A SUPPLEMENT TO

JOURNAL OF DRUGS IN DERMATOLOGY

JDD

DRUGS • DEVICES • METHODS

Topical Acne Treatment: What's Behind the Scenes in 2024

ISSN: 1545 9616

November 2024 • Volume 23 • Issue 11 (Supplement 1)

This supplement to the *Journal of Drugs in Dermatology* is supported by Ortho Dermatologics.

doi:10.36849/JDD.46941

Journal of Drugs in Dermatology

"VEHICLES ALWAYS MATTER"

Leon Kircik MD

Over the past several years, the field of acne treatments, which had been relatively unchanged, has welcomed a variety of innovations. From new molecules and mechanisms of action to previously implausible fixed combination products, prescribers have more topical treatment options than ever before. Compared to predecessor treatments, new drugs may offer enhanced efficacy and tolerability, fewer side effects, reduced risk for problems like antibiotic resistance, and more patient convenience. We as clinicians must recognize these advantages that some of the newest drugs confer.

However, while medicinal chemists and formulators had been toiling in labs, the FDA was at work modifying the requirements for demonstrating acne treatment efficacy!!! They set such a high bar that requires drugs to demonstrate *both* that a proportion of patients achieve clear or almost clear skin *and* that patients also have at least a 2-grade improvement in acne severity (both as measured by Evaluator's Global Severity Score or Investigator Global Assessment or Physician Global Assessment) from baseline. Previously, treatment success was demonstrated by *either* clear or almost clear skin *or* at least a 2-grade improvement from baseline but NOT both.

This dual assessment of treatment success helps to reduce reliance on inflammatory and non-inflammatory acne lesion counts as the only primary endpoint. While these counts are important and meaningful, there are well-identified challenges associated with the objective measure and classification of lesions.[1] (Recall, too, that overwhelming evidence shows that all acne is inflammatory. [2] Thus, binary classification of acne lesions is misleading.) In reality, most of us do not count acne lesions in a clinical practice setting; rather, we often assess the severity of the disease based on a gestalt impression.

With this understanding of acne treatment trials in mind, one can assess the significance of a relatively new triple combination, fixed-dose topical gel for acne treatment. As always, vehicles matter. In the case of a combination of clindamycin phosphate 1.2%/benzoyl peroxide (BPO) 3.1%/adapalene 0.15% gel, the first triple combination for acne, adapalene, and benzoyl peroxide are micronized and distributed in a polymeric gel to facilitate even distribution and delivery into the pilosebaceous unit.[3,4]

What is particularly striking about this formulation, as discussed in the pages ahead, is the proportion of subjects who achieved treatment success and the implications for patient management. The phase II trial assessed the triple combination, as well as marketed dyad gel combinations, and vehicle gel with only about 150 subjects in each arm of the five-arm study, making it very challenging to reach statistical significance for the triple combination. Despite that, the proportion of patients who achieved treatment success with the triple combination was significantly greater than any of the dyad gels. In phase 3 clinical trials, just over half of the participants achieved treatment success (at least a 2-grade improvement in EGSS *and* rated clear or almost clear) at week 12 with triple combination gel. This treatment success rate was higher than for any other topical treatment assessed to date in a phase 3 clinical trial although we don't scientifically compare separate clinical trials.[5]

With more treatment options than ever, dermatology providers can create customized treatments for their patients with the potential for better outcomes and patient experiences. The unique, first-of-its-kind, topical triple combination of clindamycin, benzoyl peroxide, and adapalene fixed dose gel represents a once-daily convenient therapy with demonstrated enhanced clinical trial efficacy and a favorable tolerability profile, thanks to its novel vehicle.

Therefore, "VEHICLES ALWAYS MATTER".

Leon Kircik MD

Clinical Professor of Dermatology; Icahn School of Medicine at Mount Sinai, New York, NY; Adjunct Clinical Professor of Dermatology; Indiana University School of Medicine, Indianapolis, IN; Medical Director, Physicians Skin Care, PLLC Louisville, KY; DermResearch, PLLC Louisville, KY, Skin Sciences, PLLC Louisville, KY

DISCLOSURE

Leon Kircik MD has received compensation for his editorial efforts from the Journal of Drugs in Dermatology. Leon Kircik MD has served as either an investigator, consultant, speaker, or advisory board member for Allergan, Allmirall, Biofrontera, Galderma, L'Oreal, Mayne Pharma, Ortho Dermatologics, and SUN Pharma.

REFERENCES

1. Ramli R, Malik AS, Hani AF, Jamil A. Acne analysis, grading, and computational assessment methods: an overview. *Skin Res Technol.* 2012;18(1):1-14. doi:10.1111/j.1600-0846.2011.00542.x
2. Del Rosso JQ, Kircik LH. The sequence of inflammation, relevant biomarkers, and the pathogenesis of acne vulgaris: what does recent research show and what does it mean to the clinician?. *J Drugs Dermatol.* 2013;12(8 Suppl):s109-s115.
3. Kircik LH, Draelos ZD, Berson DS. Polymeric emulsion technology applied to tretinoin. *J Drugs Dermatol.* 2019;18(4):s148-s154.
4. 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. doi:10.1007/s40257-021-00650-3
5. Harper JC, Kircik LH, Gold M, et al. Early and sustained acne lesion reductions with fixed-dose clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1% gel. *J Drugs Dermatol.* 2024;23(3):125-131. doi:10.36849/jdd.7907

doi:10.36849/JDD.46942

 ORIGINAL ARTICLE

All for One and One for All: The Three Musketeers of Topical Acne Treatment and the Current Landscape

Naiem T. Issa MD PhD,[a] Ali Shahbaz MD,[b] Leon Kircik MD[c]

[a]Forefront Dermatology, Vienna, VA; Issa Research & Consulting, LLC, Springfield, VA;
Dr. Phillip Frost Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, Miami, FL;
George Washington University School of Medicine and Health Science, Washington, DC
[b]Texas A&M School of Medicine, Austin, TX; Westlake Dermatology & Cosmetic Surgery, Austin, TX
[c]Icahn School of Medicine at Mount Sinai, New York, NY; Indiana University School of Medicine, Indianapolis, IN;
Physicians Skin Care, PLLC Louisville, KY; DermResearch, PLLC Louisville, KY; Skin Sciences, PLLC Louisville, KY

ABSTRACT

What is the ideal topical acne therapeutic? Topical therapeutics for acne vulgaris have advanced considerably over the last decade. Novel vehicular technologies have increased transdermal penetration of active molecules, enhanced their distribution across the skin surface, improved tolerability, and allowed for the incorporation of previously incompatible active compounds. Thus, fixed-combination topical therapeutics were successfully developed and are able to target multiple aspects of acne pathogenesis leading to synergism and increased efficacy. These advancements have paved the way to optimizing acne treatment while incorporating antibiotic stewardship which has become an urgent necessity.

J Drugs Dermatol. 2024;23:11(Suppl 1):s4-10.

INTRODUCTION

Acne is one of the most prevalent dermatological conditions, affecting millions worldwide. It not only has a significant physical impact, but also contributes to psychological distress, including low self-esteem and depression.[1] The necessity for optimal topical acne treatment stems from the need to manage and mitigate these impacts effectively. Optimal topical acne treatments should ideally target multiple pathways involved in acne development.[2] Traditional treatments, though often effective, may come with limitations such as skin irritation, dryness, or other adverse effects. Thus, the pursuit of optimal topical acne treatments is critical to enhancing efficacy, minimizing side effects, and improving patient adherence and satisfaction.

Lack of drug efficacy, low tolerability, and regimen complexity historically lead to poor treatment adherence and suboptimal outcomes.[3] Innovation in vehicle composition and drug delivery technologies have helped improve all metrics resulting in increased patient satisfaction and reduced overall costs.[4] For instance, benzoyl peroxide and retinoids remain cornerstone treatments, but their formulations have evolved to enhance tolerability. Micronized formulations, encapsulation technologies, and combination therapies are examples of innovations aimed at optimizing these agents' efficacy and reducing their irritating potential.[5]

Antibiotic stewardship in acne management is crucial to combating the rising threat of antibiotic resistance.[6] The widespread use of antibiotics, particularly topical clindamycin and erythromycin, has led to increased resistance among *Cutibacterium acnes* (*C. acnes*) and other bacteria. This resistance diminishes the efficacy of treatments and can complicate acne management. Effective stewardship involves using antibiotics judiciously, primarily reserving them for moderate to severe cases where other treatments have failed. Combination therapies, such as pairing antibiotics with benzoyl peroxide (BPO), are recommended to reduce resistance risk by leveraging its bactericidal properties. Limiting antibiotic use duration and transitioning to maintenance therapies with retinoids or BPO alone further helps mitigate resistance. Additionally, the development and use of non-antibiotic therapies play a vital role in reducing antibiotic reliance. By adhering to these principles, practitioners can help preserve antibiotic efficacy.

Here we discuss what traits an optimal theoretical topical acne monotherapy should possess and examine the current topical acne treatment landscape within that context.

The Four Pillars of Acne Treatment

The pathophysiology of acne is well established. It is widely accepted that acne is due to the following abnormalities in the pilosebaceous unit: (1) epidermal proliferation leading to follicular plugging (keratinization), (2) overproduction of sebum, (3) inflammation, and (4) proliferation of bacteria (*C. acnes*).[7] The development of topical acne treatments has focused on targeting one or more of these components (Table 1).

Antibiotics such as tetracyclines and clindamycin target the pathogenic bacteria *C. acnes* while also lending an anti-inflammatory effect.[8] Benzoyl peroxide (BPO) is a wide-acting bactericidal antimicrobial that also exhibits a keratolytic effect which helps with follicular plugging and keratinization.[9] BPO also is recommended in combination therapeutics due to its reduction in antibiotic resistance. Dapsone is a unique antimicrobial that also exhibits anti-neutrophil activity that helps to reduce inflammation as acne exhibits a strong neutrophilic component.[10] Clascoterone (cortexolone 17a-propionate) directly interacts with the androgen receptor and blocks its downstream signaling thereby attenuating the hormonal contribution to excess sebum production.[11] Azelaic acid, a fungus-derived dicarboxylic acid, exerts pleiotropic effects as an antimicrobial (without reported *C. acnes* resistance) and anti-inflammatory.[12] Lastly, retinoids (ie, adapalene, tretinoin, tazarotene, trifarotene) are a class of vitamin A derivatives that have simultaneous effects of reducing sebum production and pro-differentiating epidermal cells and increasing epidermal turnover.[13] Consensus guidelines for acne treatment recommend topical retinoids as first-line for any disease severity.

Fixed-combination topical acne treatments offer significant advantages over monotherapies by providing a synergistic approach that targets multiple pathogenic factors of acne simultaneously. These treatments, which combine two or more active ingredients into a single formulation, enhance efficacy by addressing various aspects of acne pathogenesis, such as reducing bacterial proliferation, decreasing inflammation, and normalizing keratinization. For example, a combination of BPO and clindamycin effectively reduces *C. acnes* and inflammation, while a retinoid combined with BPO targets both comedogenesis and bacterial growth. This multifaceted attack not only improves treatment outcomes but also simplifies the patient's skincare regimen, leading to better adherence, satisfaction, and improved quality of life.[14] Furthermore, fixed-combination treatments can reduce the likelihood of developing bacterial resistance compared to antibiotic monotherapy. By integrating multiple therapeutic actions into one product, fixed-combination topical treatments represent a superior approach to managing acne, offering enhanced efficacy, improved patient compliance, and potentially fewer side effects.

Conceptualizing the Ideal Monotherapy Topical Treatment for Acne

The recent American Academy of Dermatology (AAD) 2024 guidelines of care for the management of acne recommend multimodal topical therapy for mild, moderate, and severe acne vulgaris.[2] The global burden of acne and the increasing desire of patients for effective and tolerable treatments have led to innovative developments in topical acne therapeutics.[5] Topical acne treatments must therefore not only exhibit efficacy but also meet other criteria that increase patient compliance. It can therefore be deduced that the ideal topical treatment as monotherapy exhibits the following properties:

TABLE 1.

Acne Therapies and Resistance. Mechanisms of action of monad and fixed-combination topical acne therapies with respect to the four pillars of acne pathophysiology and antibiotic resistance.

		Keratinization	Sebum Production	Inflammation	Microbial	Antibiotic Resistance
Triad	BPO/Antibiotic/Retinoid	X	X	X	X	X
Dyad	BPO/Retinoid	X	X	X	X	X
Dyad	BPO/Antibiotic	X	--	X	X	X
Monad	Azelaic Acid	X	--	X	X	X
Monad	Clascoterone	--	X	----	--	--
Monad	BPO	X			X	X
Monad	Retinoids	X	X	X	--	--
Monad	Antibiotics	--	--	X	X	--
Monad	Dapsone	--	--	X	X	X

(1) *Efficacy in reducing acne lesions* – this hinges upon maximizing the treatment's ability to simultaneously target the four pillars of acne pathophysiology. Combination treatments have traditionally shown synergistic effects due to multiple components being targeted. This is particularly highlighted by the current dyad monotherapy topicals such as BPO/clindamycin, BPO/adapalene, and clindamycin/tretinoin where the dyads were superior to their monad components in head-to-head clinical studies.[15-18]

(2) *Low irritation and side effect profile* – topicals that exhibit low irritation and side effects such as erythema, burning, itching, and scaling result in greater adherence to therapy. This logic has been affirmed in numerous studies and was noted to be the most common risk factor for non-adherence.[19]

(3) *Minimal frequency of application* – topicals that require once daily application are generally preferred to those that require twice daily application.[20] In a study by Snyder et al, forgetfulness was noted to be the second most cited rationale for treatment non-adherence.[19] Being too busy was also reported as a significant reason for non-adherence.[19] This can be mitigated by using topical treatments requiring only once daily application.

(4) *Minimal risk of antibiotic resistance* – Antibiotics have been utilized for decades for their benefit against *C. acnes*, the key microbial pathogen in acne vulgaris.[21] Dermatologists alone account for over 8 million antibiotic prescriptions annually.[22]

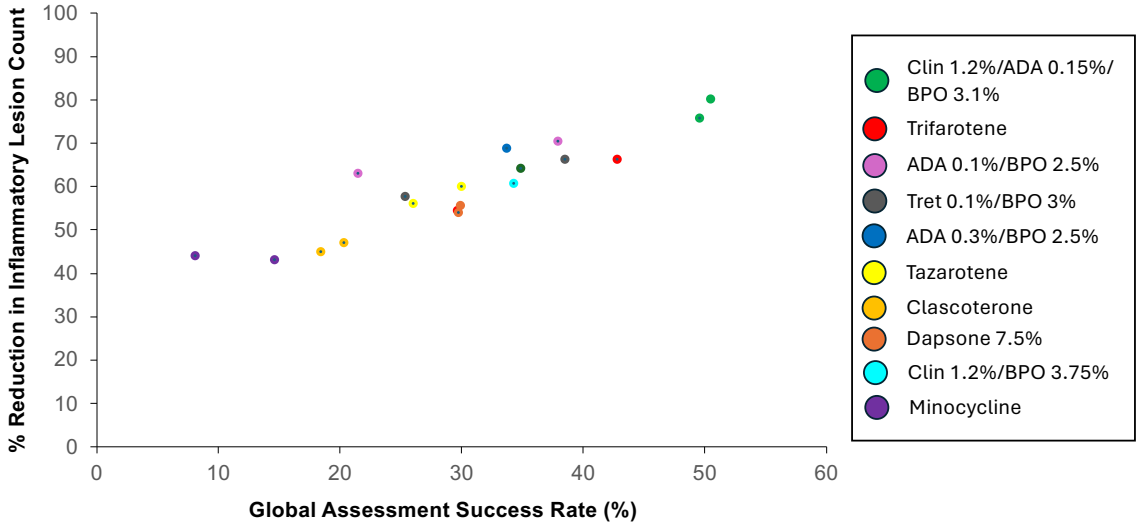
The global utilization of antibiotics over many years has led to the development of antibiotic-resistant *C. acnes*.[23] Antibiotic resistance is present in over 50% of *C. acnes* strains across many countries.[24] Resistance patterns also differ across regions due to various prescribing patterns.[25] In the United States, the greatest resistance rates were seen for erythromycin, clindamycin, and tetracycline.[22] Antibiotic stewardship is therefore of tantamount importance in daily acne treatment considerations.[26]

National and international acne treatment consensus guidelines recommend concomitant use of BPO with antibiotics or in fixed-dose combination topicals to reduce and prevent the development of antibiotic resistance.[22,27-30] BPO is successful against a wide variety of bacteria despite their resistance patterns due to its ability to oxidize bacterial cell wall proteins rather than targeting particular bacterial machinery such as ribosomal RNA.[6,31] To date, no resistance patterns to BPO have been reported.[2,30]

Vehicular Technology Advancements

Advancements in topical vehicular technology have resulted in acne treatment formulations that are more elegant, tolerable, and efficacious. Furthermore, previously incompatible active molecules that required separate applications, such as BPO and tretinoin, are now able to be co-administered.[4,5] These vehicular technologies include: (1) microsphere-containing polymers that contain the active drug in microsphere cores which degrade upon skin contact to allow for increased transdermal

FIGURE 1. Biplot of global assessment treatment success (%) and mean/median percent reduction in inflammatory lesion counts of fixed-combination and select topical monad acne vulgaris therapeutics. Endpoint data were obtained from the double-blinded, randomized, vehicle-controlled phase 3 pivotal trials.[8,17,38,52-61]



penetration, low irritation, and controlled drug release[32,33]; (2) liposomal delivery systems for enhanced transcutaneous delivery of active drug[34]; (3) microencapsulation for isolating particles from the surrounding environment via entrapping micrometer-sized particles in an inert shell (thus allowing for the combination of BPO and retinoids)[35]; (4) polymer mesh technology utilizing cross-linked aqueous polymers that allow homogenous distribution of drug microparticles[36]; and (5) micronization which allows for the consistent manufacturing of uniformly small particles of active drug that allows for enhanced cutaneous and follicular penetration.[36] The evolution of topical acne therapeutics have been intimately linked to that of vehicular technology, which has now allowed for effective stable combination formulations.

2024 Landscape of Topical Acne Treatments

As topical acne treatments have evolved, their efficacy rates have also improved compared to years prior. Of note, it is difficult to truly compare success rates of topical acne treatments, even within the context of network meta-analyses, as there has been variability in definitions of success and Investigator Global Assessments (IGA). This lack of standardization confounds the comparison of trial results for acne treatments.[37] Nonetheless, it is still possible to get a general comparative sense of efficacy.

Figure 1 displays the success rates of currently available fixed-combination therapies and select topical acne monad treatments from pivotal phase 3 trials for moderate-to-severe facial acne with respect to improvement in global assessment and reduction in inflammatory lesions count (ILC). Traditionally, global assessment success rates for topical acne treatments have generally been around 30% with only one of two phase 3 trials typically exceeding that. It is only the fixed-dose triple-combination clindamycin phosphate 1.2% / adapalene 0.15% / benzoyl peroxide 3.1% (CAB) gel that surpasses that (~50% IGA success rate in each phase 3 trial), which has not been seen in clinical studies of other acne products.[38,39] With respect to the percent reduction of ILC, fixed-dose triple-combination CAB also exhibited the greatest percent reduction (-75.7% and -80.1%; Figure 1).

Recent network metanalyses have also attempted to provide comprehensive comparisons across common topical and oral pharmacological treatments for moderate-to-severe acne. Despite the endpoints integrated for analysis differing across the studies — mean percent reduction in total, inflammatory, and noninflammatory lesions for Huang et al,[40] and percent of patients achieving success for global severity score and absolute change in inflammatory and noninflammatory lesion counts for Harper et al[41] — the outcomes were similar. The most efficacious topical acne treatment was the fixed triple-combination CAB gel. Additionally, Huang et al found it to be the second-most effective acne treatment (oral isotretinoin being the most effective) when considering oral treatments as well in the metanalysis.[40] This is notable as the triple-combination CAB gel is potentially equivalent to gold standard systemic medications but avoids potential systemic adverse events while reducing healthcare costs due to laboratory testing needs.

It is worth noting that once-daily fixed-combination therapies have proved superior to their respective monads across numerous trials. Clindamycin phosphate 1% / BPO 5% combination therapy outperformed clindamycin, BPO and vehicle monotherapies in patients with facial acne.[15,16] Adapalene 0.1% / BPO 2.5% gel also demonstrated superiority to adapalene, BPO and vehicle gel monotherapies.[42,43] Fixed-combination clindamycin phosphate 1.2% / tretinoin 0.025% gel exhibited superiority to its component monads as well.[18] Lastly, the efficacy of triple-combination CAB gel was superior to numerous dyad permutations (BPO/adapalene gel, Clindamycin/BPO gel, Clindamycin/adapalene gel) over 12 weeks across all co-primary endpoints (treatment success and absolute change from baseline in inflammatory and non-inflammatory lesions).[44] To date, there have been no comparisons between fixed-combination dyads and clascoterone.

While combining multiple topical medications results in synergism, they may also increase skin irritation and reduce tolerability. This is inherent to not only the vehicle but also the type of active molecules incorporated. BPO and retinoids typically cause scaling, burning and itching, and the combination of the two in dyads has resulted in heightened adverse effect profiles. On the other hand, clindamycin incorporated into dyads containing either BPO or a retinoid has conversely helped with tolerance and adherence likely due to its anti-inflammatory properties.[45] A metanalysis by Stuart et al[46] supports this rationale wherein clindamycin combined with BPO had lower odds of patient discontinuation due to adverse events than BPO alone or BPO/adapalene combinations. A more recent network analysis performed by Huang et al assessed the odds ratios of discontinuation due to adverse events and found discontinuation rates to be generally low across all treatments (which included clascoterone, all monad retinoids, clindamycin and BPO, as well as all fixed-combination products).[40] However, the top three topicals with greatest odds ratio of discontinuation were trifarotene, tazarotene, and the combination of retinoid with BPO whereas clascoterone had the lowest odds ratio of discontinuation. Later-generation topical retinoid monads had greater rates of discontinuation than fixed-combination therapeutics, possibly due to their unique targeting of different isoforms of the retinoic acid receptor (RAR). Moreover, the topical adapalene with BPO combination group exhibited side effects more commonly than other fixed-combination

treatments, which is in line with the metanalysis by Stuart et al.[46] Notably, the fixed-dose triple-combination CAB gel appears to have a better safety and tolerability profile than BPO/adapalene with fewer severe cases of burning and stinging in a phase 2 study.[44] This may be attributed to both the anti-inflammatory effect of clindamycin and the gel vehicle formulation with polymeric mesh and microionized actives allowing for a more uniform distribution. Furthermore, CAB gel was well tolerated under exaggerated conditions in a phase 1 repeat insult patch test (RIPT) and cumulative insult patch test (CIPT).[47]

DISCUSSION

Unmet needs in acne treatment have generally been the need for topicals with greater efficacy and tolerability across all skin types with the least frequency of application to maximize treatment adherence. Furthermore, antibiotic stewardship in acne treatment has become tantamount given the global rise in antibiotic-resistant *C. acnes*.[23,24] With respect to topical therapeutics, fixed-combination therapies or concerted stepwise use of monad therapies have helped in optimizing efficacy. The strong recommendation for inclusion of BPO in acne treatment guidelines from numerous national and international working groups has also reduced *C. acnes* antibiotic resistance.[28-30,48]

The landscape of topical acne therapeutics has advanced remarkably over the last decade to help meet the aforementioned needs. Newer vehicles increase efficacy of monad therapies due to enhanced transcutaneous drug delivery. Moreover, novel vehicular technologies such as micronization now allow for the unprecedented combination of previously incompatible active drugs such as BPO and retinoids. This is exemplified by the formulation of the first-in-class fixed triple-combination CAB gel.

One may argue that it is difficult to properly compare all the fixed-combination topicals given the lack of rigorous phase 3 head-to-head trials and that there is variability in definitions of treatment success (ie, EGSS, IGA, and Investigator's Static Global Assessment (ISGA)).[37,49] Network metanalysis also falls somewhat short despite their statistical rigor given the above. However, comparisons may be made through using the number needed to treat (NNT).[50] The NNT is a simple way to indirectly compare drug efficacy across clinical trials when head-to-head studies are not available as it is a descriptor that represents the number of patients needed to be on treatment to achieve one additional success versus vehicle. The lower the NNT, the better the outcome. An NNT of 1 would be considered the best outcome where every treated person achieves treatment success while no one on vehicle responds. Feldman et al calculated the for various fixed-combination topical acne treatments and found the triple-combination CAB gel to have the lowest NNT (4 and 5) across the two pivotal trials followed by adapalene 0.3%/BPO 2.5% gel (NNT of 5).[51]

CONCLUSION

The ideal topical acne therapeutic is efficacious and tolerable with once-daily application to allow for treatment adherence. Furthermore, it must reduce the risk of antibiotic resistance. Advancements in vehicular technologies have allowed for the development of tolerable fixed-combination products that elegantly combine previously incompatible active drugs to fit these criteria. Using different indirect comparison methodologies (ie, network metanalysis, NNT), the fixed-combination triple combination CAB gel appears to be the most efficacious once-daily topical therapeutic with acceptable tolerability profile and ability to minimize antibiotic resistance to date.

DISCLOSURES

Leon Kircik MD has served as either an investigator, consultant, speaker, or advisory board member for Allergan, Allmirall, Biofrontera, Galderma, L'Oreal, Mayne Pharma, Ortho Dermatologics, and SUN Pharma.

Naiem T. Issa has received funding from the following entities either as a speaker, consultant, advisor, or investigator Bristol Myers Squibb, Castle Biosciences, Dermavant Sciences, DermTech, Galderma, LEO Pharma, Lilly, National Eczema Association, Ortho Dermatologics, Pfizer, RBC Consultants, Verrica Pharmaceuticals, and WebMD.

Ali Shahbaz, MD FAAD FRCPC has received funding from the following entities either as a speaker, consultant, advisor, or investigator Bristol Myers Squibb, UCB, Abbvie, Incyte, Johnson & Johnson, Arcutis, Dermavant Sciences, Galderma, Novartis, LEO Pharma, RBC Consultants, Beieirsdorf, L'Oreal, and Allergan.

REFERENCES

1. Tan JK, Bhate K. A global perspective on the epidemiology of acne. *Br J Dermatol.* 2015;172 (Suppl 1):3-12.
2. Reynolds RV, Yeung H, Cheng CE, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol.* 2024;90(5):1006.e1001-1006.e1030.
3. Reich K, Daudén E. Treatment adherence: a hurdle for real-life effectiveness in psoriasis? *J Eur Acad Dermatol Venereol.* 2014;28(Suppl 2):1-3.
4. Stein Gold L, Kwong P, Draelos Z, et al. Impact of topical vehicles and cutaneous delivery technologies on patient adherence and treatment outcomes in acne and rosacea. *J Clin Aesthet Dermatol.* 2023;16(5):26-34.
5. Issa NT, Kircik L. Update on combined topical products for treating acne: leaping from dyads. *J Drugs Dermatol.* 2024;23(4):SF378083bs378084-SF378083bs378010.
6. Issa NT, Kircik LH. Antibiotic stewardship in acne: 2023 update. *J Drugs Dermatol.* 2024;23(2):SF37896s37894-SF378969s378910.
7. Zouboulis CC, Eady A, Philpott M, et al. What is the pathogenesis of acne? *Exp Dermatol.* 2005;14(2):143-152.
8. Del Rosso J, Sugarman J, Green L, et al. Efficacy and safety of microencapsulated benzoyl peroxide and microencapsulated tretinoin for the treatment of acne vulgaris: Results from two phase 3 double-blind, randomized, vehicle-controlled studies. *J Am Acad Dermatol.* 2023;89(4):719-727.
9. Leung AK, Barankin B, Lam JM, et al. Dermatology: how to manage acne vulgaris. *Drugs Context.* 2021;10.
10. Ross CM. The treatment of acne vulgaris with dapsone. *Br J Dermatol.* 1961;73:367-370.
11. Peterson H, Kircik L, Armstrong AW. Clascoterone cream 1%: mechanism of action, efficacy, and safety of a novel, first-in-class topical antiandrogen therapy for acne. *J Drugs Dermatol.* 2023;22(6):SF350992s350997-SF350992s350914.
12. Schulte BC, Wu W, Rosen T. Azelaic acid: evidence-based update on mechanism of action and clinical application. *J Drugs Dermatol.* 2015;14(9):964-968.
13. Chien A. Retinoids in acne management: review of current understanding, future considerations, and focus on topical treatments. *J Drugs Dermatol.* 2018;17(12):s51-55.
14. Hayran Y, İncel Uysal P, Öktem A, et al. Factors affecting adherence and patient satisfaction with treatment: a cross-sectional study of 500 patients with acne vulgaris. *J Dermatolog Treat.* 2021;32(1):64-69.
15. Warner GT, Plosker GL. Clindamycin/benzoyl peroxide gel: a review of its use in the management of acne. *Am J Clin Dermatol.* 2002;3(5):349-360.
16. Xu JH, Lu QJ, Huang JH, et al. A multicentre, randomized, single-blind comparison of topical clindamycin 1%/benzoyl peroxide 5% once-daily gel versus clindamycin 1% twice-daily gel in the treatment of mild to moderate acne vulgaris in Chinese patients. *J Eur Acad Dermatol Venereol.* 2016;30(7):1176-1182.
17. Gollnick HP, Draelos Z, Glenn MJ, 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):1180-1189.
18. Jarratt MT, Brundage T. Efficacy and safety of clindamycin-tretinoin gel versus clindamycin or tretinoin alone in acne vulgaris: a randomized, double-blind, vehicle-controlled study. *J Drugs Dermatol.* 2012;11(3):318-326.
19. Snyder S, Crandell I, Davis SA, et al. Medical adherence to acne therapy: a systematic review. *Am J Clin Dermatol.* 2014;15(2):87-94.
20. Yentzer BA, Ade RA, Fountain JM, et al. Simplifying regimens promotes greater adherence and outcomes with topical acne medications: a randomized controlled trial. *Cutis.* 2010;86(2):103-108.
21. Rusu A, Buta EL. The development of third-generation tetracycline antibiotics and new perspectives. *Pharmaceutics.* 2021;13(12).
22. Del Rosso JQ, Webster GF, Rosen T, et al. Status report from the scientific panel on antibiotic use in dermatology of the american acne and rosacea society: part 1: antibiotic prescribing patterns, sources of antibiotic exposure, antibiotic consumption and emergence of antibiotic resistance, impact of alterations in antibiotic prescribing, and clinical sequelae of antibiotic use. *J Clin Aesthet Dermatol.* 2016;9(4):18-24.
23. 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.
24. Walsh TR, Efthimiou J, Dréno B. Systematic review of antibiotic resistance in acne: an increasing topical and oral threat. *Lancet Infect Dis.* 2016;16(3):e23-33.
25. Platsidaki E, Dessinioti C. Recent advances in understanding Propionibacterium acnes (Cutibacterium acnes) in acne. *F1000Res.* 2018;7.
26. Dreno B, Thiboutot D, Gollnick H, et al. Antibiotic stewardship in dermatology: limiting antibiotic use in acne. *Eur J Dermatol.* 2014;24(3):330-334.
27. Thiboutot D, Gollnick H, Bettoli V, et al. New insights into the management of acne: an update from the Global Alliance to Improve Outcomes in Acne group. *J Am Acad Dermatol.* 2009;60(5 Suppl):S1-50.
28. Thiboutot DM, Dréno B, Abanmi A, et al. Practical management of acne for clinicians: An international consensus from the Global Alliance to Improve Outcomes in Acne. *J Am Acad Dermatol.* 2018;78(2 Suppl 1):S1-S23.e21.
29. Reynolds RV, Yeung H, Cheng CE, et al. Guidelines of care for the management of acne vulgaris. *J Am Acad Dermatol.* 2024.
30. 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.
31. Baldwin H, Webster G, Stein Gold L, et al. 50 years of topical retinoids for acne: evolution of treatment. *Am J Clin Dermatol.* 2021;22(3):315-327.
32. Vyas A, Kumar Sonker A, Gidwani B. Carrier-based drug delivery system for treatment of acne. *ScientificWorldJournal.* 2014;2014:276260.
33. Kircik LH. Microsphere technology: hype or help? *J Clin Aesthet Dermatol.* 2011;4(5):27-31.
34. Garg T. Current nanotechnological approaches for an effective delivery of bio-active drug molecules in the treatment of acne. *Artif Cells Nanomed Biotechnol.* 2016;44(1):98-105.

35. Ciriminna R, Sciortino M, Alonzo G, et al. From molecules to systems: sol-gel microencapsulation in silica-based materials. *Chem Rev.* 2011;111(2):765-789.

36. Rosso JD, Harper J, Pillai R, Moore R. Tretinoin photostability: comparison of micronized tretinoin gel 0.05% and tretinoin gel 0.025% following exposure to fluorescent and solar light. *J Clin Aesthet Dermatol.* 2013;6(2):25-28.

37. Stein Gold L, Tan J, Kircik L. Evolution of acne assessments and impact on acne medications: an evolving, imperfect paradigm. *J Drugs Dermatol.* 2016;15(1):79-86.

38. Stein Gold L, Lain E, Del Rosso JQ, 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;89(5):927-935.

39. Kircik LH, Stein Gold L, Gold M, et al. Triple combination clindamycin phosphate 1.2%/adapalene 0.15%/benzoyl peroxide 3.1% for acne: efficacy and safety from a pooled phase 3 analysis. *Dermatol Ther (Heidelb).* 2024;14(5):1211-1227.

40. 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.

41. Harper JC, Baldwin H, Choudhury SP, et al. Treatments for moderate-to-severe acne vulgaris: a systematic review and network meta-analysis. J *Drugs Dermatol.* 2024;23(4):216-226.

42. Tan J, Gollnick HP, Loesche C, et al. Synergistic efficacy of adapalene 0.1%-benzoyl peroxide 2.5% in the treatment of 3855 acne vulgaris patients. *J Dermatolog Treat.* 2011;22(4):197-205.

43. Feldman SR, Tan J, Poulin Y, et al. The efficacy of adapalene-benzoyl peroxide combination increases with number of acne lesions. *J Am Acad Dermatol.* 2011;64(6):1085-1091.

44. 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.

45. Del Rosso JQ, Schmidt NF. A review of the anti-inflammatory properties of clindamycin in the treatment of acne vulgaris. *Cutis.* 2010;85(1):15-24.

46. 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.

47. Draelos ZD, Tanghetti EA, Kircik LH, et al. Dermal sensitization, safety, and tolerability of triple-combination clindamycin phosphate 1.2%/benzoyl peroxide 3.1%/adapalene 0.15% gel from three clinical trials. *J Dermatolog Treat.* 2023;34(1):2220446.

48. Nast A, Dréno 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.

49. Zarchi K, Jemec GBE. Severity assessment and outcome measures in acne vulgaris. *Current Dermatology Reports.* 2012;1(3):131-136.

50. Mendes D, Alves C, Batel-Marques F. Number needed to treat (NNT) in clinical literature: an appraisal. *BMC Med.* 2017;15(1):112.

51. Feldman SR, Han G, Callender VD, et al. Benefit of topical combination therapy for acne: analyzing effect size using number needed to treat. *J Drugs Dermatol.* 2024;23(2):42-49.

52. Tan J, Thiboutot D, Popp G, et al. Randomized phase 3 evaluation of trifarotene 50 µg/g cream treatment of moderate facial and truncal acne. *J Am Acad Dermatol.* 2019;80(6):1691-1699.

53. Hebert A, Thiboutot D, Stein Gold L, et al. Efficacy and safety of topical clascoterone cream, 1%, for treatment in patients with facial acne: two phase 3 randomized clinical trials. *JAMA Dermatol.* 2020;156(6):621-630.

54. Tanghetti EA, Werschler WP, Lain T, et al. Tazarotene 0.045% lotion for once-daily treatment of moderate-to-severe acne vulgaris: results from two phase 3 trials. J Drugs Dermatol. 2020;19(1):70-77.

55. Stein Gold LF, Jarratt MT, Bucko AD, et al. Efficacy and safety of once-daily dapsone gel, 7.5% for treatment of adolescents and adults with acne vulgaris: first of two identically designed, large, multicenter, randomized, vehicle-controlled trials. J Drugs Dermatol. 2016;15(5):553-561.

56. Eichenfield LF, Lain T, Frankel EH, et al. Efficacy and safety of once-daily dapsone gel, 7.5% for treatment of adolescents and adults with acne vulgaris: second of two identically designed, large, multicenter, randomized, vehicle-controlled trials. J Drugs Dermatol. 2016;15(8):962-969.

57. Raoof TJ, Hooper D, Moore A, et al. Efficacy and safety of a novel topical minocycline foam for the treatment of moderate to severe acne vulgaris: A phase 3 study. J Am Acad Dermatol. 2020;82(4):832-837.

58. Thiboutot DM, Weiss J, Bucko A, et al. Adapalene-benzoyl peroxide, a fixed-dose combination for the treatment of acne vulgaris: results of a multicenter, randomized double-blind, controlled study. J Am Acad Dermatol. 2007;57(5):791-799.

59. Stein Gold L, Weiss J, Rueda MJ, et al. 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.

60. 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):1083-1089.

61. Thiboutot D, Zaenglein A, Weiss J, et al. 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.

AUTHOR CORRESPONDENCE

Leon Kircik MD

E-mail:..... wedoderm@yahoo.com

doi:10.36849/JDD.46940

JOURNAL OF DRUGS IN DERMATOLOGY
JDD
DRUGS • DEVICES • METHODS