A SYSTEMATIC LITERATURE REVIEW AND NETWORK META-ANALYSIS OF COMPARATIVE EFFICACY OF TOPICAL FIXED-DOSE COMBINATION TREATMENTS FOR MODERATE TO SEVERE ACNE VULGARIS

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SYNOPSIS:

- Several topical and oral monotherapies/combinations are available for treating moderate to severe acne vulgaris and a few are currently under review with the United States (US) Food and Drug Administration (FDA).
- This Systematic Literature Review (SLR)/Network Meta-Analysis (NMA) assessed the comparative efficacy of topical Fixed-Dose Combinations (FDCs) based on the treatment success endpoint *the proportion of patients achieving ≥2 grade reduction AND "Clear" or "Almost clear" status by week 12 on the Investigator's Global Assessment (IGA) or equivalent [Evaluator's Global Severity Score (EGSS) and Investigator's Static Global Assessment (ISGA)] scales*.
- The NMA demonstrated that the topical triple-agent FDC gel of clindamycin phosphate 1.2%, adapalene 0.15%, and benzoyl peroxide 3.1% was superior to other topical FDCs.

OBJECTIVE:

- The objective of this study was to compare the efficacy of topical FDCs for the treatment of moderate to severe acne vulgaris.

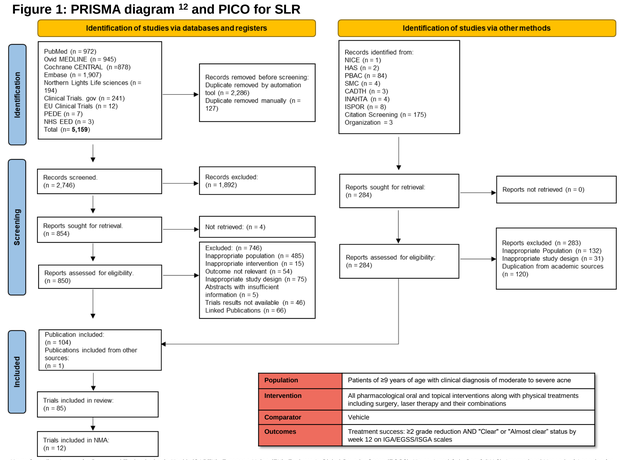
METHODS:

- Academic (MEDLINE, Embase, Cochrane CENTRAL, Paediatric Economic Database Evaluation and National Health Service Economic Evaluation Database) and non-academic databases (Health Technology Assessment databases, conference abstracts, and trial registries) were searched in May 2022, for identifying Randomized Controlled Trials (RCTs), with ≥1 topical FDC (currently approved/under review with FDA).
- RCTs included in the analysis evaluated acne severity using IGA or EGSS or ISGA scales.
- A Bayesian network meta-regression was conducted using the proportion of patients with moderate acne, mean inflammatory and non-inflammatory lesion counts at baseline as covariates for acne severity.
- The Bayesian simulation approach was used to develop a posterior rank order to assess the most efficacious treatment.
- The risk of bias was assessed with Cochrane Risk of Bias (RoB) v2.0 for quality assessment.[1]

RESULTS:

- The SLR identified twelve Phase II/III/IV RCTs comprising 8,349 patients across eight treatment groups, from 5,159 citation (Figure 1 & Table 1).[2-11] Among these, eight studies were of high-quality as per RoB assessment. [2,4,6,7,8,9,10]
- The network diagram for 12 studies consisting eight treatment groups is presented at Figure 2.
- Topical FDC of clindamycin phosphate 1.2%, adapalene 0.15%, and benzoyl peroxide 3.1% (first triple-agent FDC) gel was clinically superior to other FDCs. The odds ratio for treatment success with topical triple-agent FDC was estimated to be 7.61 (95% Credible interval: 4.44 – 13.20) vs. Vehicle gel (Figure 3).
- The posterior rank plot suggested that topical triple-agent FDC was likely to be the most efficacious treatment among all topical FDCs with very low uncertainty around its superiority (Figure 4).

Figure 1: PRISMA diagram [12] and PICO for SLR



Keys; Canadian Agency for Drugs and Technologies in Health (CADTH), European Union (EU), Evaluator's Global Severity Score (EGSS), Haute Autorité de Santé (HAS), International Network of Agencies for Health Technology Assessment (INAHTA), Investigator's Global Assessment (IGA), Investigator's Static Global Assessment (ISGA), National Health Service Economic Evaluation Database (NHS EED), National Institute for Health and Care Excellence (NICE), Paediatric Economic Database Evaluation (PEDE), Pharmaceutical Benefits Advisory Committee (PBAC), Population Intervention Comparator Outcome (PICO), Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), Scottish Medicines Consortium (SMC), Systematic Literature Review (SLR), The Professional Society for Health Economics and Outcomes Research (ISPOR)

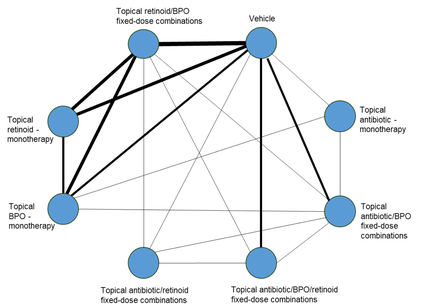
Table 1: Baseline characteristics and quality of included studies

Study	Phase	Quality	Intervention	Moderate patients (%)	Age (mean)	Female (%)	ILS (mean)	NILS (mean)
Stein Gold et al. 2023 (V01-126A-301 2021)[2]	III	High	Topical IDP-126 gel (clindamycin phosphate 1.20% / benzoyl peroxide 3.10% / adapalene 0.15%)	87.7%	20.2	61.5%	36.4	50.7
			Vehicle	95.1%	19.8	50.8%	37.1	45.9
Stein Gold et al. 2023 (V01-126A-302 2021)[2]	III	High	Topical IDP-126 gel (clindamycin phosphate 1.20% / benzoyl peroxide 3.10% / adapalene 0.15%)	90.8%	20.2	57.5%	37.4	48.2
			Vehicle	95.0%	21.4	61.7%	37.7	49.3
Del Rosso et al. 2021 (SGT-65-04)[3]	III	Some concerns	Topical benzoyl peroxide 3.00% / tretinoin 0.10%	89.3%	20.9	62.3%	33.5	48.6
			Vehicle	92.3%	21.4	58.0%	33.5	47.1
Del Rosso et al. 2021 (SGT-65-05)[3]	III	Some concerns	Topical benzoyl peroxide 3.00% / tretinoin 0.10%	90.3%	20.1	59.7%	28.2	44.6
			Vehicle	93.0%	20.3	53.5%	27.5	44.9
Stein Gold et al. 2021[4]	II	High	Topical IDP-126 gel (clindamycin phosphate 1.20% / benzoyl peroxide 3.10% / adapalene 0.15%)	84.9%	19.9	64.4%	39.0	51.8
			Topical benzoyl peroxide 3.10% / adapalene 0.15%	79.3%	19.2	57.3%	39.0	48.0
			Topical clindamycin phosphate 1.20% / benzoyl peroxide 3.01%	84.9%	19.6	62.3%	40.0	49.2
			Topical clindamycin phosphate 1.20% / adapalene 0.15%	86.0%	19.4	62.0%	38.2	51.1
			Vehicle	85.8%	19.6	60.1%	38.2	50.7
Webster et al. 2020[5]	II	Some concerns	Topical benzoyl peroxide 3.00%	85.6%	22.0	61.9%	27.9	42.7
			Topical tretinoin 0.05%	86.4%	22.0	65.3%	26.7	41.7
			Topical tretinoin 0.10%	90.7%	23.0	69.5%	26.2	42.4
			Topical retinoid 0.05% / benzoyl peroxide 3.00%	88.9%	22.4	64.1%	27.8	43.4
			Topical retinoid 0.10% / benzoyl peroxide 3.00%	87.9%	21.9	58.6%	26.7	42.9
			Vehicle	88.7%	21.2	60.9%	28.6	42.5
Dreno et al. 2018[6]	IV	High	Topical adapalene 0.30% / benzoyl peroxide 2.50%	92.5%	21.5	65.7%	17.8	22.0
			Vehicle	92.5%	21.5	65.7%	18.0	22.0
Stein Gold et al. 2016[7]	III	High	Topical adapalene 0.30% / benzoyl peroxide 2.50%	51.2%	20.1	52.1%	39.2	58.9
			Vehicle	48.4%	18.5	52.2%	36.4	60.7
Pariser et. al. 2014[8]	III	High	Topical clindamycin Phosphate 1.20% / benzoyl peroxide 3.75%	83.8%	18.2	48.6%	27.2	38.3
			Vehicle	81.6%	19.3	48.6%	26.7	37.2
Eichenfield et al. 2013[9]	III	High	Topical adapalene 0.10% / benzoyl peroxide gel 2.50%	100.0%	23.2	76.8%	13.8	36.7
			Vehicle	100.0%	24.5	75.5%	16.6	39.9
Gollnick et al. 2009[10]	III	High	Topical adapalene 0.10% / benzoyl peroxide 2.50%	100.0%	19.5	56.3%	26.0	45.0
			Topical adapalene gel 0.10%	100.0%	18.5	54.8%	27.0	46.0
			Topical benzoyl peroxide 2.50%	100.0%	18.9	55.4%	26.0	45.0
			Vehicle	100.0%	19.2	58.4%	26.0	46.0
Thiboutot et al. 2008[11]	III	Some concerns	Topical clindamycin 1.20% / benzoyl peroxide 2.50%	80.7%	19.2	51.2%	26.4	47.4
			Topical clindamycin phosphate 1.20%	80.4%	19.6	51.7%	26.3	45.3
			Topical benzoyl peroxide 2.50%	82.4%	19.1	56.2%	25.8	46.8
			Vehicle	80.8%	19.4	48.6%	26.1	44.0

FDCs | High quality - low risk of bias study | Some concerns in quality of the study

Keys; Inflammatory lesions count (ILS), Non-inflammatory lesions count(NILS)

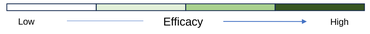
Figure 2: Network diagram of treatments compared



Key: Benzoyl peroxide (BPO)

Figure 3: League table for pair-wise efficacy comparison between treatments

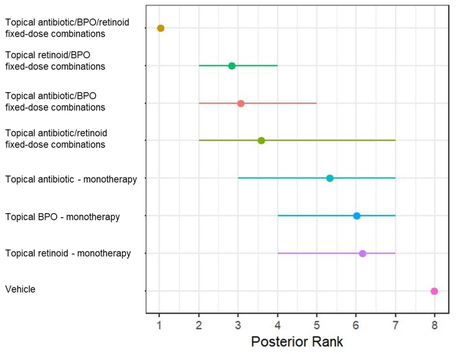
	Vehicle	Topical antibiotic/BPO/retinoid fixed-dose combinations	Topical antibiotic/BPO fixed-dose combinations	Topical antibiotic/retinoid fixed-dose combinations	Topical retinoid/BPO fixed-dose combinations	Topical antibiotic - monotherapy	Topical BPO - monotherapy
Topical antibiotic/BPO/retinoid fixed-dose combinations	**7.61 (4.44, 13.2)**						
Topical retinoid/BPO fixed-dose combinations	**3.30 (2.19, 4.95)**	**0.45 (0.25, 0.82)**					
Topical antibiotic/retinoid fixed-dose combinations	**3.05 (1.57, 6.3)**	**0.41 (0.2, 0.82)**	0.90 (0.50, 1.82)				
Topical antibiotic/BPO fixed-dose combinations	**3.45 (2.62, 4.80)**	**0.45 (0.25, 0.82)**	1.00 (0.67, 1.82)	1.11 (0.55, 2.23)			
Topical antibiotic - monotherapy	**2.15 (1.23, 3.88)**	**0.27 (0.12, 0.61)**	0.67 (0.37, 1.22)	0.67 (0.27, 1.65)	0.61 (0.33, 1.11)		
Topical BPO - monotherapy	**1.93 (1.35, 2.85)**	**0.25 (0.14, 0.45)**	**0.61 (0.37, 0.90)**	0.61 (0.30, 1.35)	**0.54 (0.37, 0.82)**	0.90 (0.50, 1.65)	
Topical retinoid - monotherapy	**1.88 (1.26, 2.97)**	**0.25 (0.12, 0.50)**	**0.55 (0.33, 1.00)**	0.61 (0.27, 1.35)	**0.55 (0.38, 0.81)**	0.90 (0.45, 1.65)	1.00 (0.61, 1.49)



Key: Benzoyl peroxide (BPO)

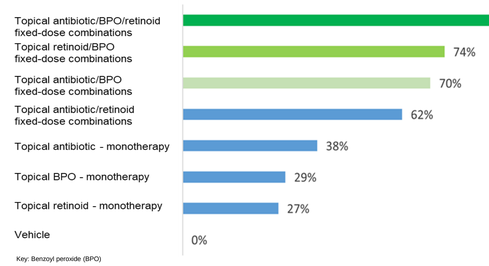
Note: Each cell represents the comparison (Odds ratio and 95% Credible Interval) of the row treatment versus column treatment. All bolded values are statistically significant at the 0.05 significant level.

Figure 4: Posterior rank plot assessing the most efficacious treatment group



Key: Benzoyl peroxide (BPO)

Figure 5: SUCRA for assessing the most efficacious treatment group



Key: Benzoyl peroxide (BPO)

- A Surface Under the Cumulative Ranking (SUCRA) value of 100% indicates that the topical triple-agent FDC has the highest probability of being the most effective among all the comparators in the NMA (Figure 5).

CONCLUSION:

The topical triple-agent FDC of clindamycin phosphate 1.2%, adapalene 0.15%, and benzoyl peroxide 3.1% gel, which is currently under FDA review (Prescription Drug User Fee Act date 10/20/2023), was clinically superior to all other topical FDC treatments for moderate to severe acne vulgaris.

REFERENCES:

1. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. Bmj. 2019;366:l4898.
2. Stein Gold L, Lain E, Del Rosso JQ, Gold M, Draelos ZD, Eichenfield LF, et al. Clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1% gel for moderate-to-severe acne: Efficacy and safety results from two randomized phase 3 trials. J Am Acad Dermatol. 2023.
3. Del Rosso J, Levy-Hacham O, Mizrahi O. Efficacy and safety of microencapsulated benzoyl peroxide 3% and microencapsulated tretinoin 0.1%(E-Bpo/E-Atra) in acne vulgaris: results from two randomized controlled clinical trials. SKIN The Journal of Cutaneous Medicine. 2021;5(1):s24-s.
4. Stein Gold L, Baldwin H, Kircik LH, Weiss JS, Pariser DM, Callender V, 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.
5. Webster GF, Sugarman J, Levy-Hacham O, Toledano O. Microencapsulated Benzoyl Peroxide and Tretinoin for the Treatment of Acne Vulgaris: Results from a Phase 2 Multicenter, Double-Blind, Randomized, Vehicle-Controlled Study. Skinmed. 2020;18(6):343-51.
6. Dréno B, Bissonnette R, Gagné-Henley A, Barankin B, Lynde C, Kerrouche N, et al. Prevention and reduction of atrophic acne scars with adapalene 0.3%/benzoyl peroxide 2.5% gel in subjects with moderate or severe facial acne: results of a 6-month randomized, vehicle-controlled trial using intra-individual comparison. American Journal of Clinical Dermatology. 2018;19:275-86.
7. Stein Gold L, Weiss J, Rueda MJ, Liu H, Tanghetti E. Moderate and Severe Inflammatory Acne Vulgaris Effectively Treated with Single-Agent Therapy by a New Fixed-Dose Combination Adapalene 0.3 %/Benzoyl Peroxide 2.5 % Gel: A Randomized, Double-Blind, Parallel-Group, Controlled Study. Am J Clin Dermatol. 2016;17(3):293-303.
8. Pariser DM, Rich P, Cook-Bolden FE, Korotzer A. An aqueous gel fixed combination of clindamycin phosphate 1.2% and benzoyl peroxide 3.75% for the once-daily treatment of moderate to severe acne vulgaris. J Drugs Dermatol. 2014;13(9):1083-9.
9. Eichenfield LF, Draelos Z, Glenn MJ, Rosoph LA, Kaszuba A, Cornelison R, et al. Adapalene-benzoyl peroxide, a unique fixed-dose combination topical gel for the treatment of acne vulgaris: a transatlantic, randomized, double-blind, controlled study in 1670 patients. Br J Dermatol. 2009;161(5):1180-9.
10. Gollnick HP, Draelos Z, Glenn MJ, Webster G, Calvarese B, Chen D. An aqueous gel fixed combination of clindamycin phosphate 1.2% and benzoyl peroxide 2.5% for the once-daily treatment of moderate to severe acne vulgaris: assessment of efficacy and safety in 2813 patients. J Am Acad Dermatol. 2008;59(5):792-800.
11. Thiboutot D, Zaenglein A, Weiss J, Webster G, Calvarese B, Chen D. An aqueous gel fixed combination of clindamycin phosphate 1.2% and benzoyl peroxide 2.5% for the once-daily treatment of moderate to severe acne vulgaris: assessment of efficacy and safety in 2813 patients. J Am Acad Dermatol. 2008;59(5):792-800.
12. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Bmj. 2021;372:n71.

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