15)	-0.15 (-0.97, 0.65)	0.46 (-0.35, 1.30)	0.34 (-0.33, 1.02)	**1.05 (0.26, 1.79)**	**0.96 (0.24, 1.67)**	**0.84 (0.10, 1.56)**	**0.95 (0.26, 1.63)**

(B)

	Vehicle/ Placebo	Oral antibiotic - monotherapy	Physical therapies	Topical antibiotic/BPO fixed-dose combinations	Topical antibiotic/BPO /retinoid fixed-dose combinations	Topical antibiotic/retinoid fixed-dose combinations	Topical retinoid/BPO fixed-dose combinations	Topical antibiotic - monotherapy	Topical BPO - monotherapy	Other topical (RX) monotherapy	Topical retinoid – monotherapy
Oral antibiotic - monotherapy	**-3.71 (-5.09, -2.39)**										
Physical therapies	-4.67 (-10.1, 0.95)	-0.96 (-6.59, 4.76)									
Topical antibiotic/BPO fixed-dose combinations	**-6.62 (-8.27, -4.95)**	**-2.91 (-5.11, -0.78)**	-1.95 (-7.68, 3.83)								
Topical antibiotic/BPO/ retinoid fixed-dose combinations	**-8.21 (-10.33, -6.13)**	**-4.50 (-7.00, -2.05)**	-3.55 (-9.32, 2.03)	-1.60 (-4.22, 0.87)							
Topical antibiotic/retinoid fixed-dose combinations	**-5.08 (-6.54, -3.64)**	-1.37 (-3.35, 0.57)	-0.41 (-6.12, 5.23)	1.54 (-0.57, 3.63)	**3.13 (0.70, 5.66)**						
Topical retinoid/BPO fixed-dose combinations	**-5.34 (-6.67, -4.06)**	-1.63 (-3.54, 0.19)	-0.67 (-6.31, 4.82)	1.26 (-0.74, 3.21)	**2.87 (0.53, 5.20)**	-0.26 (-2.16, 1.57)					
Topical antibiotic - monotherapy	**-3.27 (-4.41, -2.19)**	0.44 (-1.33, 2.13)	1.40 (-4.39, 6.91)	**3.34 (1.47, 5.18)**	**4.94 (2.64, 7.25)**	**1.81 (0.37, 3.30)**	**2.07 (0.50, 3.77)**				
Topical BPO - monotherapy	**-3.63 (-5.10, -2.17)**	0.09 (-1.90, 2.07)	1.04 (-4.76, 6.65)	**2.99 (1.02, 4.96)**	**4.59 (2.02, 7.20)**	1.45 (-0.48, 3.48)	**1.72 (0.01, 3.52)**	-0.35 (-2.05, 1.39)			
Other topical (RX) monotherapy	**-3.59 (-4.69, -2.53)**	0.12 (-1.62, 1.76)	1.06 (-4.65, 6.65)	**3.03 (1.06, 4.99)**	**4.63 (2.29, 7.00)**	1.49 (-0.32, 3.22)	**1.76 (0.10, 3.36)**	-0.31 (-1.84, 1.23)	0.04 (-1.77, 1.84)		
Topical retinoid - monotherapy	**-3.39 (-4.06, -2.74)**	0.32 (-1.20, 1.82)	1.28 (-4.27, 6.79)	**3.23 (1.41, 4.94)**	**4.82 (2.63, 7.06)**	**1.69 (0.21, 3.23)**	**1.95 (0.63, 3.30)**	-0.12 (-1.34, 1.07)	0.23 (-1.26, 1.70)	0.19 (-1.06, 1.41)	
Combinations of double-agent fixed-dose topical treatments with oral antibiotic	**-10.40 (-13.44, -7.41)**	**-6.69 (-9.42, -3.96)**	-5.73 (-12.06, 0.38)	**-3.78 (-7.32, -0.42)**	-2.18 (-5.87,1.45)	**-5.32 (-8.67, -2.04)**	**-5.06 (-8.32, -1.72)**	**-7.12 (-10.42, -3.96)**	**-6.77 (-10.13, -3.41)**	**-6.81 (-10.00, -3.65)**	**-7.01 (-10.14 -3.97)**

(C)

	Vehicle/ Placebo	Oral antibiotic - monotherapy	Physical therapies	Topical antibiotic/BPO fixed-dose combinations	Topical antibiotic/BPO /retinoid fixed-dose combinations	Topical antibiotic/retinoid fixed-dose combinations	Topical retinoid/BPO fixed-dose combinations	Topical antibiotic - monotherapy	Topical BPO - monotherapy	Other topical (RX) monotherapy	Topical retinoid – monotherapy
Oral antibiotic - monotherapy	**-2.60 (-5.03, -0.08)**										
Physical therapies	0.20 (-5.94, 6.40)	2.85 (-4,.04 9.41)									
Topical antibiotic/BPO fixed-dose combinations	**-8.34 (-11.00, -5.72)**	**-5.73 (-9.40, -2.20)**	**-8.50 (-15.32, -1.95)**								
Topical antibiotic/BPO/ retinoid fixed-dose combinations	**-13.41 (-16.69, -10.32)**	**-10.83 (-15.17, -6.71)**	**-13.62 (-20.43, -6.40)**	**-5.10 (-9.01, -1.22)**							
Topical antibiotic/retinoid fixed-dose combinations	**-8.32 (-10.95, -5.76)**	**-5.73 (-9.51, -2.10)**	**-8.50 (-15.02, -2.12)**	0.02 (-3.39, 3.52)	**5.19 (1.22, 9.00)**						
Topical retinoid/BPO fixed-dose combinations	**-9.79 (-11.97, -7.65)**	**-7.22 (-10.51, -3.92)**	**-10.06 (-16.51, -3.50)**	-1.53 (-4.52, 1.89)	3.61 (-0.10, 7.33)	-1.54 (-4.71, 1.69)					
Topical antibiotic - monotherapy:	**-3.79 (-5.71, -1.84)**	-1.23 (-4.42, 1.91)	-4.04 (-10.51, 2.46)	**4.52 (1.63, 7.53)**	**9.65 (5.91, 13.25)**	**4.55 (2.04, 7.10)**	**6.00 (3.30, 8.91)**				
Topical BPO - monotherapy	**-4.59 (-7.04, -2.06)**	-2.03 (-5.52, 1.63)	-4.83 (-11.32, 1.71)	**3.73 (0.50, 7.24)**	**8.80 (4.91, 12.86)**	**3.73 (0.52, 7.33)**	**5.24 (2.36, 8.11)**	-0.86 (-3.61, 2.26)			
Other topical (RX) monotherapy	**-5.32 (-7.06, -3.52)**	-2.73 (-5.85, 0.31)	-5.53 (-12.02, 0.91)	3.00 (-0.21, 6.32)	**8.14 (4.62, 11.91)**	3.02 (-0.14, 6.21)	**4.52 (1.71, 7.32)**	-1.54 (-4.12, 1.14)	-0.72 (-3.80, 2.31)		
Topical retinoid - monotherapy	**-7.14 (-8.29, -6.01)**	**-4.53 (-7.32, -1.98)**	**-7.30 (-13.71, -1.12)**	1.23 (-1.63, 4.03)	**6.33 (3.00, 9.70)**	1.24 (-1.51, 3.91)	**2.62 (0.45, 4.90)**	**-3.31 (-5.52, -1.24)**	-2.61 (-5.20, 0.02)	-1.83 (-3.94, 0.39)	
Combinations of double-agent fixed-dose topical treatments with oral antibiotic	**-17.74 (-22.56, -12.85)**	**-15.12 (-19.41, -11.02)**	**-17.92 (-25.71, -9.94)**	**-9.43 (-14.90, -4.00)**	-4.32 (-10.24, 1.46)	**-9.40 (-15.01, -3.92)**	**-7.92 (-13.23, -2.63)**	**-13.93 (-19.32, -8.61)**	**-13.13 (-18.74, -7.71)**	**-12.42 (-17.61, -7.23)**	**-10.62 (-15.71, -5.62)**

Results are presented as row vs column. Values in cells represent estimated log-odds ratios and mean differences with their 95% credible intervals (95% CrI). All values in bold are statistically significant at the 0.05 significant level.

FIGURE 4. Posterior rank analysis. (A) Proportion of patients with ≥2 grade reduction from baseline and "clear" or "almost clear" skin. (B) Absolute change in inflammatory lesions. (C) Absolute change in noninflammatory lesions.

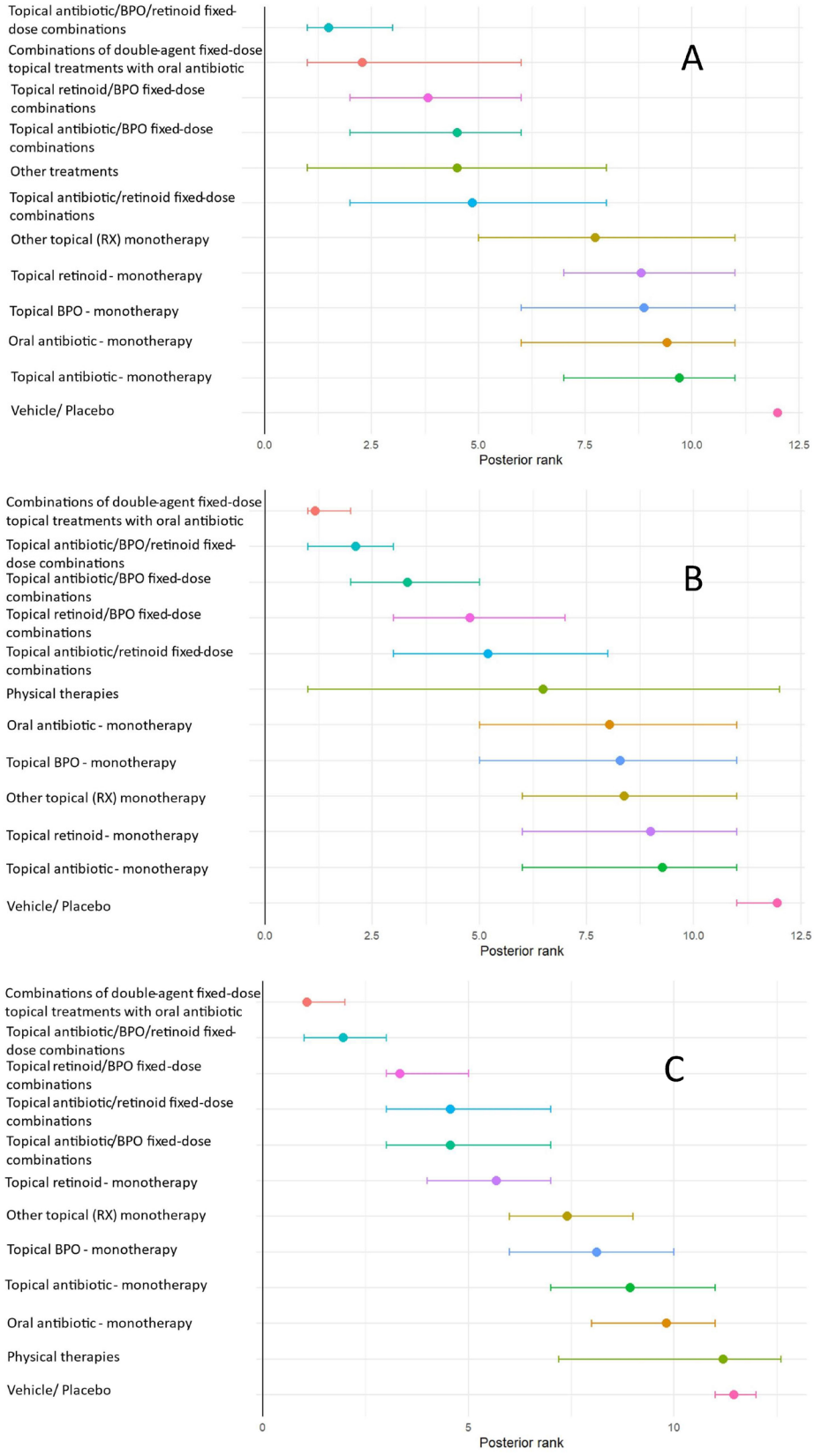
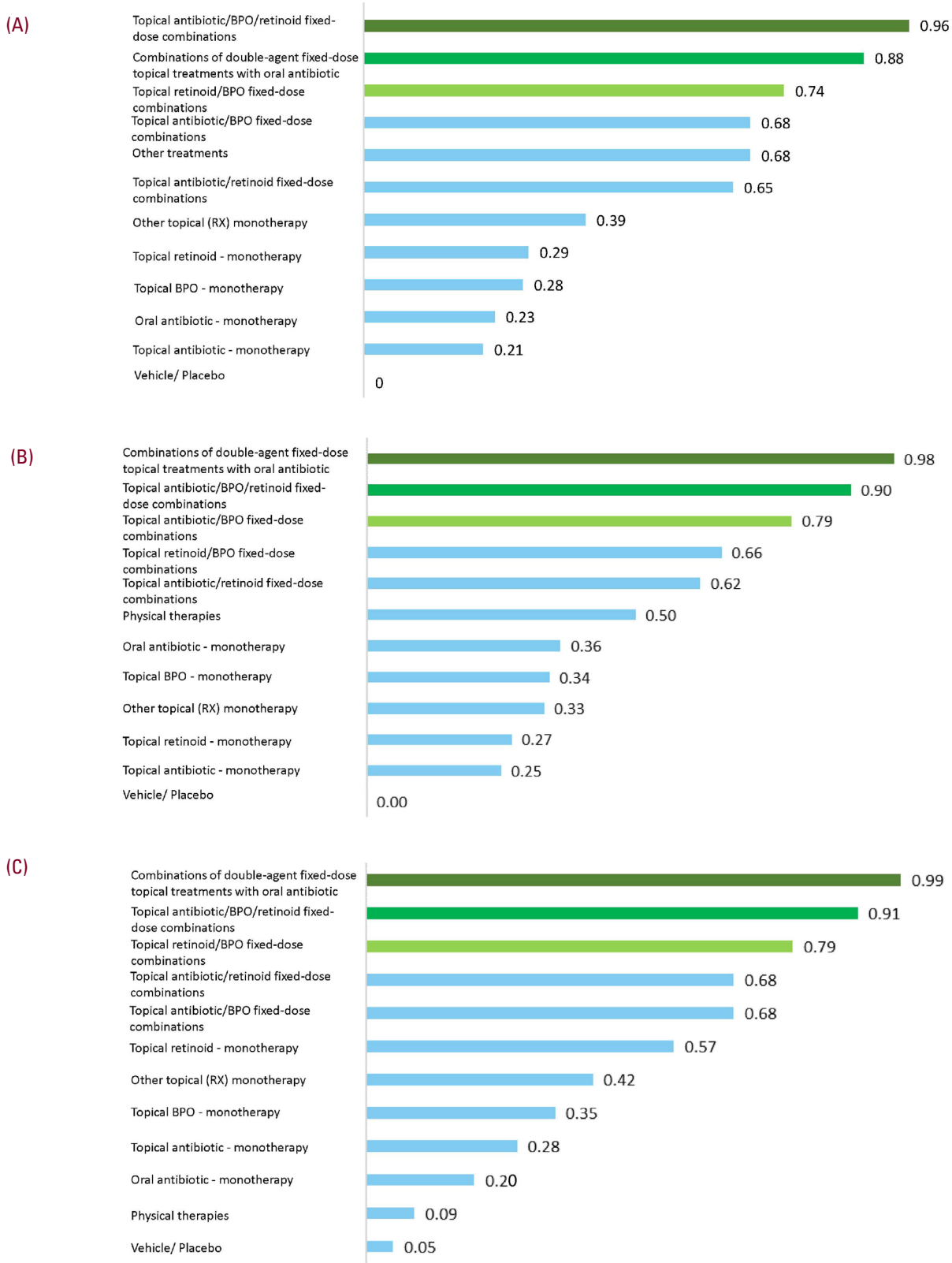


FIGURE 5. Surface under cumulative ranking plots. (A) Proportion of patients with ≥2 grade reduction from baseline and "clear" or "almost clear" skin. (B) Absolute change in inflammatory lesions. (C) Absolute change in noninflammatory lesions.



conducted meta-regression to identify potential treatment effect modifiers, which we then used to select covariates in the NMA. We also used class models to improve the precision of treatment effects and connect previously unconnected networks, expanding the evidence base.

Limitations

Our study excluded articles in languages other than English, but this has not been shown to bias the results of SLR/NMA.[45] Due to the limited number of studies available, we were unable to analyze specific dosing schedules or formulations separately. During the feasibility assessment, we observed that the proportion of patients with moderate acne might influence treatment outcomes, but 31% of studies did not report this proportion at baseline. Thus, we could not perform network meta-regression to account for this potential effect modifier. Differences in study characteristics and geographical locations might have acted as effect modifiers, introducing heterogeneity into the analysis. Results for some treatments were based on limited evidence and network connections. Nevertheless, a study-level threshold analysis demonstrated the robustness of the NMA results against all influences from study bias and sampling variation.

CONCLUSION

In conclusion, this NMA synthesized data from a wide range of treatments for moderate-to-severe acne vulgaris. Topical triple-agent FDC gel was the most efficacious treatment based on the treatment success outcome, surpassing both topical/oral monotherapies and topical double-agent fixed-dose combinations.

DISCLOSURES

AAD was an employee and stakeholder at Bausch Health US LLC at the time of the study. TL is an employee and stockholder at Ortho Dermatologics. ARC, BG, DD, DR, HB, JCH, JKLT, MSA, SB, SKD, and SPC have received consulting fees from Bausch Health US, LLC. GJ was an employee of Bausch Health US, LLC when the study was conducted and may hold stock in Bausch Health. JCH is an advisor, investigator, and speaker for Bausch Health US, LLC. HB is an advisor, investigator, and speaker for Bausch Health US, LLC and Galderma; investigator, and speaker for Almirall US, LLC; investigator for Sol Gel Technologies Ltd.; advisor, speaker for Sun Pharma; and speaker for Novan, Inc. JKLT is a consultant, advisor, speaker, honoraria for Bausch Health US, LLC, Cutera, Inc, Galderma, L'Oreal, and Walgreens Boots Alliance.

Funding: The study was funded by Bausch Health US LLC.

ACKNOWLEDGMENT

Jonathan Latham of PharmaScribe LLC provided medical writing services.

REFERENCES

1. Moradi Tuchayi S, Makrantonaki E, Ganceviciene R, etal. Acne vulgaris. *Nat Rev Dis Primers.* 2015;1:15029.
2. Zeichner JA. Evaluating and treating the adult female patient with acne. *J Drugs Dermatol.* 2013;12(12):1416-1427.
3. Global Health Data Exchange. Available at: https://vizhub.healthdata.org/gbd-results/. Accessed December 9, 2022.
4. Lim HW, Collins SAB, Resneck JS Jr, et al. The burden of skin disease in the United States. *J Am Acad Dermatol.* 2017;76(5):958-972 e952.
5. Zaenglein AL, Pathy AL, Schlosser BJ, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol.* 2016;74(5):945-973 e933.
6. Asai Y, Baibergenova A, Dutil M, et al. Management of acne: Canadian clinical practice guideline. *CMAJ.* 2016;188(2):118-126.
7. Nast A, Dreno B, Bettoli V, et al. European evidence-based (S3) guideline for the treatment of acne – update 2016 – short version. *J Eur Acad Dermatol Venereol.* 2016;30(8):1261-1268.
8. Mavranezouli I, Daly CH, Welton NJ, et al. A systematic review and network meta-analysis of topical pharmacological, oral pharmacological, physical and combined treatments for acne vulgaris. Br J Dermatol. 2022;187(5):639-649.
9. Williams HC, Dellavalle RP, Garner S. Acne vulgaris. *Lancet.* 2012;379(9813):361-372.
10. Stuart B, Maund E, Wilcox C, et al. Topical preparations for the treatment of mild-to-moderate acne vulgaris: systematic review and network meta-analysis. *Br J Dermatol.* 2021;185(3):512-525.
11. Shi Q, Tan L, Chen Z, et al. Comparative efficacy of pharmacological and nonpharmacological interventions for acne vulgaris: a network meta-analysis. *Front Pharmacol.* 2020;11:592075.
12. Huang CY, Chang IJ, Bolick N, et al. Comparative efficacy of pharmacological treatments for acne vulgaris: a network meta-analysis of 221 randomized controlled trials. *Ann Fam Med.* 2023;21(4):358-369.
13. Harper J, Dashputre AA, Serra E, et al. Burden of moderate-to-severe acne vulgaris among commercially insured patients in the US: a claims-based analysis. *J Manag Care Pharm.* 2023;29(10-a):S104.
14. The Retraction Watch Database. The Center for Scientific Integrity; 2018. http://retractiondatabase.org. Access date: May 12, 2023.
15. FDA. Acne Vulgaris: Establishing Effectiveness of Drugs Intended for Treatment. Guidance for Industry. 2018; https://www.fda.gov/regulatory-information/search-fda-guidance-documents/acne-vulgaris-establishing-effectiveness-drugs-intended-treatment. Access date: March 5, 2023
16. Nast A, Dreno B, Bettoli V, et al. European evidence-based (S3) guidelines for the treatment of acne. *J Eur Acad Dermatol Venereol.* 2012;26 Suppl 1:1-29.
17. FDA. Draft Guidance for Industry on Acne Vulgaris: Developing Drugs for Treatment Availability. 2005. https://www.federalregister.gov/documents/2005/09/19/05-18512/draft-guidance-for-industry-on-acne-vulgaris-developing-drugs-for-treatment-availability. Access date: March 5, 2023
18. FDA. Development & Approval Process | Drugs. 2022; https://www.fda.gov/drugs/development-approval-process-drugs. Access date: March 5, 2023
19. National Guideline Alliance (UK). *Management options for moderate to severe acne – network meta-analyses: Acne vulgaris: management: Evidence review F1.* London: National Institute for Health and Care Excellence (NICE); 2021.
20. Nathan N, Sullivan SD. The utility of metformin therapy in reproductive-aged women with polycystic ovary syndrome (PCOS). *Curr Pharm Biotechnol.* 2014;15(1):70-83.
21. Li T, Higgins JPT, (editors) DJ. Chapter 5: Collecting data. In: Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, ed. *Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019):* Cochrane; 2019.
22. Husereau D, Drummond M, Augustovski F, et al. Consolidated Health Economic Evaluation Reporting Standards 2022 (CHEERS 2022) Statement: Updated reporting guidance for health economic evaluations. *Value Health.* 2022;25(1):3-9.
23. Aluko P GE, Craig D, Henderson C, et al on behalf of the Campbell and Cochrane Economics Methods Group. Chapter 20: Economic Evidence. In: Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, ed. *Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019):* Cochrane; 2019.
24. Jansen JP, Trikalinos T, Cappelleri JC, et al. Indirect treatment comparison/network meta-analysis study questionnaire to assess relevance and credibility to inform health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. *Value Health.* 2014;17(2):157-173.
25. Hoaglin DC, Hawkins N, Jansen JP, et al. Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 2. *Value Health.* 2011;14(4):429-437.

26. Cope S, Zhang J, Saletan S, et al. A process for assessing the feasibility of a network meta-analysis: a case study of everolimus in combination with hormonal therapy vs chemotherapy for advanced breast cancer. *BMC Med.* 2014;12(1):93.
27. Dias S, Ades AE, Welton NJ, et al. *Network Meta-analysis for Decision-making*. John Wiley & Sons; 2018.
28. Dias S, Welton NJ, Sutton AJ, et al. NICE DSU Technical Support Document 4: Inconsistency in Networks of Evidence Based on Randomised Controlled Trials. 2011.
29. Corbett MS, Higgins JP, Woolacott NF. Assessing baseline imbalance in randomized trials: implications for the Cochrane risk of bias tool. *Res Synth Methods*. 2014;5(1):79-85.
30. Phillippo DM, Dias S, Welton NJ, et al. Threshold analysis as an alternative to GRADE for assessing confidence in guideline recommendations based on network meta-analyses. *Ann Intern Med.* 2019;170(8):538-546.
31. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med.* 2009;151(4):264-269, W264.
32. Rethlefsen ML, Kirtley S, Waffenschmidt S, et al. PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. *Syst Rev.* 2021;10(1):39.
33. Hutton B, Salanti G, Caldwell DM, et al. The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med. 2015;162(11):777-784.
34. CABTREO (clindamycin phosphate, adapalene, and benzoyl peroxide) topical gel. Prescribing information. Bausch Health US, LLC. 2023.
35. Dreno B, Kaufmann R, Talarico S, et al. Combination therapy with adapalene-benzoyl peroxide and oral lymecycline in the treatment of moderate to severe acne vulgaris: a multicentre, randomized, double-blind controlled study. *Br J Dermatol.* 2011;165(2):383-390.
36. Gold LS, Cruz A, Eichenfield L, et al. Effective and safe combination therapy for severe acne vulgaris: a randomized, vehicle-controlled, double-blind study of adapalene 0.1%-benzoyl peroxide 2.5% fixed-dose combination gel with doxycycline hyclate 100 mg. *Cutis.* 2010;85(2):94-104.
37. Eichenfield LF, Gold LS, Nahm WK, et al. Results of a phase 2, randomized,vehicle-controlled study evaluating the efficacy, tolerability, and safety of daily or twice daily SB204 for the treatment of acne vulgaris. *J Drugs Dermatol.* 2016;15(12):1496-15027.
38. Dogra S, Sumathy TK, Nayak C, et al. Efficacy and safety comparison of combination of 0.04% tretinoin microspheres plus 1% clindamycin vs their monotherapy in patients with acne vulgaris: a phase 3, randomized, double-blind study. *J Dermatolog Treat.* 2021;32(8):925-933.
39. Tanghetti EA, Kircik LH, Green LJ, et al. A phase 2, multicenter, double-blind, randomized, vehicle-controlled clinical study to compare the safety and efficacy of a novel tazarotene 0.045% lotion and tazarotene 0.1% cream in the treatment of moderate-to-severe acne vulgaris. *J Drugs Dermatol.* 2019;18(6):542.
40. Photocure. Efficacy and Safety Study With Visonac Photodynamic Therapy (PDT). https://classic.clinicaltrials.gov/show/NCT00933543; 2009.
41. Dessinioti C, Katsambas A. Antibiotics and antimicrobial resistance in acne: epidemiological trends and clinical practice considerations. *Yale J Biol Med.* 2022;95(4):429-443.
42. Stein Gold L, Baldwin H, Kircik LH, et al. Efficacy and safety of a fixed-dose clindamycin phosphate 1.2%, benzoyl peroxide 3.1%, and adapalene 0.15% gel for moderate-to-severe acne: a randomized phase II study of the first triple-combination drug. *Am J Clin Dermatol.* 2022;23(1):93-104.
43. Mavranezouli I, Daly CH, Welton NJ, et al. A systematic review and network meta-analysis of topical pharmacological, oral pharmacological, physical and combined treatments for acne vulgaris*. *Br J Dermatol.* 2022;187(5):639-649.
44. Dhir R, Gehi NP, Agarwal R, et al. Oral isotretinoin is as effective as a combination of oral isotretinoin and topical anti-acne agents in nodulocystic acne. *Indian J Dermatol Venereol Leprol.* 2008;74(2):187.
45. Morrison A, Polisena J, Husereau D, et al. The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. *Int J Technol Assess Health Care.* 2012;28(2):138-144.

AUTHOR CORRESPONDENCE

Subrata Bhattacharyya MS
E-mail:..... subrata@pharmaquant.org