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Update on Combined Topical Products for Treating Acne: Leaping From Dyads

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ABSTRACT

Antibiotic resistance and treatment adherence remain significant challenges for acne treatment. Advances in topical formulations have ushered in an era of fixed combination topical therapeutics that are well-tolerated and more efficacious. In addition, their once-daily application leads to increased treatment adherence. This article discusses formulation strategies that allow for the coadministration of active drugs and reviews all commercially available fixed-combination topical acne treatments.

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INTRODUCTION

The pathogenesis of acne vulgaris is multifactorial. Four major processes occur in tandem that leads to the development and propagation of acne: (1) excess sebum production, (2) follicular plugging due to epidermal hyperproliferation, (3) proliferation of *Cutibacterium acnes* (formerly *Propionibacterium acnes*), and (4) inflammation.[1] Dysregulation of the epidermis and pilosebaceous unit due to inflammatory changes and dysbiosis leads to the formation of comedones, papules, pustules, and cystic nodules.[2] As such, acne treatment is aimed at mediating these four pillars of pathogenesis.

Retinoids are the mainstay of treatment given their pleiotropic effects on sebaceous gland function and epidermal turnover and differentiation.[3] Antibiotics such as lincosamides (eg, clindamycin) and tetracyclines are also utilized given their antimicrobial effect on *C. acnes* as well as their anti-inflammatory effects.[4] Benzoyl peroxide (BPO) is a unique antimicrobial exhibiting bactericidal activity through oxidation of bacterial proteins thus damaging the cell wall in a non-targeted manner.[5] This mechanism affords BPO as an agent that could not only circumvent but also prevent antibiotic resistance.[6] BPO also exhibits comedolytic and keratolytic activity thus aiding with unplugging of the pilosebaceous unit.[6]

International consensus guidelines for acne treatment recommend topical treatments for any acne disease severity (mild, moderate, or severe).[4,7,8] Topical retinoids are considered the first line as they affect almost all pillars of acne pathogenesis. Topical antibiotics are also recommended in combination with retinoids to target the dysbiosis due to *C. acnes*. However, given the significant concern for antibiotic resistance, BPO is the preferred antimicrobial agent due to its non-targeted mechanism of action as an oxidizing agent.[4] Oral antibiotics and oral retinoids are also recommended with increasing disease severity or in the case of failure of topical therapies.

The need for multiple therapeutic agents to combat acne pathogenesis has traditionally required multiple individual topical therapeutics to be applied at different times of day and with specific layering instructions. Furthermore, simultaneous application of specific active molecules is not advised as they may cause concomitant instability. For example, the oxidative property of BPO causes the degradation of tretinoin rendering it ineffective.[9] As a result, acne treatment regimens have required multi-step routines to optimize efficacy. In addition, each individually formulated topical agent has a unique tolerability profile. Thus, the need for a multi-step approach combined with an unpredictable range of tolerability adverse events (AEs) have contributed to poor patient adherence to treatment resulting in treatment failures.[10,11]

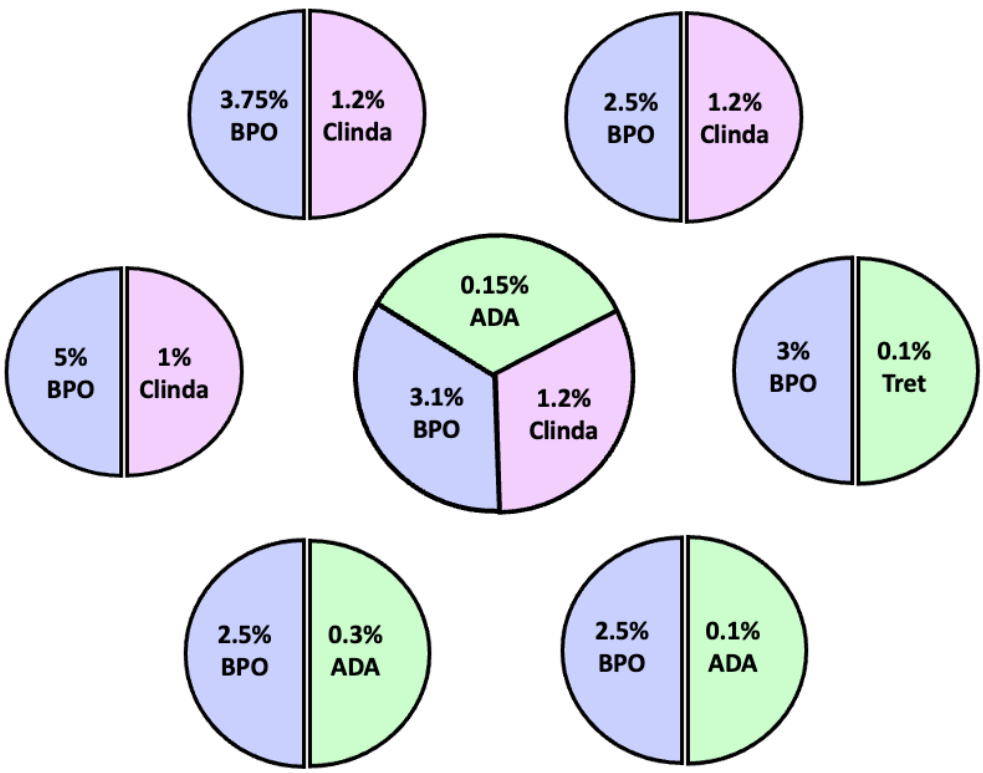
For years there has been an unmet need for topical therapeutics for acne to increase patient adherence and reduce tolerability issues related to treatment. Recent advancements in formulation technologies have allowed for combination products with improved tolerability profiles that have led to synergism in efficacy while improving patient adherence.[3]These advancements are discussed next.

Advancements in Topical Formulations for Acne Therapeutics

Optimizing topical delivery of drugs for skin disease is critical for both efficacy and tolerability. The evolution of vehicle technology has allowed for greater tolerability and the development of fixed-dose combinations that lend to improved treatment outcomes and patient satisfaction while reducing overall treatment costs. These technologies have also allowed for the coadministration of previously incompatible active agents that required separate applications such as BPO and tretinoin.[12]

Polymer technologies utilize microspheres which are tiny biodegradable polymer-based spheres containing active drugs throughout their cores.[13,14] They allow for controlled drug release without increasing transdermal penetration once the microspheres are degraded upon application on the skin thereby minimizing irritation.[14] Liposomal delivery systems enhance the transcutaneous delivery of active drugs as liposomes are spherical amphiphilic vesicles – hydrophilic on one side and lipophilic on the other. As such, they can encase both hydrophilic and lipophilic drugs and improve their therapeutic potential.[15] Microencapsulation is an additional novel technology that allows for the combination of BPO and retinoids. Microencapsulation is the process of entrapping micrometer-sized particles in an inert shell that isolates those particles from the surrounding environment.[16] Silica microencapsulation technology allows for the combination of active drugs via separate encapsulation of individual drugs and further provides controlled release.

FIGURE 1. Topical fixed-dose combination therapeutics utilized for the treatment of acne vulgaris. ADA = adapalene, BPO = benzoyl peroxide, Clinda = clindamycin.



Polymer emulsion or polymer mesh technology is based on the utilization of a crosslinked polymer to structure an aqueous vehicle and provide a homogenous dispersion of microparticles. Polymer mesh technology allows for the utilization of a minimum quantity of structuring agent in an aqueous phase and allows the elimination of emulsifiers, waxes, and other inactive ingredients that may interfere with the delivery of active to the skin. It is combined with the use of micronized active ingredients. Drug-active micronization is a unique formulation process that is often confused with microspheres and microencapsulation. It is distinct in that it is a consistent manufacturing of a designated size range of smaller particles of active ingredient.[17] Micronization therefore creates uniformly small enough particle sizes that allows for enhanced cutaneous and follicular penetration with a more even distribution upon topical application when incorporated into a vehicle.

Synergism in Topical Acne Combination Products: Decades of Dyads Before a Triad

While numerous single-agent topical antimicrobials and retinoids exist, antibiotic resistance, poor active delivery, and poor treatment adherence (sometimes due to irritation) are major contributors to treatment failures.[11] With the advancement of vehicle formulation technologies, topical fixed-dose combination products have been developed that allow for increased adherence given their once-daily application as a single treatment bypassing the need for multiple topicals with multiple applications. Fixed-dose combination products have also allowed for a combination of agents that were initially prohibitive (eg, BPO and tretinoin due to oxidation) and further provide synergy in efficacy.[18] The currently approved fixed-dose combination products are discussed next.

BPO-Clindamycin Combinations

Formulations combining clindamycin with BPO have been developed to reduce antibiotic resistance due to clindamycin while maximizing antimicrobial and anti-inflammatory effects. The initial combination products were clindamycin phosphate 1% and BPO 5% (CDP 1%/BPO 5%) gels. Several clinical trials assessed the efficacies of these gel formulations compared to clindamycin, BPO, and vehicle monotherapies alone.[19] Xu et al also found CDP 1%/BPO 5% to be superior to clindamycin 1% gel monotherapy in a single-blind randomized comparison trial of 1016 subjects with mild-to-moderate acne over 12 weeks.[20] More recently, a gel formulation containing CDP 1.2%/BPO 3.75% was developed. Pariser et al investigated the efficacy of once-daily CDP 1.2%/BPO 3.75% in 498 subjects with moderate-to-severe acne over 12 weeks compared to vehicle.[21] 34.3% and 15.6% of subjects in the CDP 1.2%/BPO 3.75% and vehicle groups, respectively, achieved treatment success (at least 2-grade improvement in Evaluator's Global Severity Score EGSS) at week 12. Post-hoc analyses found superior reductions in lesion count in the CDP 1.2%/BPO 3.75% group compared to the vehicle as early as week 4 and that Hispanics tolerated treatment well and were not found to be more susceptible to irritation.[22,23] Lastly, there is also a CDP 1.2%/BPO 2.5% gel formulation.[24] Eichenfield et al showed the superiority of CDP 1.2%/BPO 2.5% gel to the vehicle over 12 weeks in adolescents with skin of color with a favorable cutaneous tolerability profile.[25]

BPO-Retinoid Dyads

The first fixed-dose combination BPO-retinoid approved for once-daily treatment of acne is adapalene 0.1%/benzoyl peroxide 2.5% (0.1% ADA/BPO) gel.[26] A randomized double-blind controlled trial of 1670 subjects showed synergism of once-daily application of 0.1% ADA/BPO gel over each monad (adapalene 0.1%, BPO 2.5% monotherapies) and vehicle gel over 12 weeks of treatment.[26] A pooled assessment from 3 randomized, double-blind, controlled studies showed 0.1% ADA/BPO gel to be significantly more effective than adapalene, BPO, and gel vehicle monotherapies despite acne lesion counts with the relative benefit of the combination gel increasing with higher lesion counts at baseline.[27,28] One study also demonstrated a 97% reduction in antibiotic-resistant and antibiotic-susceptible *C. acnes* strains after four weeks of once-daily application.[29]

As topical treatments alone have not traditionally been seen as suitable for severe non-nodulocystic papulopustular acne, a higher concentration of adapalene in fixed combination with BPO was developed. Stein Gold et al assessed the efficacy of once-daily adapalene 0.3%/benzoyl peroxide 2.5% (0.3% ADA/BPO) gel compared to vehicle in a randomized, double-blind, parallel-group controlled study comprising 503 subjects.[30] 0.3% ADA/BPO was superior in the co-primary endpoints of Investigatory Global Assessment (IGA) success rate (clear/almost clear, at least a 2-grade change) and change in inflammatory and non-inflammatory lesion counts at week 12. An early onset of action was noted as early as week 1. Notably, this trial also focused on the severe acne population (IGA 4) and utilized a stricter secondary endpoint of a 3-point IGA reduction. 0.3% ADA/BPO demonstrated superiority over vehicle for this secondary endpoint. A post-hoc analysis stratifying subjects based on age and gender further found 0.3% ADA/BPO to be equally effective and safe regardless of age and gender.[31] 0.3% ADA/BPO is also effective in all skin phototypes and is effective, tolerable, and improves post-inflammatory hyperpigmentation in patients with skin of color.[32,33]

Tretinoin has also been successfully combined with BPO via microencapsulation technology.[34] A formulation containing encapsulated BPO 3%/encapsulated tretinoin 0.1% (E-BPO/T) cream has been investigated in 571 subjects 9 years of age or older with moderate to severe acne.[35] Once-daily application of E-BPO/T was significantly superior to the vehicle with respect to changes from baseline in both inflammatory and noninflammatory lesion counts across both parallel, randomized, controlled trials.[35]

Clindamycin-Tretinoin Combination

Clindamycin has also been combined with tretinoin in a gel formulation (CDP 1.2%/tretinoin 0.025%).[36] A pooled analysis of 4550 subjects across three pivotal trials showed CDP/tretinoin to be effective in treating both inflammatory and non-inflammatory acne lesions as early as 2 weeks into treatment.[37,38] The formulation is also unique in that it contains a combination of solubilized and crystalline retinoid that allows for both rapid and slower prolonged follicular penetration, leading to deeper penetration of clindamycin.[37] Furthermore, CDP/tretinoin exhibited greater efficacy compared to each monad.[39] A post hoc analysis in 797 subjects from the parallel 12-week pivotal trials also showed that acne subjects with Fitzpatrick skin types IV-VI exhibited efficacy and tolerability that was comparable to subjects with Fitzpatrick skin types I-III.[40]

As clindamycin is being used unopposed (ie, no BPO is used in conjunction), there is a significant risk of developing antibiotic resistance in *C. acnes*.[41] In fact, antibiotic resistance rates across the globe continue to rise, ranging from 50–93% in European countries with many countries reporting antibiotic resistance in more than 50% of *C. acnes* strains.[42,43] Given that antibiotics are the cornerstone of acne treatment and that millions of individuals receive antibiotics worldwide for acne annually, antibiotic stewardship must be embraced to maintain the efficacy of current and future treatments.

Tolerability

While the aforementioned topical dyads exhibit largely similar efficacies in the treatment of acne, they do differ in tolerability. This is important in treatment decision-making as current guidelines recommend BPO-containing dyads over those that do not contain BPO due to risk of developing antibiotic resistance.[8] Few studies directly assessed the tolerability of these dyads against each other, however. Gonzalez et al performed a randomized, single-blind, split-face study comparing the tolerability profiles of clindamycin 1%/BPO 2.5% gel versus adapalene 0.1%/BPO 2.5% gel in 45 subjects over 2 weeks and found that clindamycin/BPO was better tolerated than adapalene/BPO.[44] Bhatia et al found adapalene 0.3%/BPO 2.5% gel to be less tolerable than clindamycin-BPO 3.75% gel in a 21-day split-face study in healthy volunteers with no apparent facial redness or dryness.[45] Goreshi et al performed a double-blind, randomized split-faced study comparing the tolerability of clindamycin 1.2%/tretinoin 0.025% to adapalene 0.1%/BPO 2.5% applied daily for 21 days.[46] Subjects reported significantly less burning, stinging, and pruritus with adapalene 0.1%/BPO 2.5% thus demonstrating significantly less skin irritancy compared to clindamycin 1.2%/tretinoin 0.025%. Aschoff et al similarly showed adapalene 0.1%/BPO 2.5% to be better tolerated compared to clindamycin 1.2%/tretinoin 0.025% in a 3-week blinded, randomized, split-faced study in 22 subjects with mild to moderate acne vulgaris.[47] To date, no studies have been conducted comparing the tolerability of tretinoin 0.1%/BPO 0.3% cream to the other dyads.

IDP-126: The First-In-Class Triple Combination Topical Therapeutic

In 2023, a novel first-in-class triple combination topical gel - IDP-126 - was approved by the FDA for once-daily application for the treatment of acne in patients aged 12 and older.[48] While several BPO/adapalene or BPO/clindamycin dyad formulations have been approved, IDP-126 is the first topical product to incorporate three bioactive pharmaceutical agents. IDP-126 contains fixed-dose clindamycin phosphate 1.2%, BPO 3.1%, and adapalene 0.15% in a polymeric mesh gel with micronized particles of BPO and adapalene. Micronized BPO and adapalene allow for a stable combination of ingredients and smaller particle sizes which more effectively penetrate the pilosebaceous unit.[49] The polymeric mesh allows for even distribution of the active agents on the skin utilizing a vehicle formulated with an aqueous gel without alcohol, occluding agents, surfactants, or preservatives while containing the hydrating humectant propylene glycol.[50] Furthermore, the polymeric mesh vehicle with micronized ingredients may provide better tolerability, which has been an obstacle with the prior topical dyad combinations.[51,52]

Once daily application of IDP-126 was recently studied in a phase 2 randomized, double-blind, parallel-group, vehicle-controlled clinical trial in 741 subjects aged >= 9 years with moderate-to-severe acne over 12 weeks.[53] Acne severity was graded using the Evaluator's Global Severity Score (EGSS) with scores of 3 and 4 corresponding to moderate and severe acne, respectively. Subjects were equally randomized into one of five treatment groups: IDP-126, vehicle, and one of three component dyads formulated with the same active drug concentration and within the same vehicle as IDP-126. The dyads are as follows: (1) BPO 3.1%/adapalene 0.15% gel, (2) clindamycin phosphate 1.2%/BPO 3.1% gel, and (3) clindamycin phosphate 1.2%/adapalene 0.15%

gel. Co-primary endpoints were the percentage of participants achieving treatment success at week 12 and the absolute changes from baseline to week 12 in inflammatory and non-inflammatory lesion counts. Treatment success was defined as a >= 2-grade reduction from baseline in EGSS and a score of 0 (clear) or 1 (almost clear). Patient-reported quality-of-life outcomes were also secondarily assessed through the Acne-Specific Quality of Life (Acne-QoL) questionnaire administered at baseline and week 12.

At week 12, 52.5% of subjects with IDP-126 achieved treatment success which is significantly greater than the three dyad gels (range 27.8-30.5%) and vehicle gel (8.1%). Success in the IDP-126 group was 1.7-1.8 times greater than with the component dyads, suggesting potential further improvement with the triple combination over the different dual combinations.[18] The same trend in superiority was observed in absolute mean reductions in inflammatory and noninflammatory lesions from baseline to week 12. Furthermore, treatment success, absolute mean reductions in inflammatory and noninflammatory lesion counts, and least-squares mean percent changes in acne lesion counts were all significantly greater in the IDP-126 group compared to vehicle as early as weeks 4, 2, and 2, respectively, suggesting a fast onset of action. With respect to patient-reported QoL, Acne-QoL scores at week 12 were numerically greater for the IDP-126 group vs all three dyad treatment groups and vehicle across all domains.

Subsequent phase 3 studies assessed the efficacy and safety of IDP-126 compared to vehicle.[54] Across the two multicenter, randomized, double-blind, parallel-group, vehicle-controlled studies, a total of 363 patients aged 9 and older with moderate or severe acne (EGSS 3 or 4) were enrolled and randomized 2:1 to once-daily IDP-126 or vehicle gel. Co-primary and secondary efficacy endpoints were the same as in the phase 2 study noted above. IDP-126 was superior to vehicle gel for all co-primary and secondary endpoints across both studies. Treatment success (EGSS 0 or 1 with >= 2-point reduction) at week 12 was achieved by 49.6% and 50.5% in the IDP-126 group compared to 24.9% and 20.5% in the vehicle group (studies 1 and 2, respectively). A significantly greater absolute mean reduction, as well as least-squares, mean percent change in inflammatory and noninflammatory lesions was seen in the IDP-126 group versus the vehicle group at week 12. IDP-126 also exhibited significantly greater percent changes in lesion reduction as early as week 4. These results are consistent with those from the phase 2 study noted above. Moreover, when contextualizing these results with the 10- and 12-week phase 3 trials of other commercially available dyads, IDP-126 exhibited the greatest numeric mean percent reductions in inflammatory and noninflammatory lesions. As no head-to-head parallel group studies were conducted, no direct comparisons can currently be made, however. A post-hoc analysis of pooled phase 3 data also showed meaningful improvements in quality-of-life measures that correlated with EGSS scores.[55] Furthermore, a recent meta-analysis assessing pharmacological treatments for acne placed the triple combination as the second most efficacious treatment for total lesion reduction after isotretinoin.[56]

IDP-126 was also well tolerated. There was a low rate of discontinuation (<4%) due to treatment-emergent adverse events (TEAE), and no participants experienced serious AEs. Regarding safety and tolerability, there were early but transient increases in severity for burning, stinging, itching, erythema, and scaling from baseline to week 2 but were considered mild (score below 1) on average. The phase 2 tolerability data also showed that IDP-126 may have a better tolerability profile compared with the BPO/adapalene dyad.[53] In addition, a post hoc analysis further demonstrated that skin of color patients tolerated IDP-126 well and experienced improvement in erythema without increases in hyperpigmentation or hypopigmentation.[57]

DISCUSSION

Acne vulgaris continues to be a pervasive dermatologic condition affecting the quality of life for billions of people worldwide. Advances in drug formulations and vehicle technologies over the last decade have allowed for the combination of active molecules that traditionally would destabilize each other thereby rendering them ineffective. These combinations have allowed for an increase in efficacy and a reduction in the development of antibiotic resistance in those formulations that contain BPO.[58] Furthermore, combination topicals have resulted in greater compliance with treatment by patients given lower dosing frequencies and the reduced number of topicals needed to use in daily acne treatment regimens.[59]

Tolerability is also critical for patient compliance. While the vehicle composition and formulation are critical for the tolerability of topical treatments, as evident by the polymeric mesh technology, it is thought that clindamycin exhibits anti-inflammatory effects that may optimize tolerability. Split-face studies comparing topical dyads have demonstrated that clindamycin phosphate/BPO is less irritating than adapalene/BPO.[44,60,61] A meta-analysis by Stuart et al also showed that the odds of patient withdrawal due to adverse effects was lower when clindamycin was combined with BPO compared to BPO alone or BPO combined with adapalene.[51]

CONCLUSION

Topical drug formulation technologies have advanced and allowed for the development of topical acne treatments that contain two or three formerly incompatible active molecules thus allowing for simultaneously targeting multiple pathophysiologic mechanisms underlying acne vulgaris. These formulations allow for synergistic efficacy, reduced application frequency, reduced number of topicals utilized in daily acne treatment routines, and improved tolerability. These factors comprehensively aid in the reduction of antibiotic resistance with acne therapy while improving patient compliance with treatment regimens.

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.

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