

Inflammatory Acne Treatment: Review of Current and New Topical Therapeutic Options

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ABSTRACT

Acne vulgaris (AV) is an inflammatory skin disease characterized by the presence of comedones, papules, pustules, and nodules. Consensus guidelines recommend the use of combination therapy using different drugs with complementary mechanisms of action to best address as many acne pathogenic factors as possible at the same time. Topical acne medications exist as individual agents that may be combined in physician-recommended regimens or as pre-formulated fixed-dose combination products. In addition, there are several new and promising topical therapies currently being developed that work by different mechanisms of action from traditionally used acne therapies. The following review will cover commonly used drugs, newcomers to the market, and what the future holds for the topical treatment of AV.

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INTRODUCTION

Acne vulgaris (AV) is the single most common reason that patients visit dermatologists.[1] An estimated 40 to 50 million Americans suffer from it, including 95% of teenage boys and 85% of teenage girls.[2,3,4] Acne imparts a significant psychosocial burden, and the effect has been likened to that of systemic diseases such as diabetes, asthma, and epilepsy.[5] Body image issues, anxiety, depression, poor self-esteem, and social disturbances affect up to half of adolescents with acne.[6,7] For all of these reasons, effective treatments are a necessity.

Acne is an inflammatory disease. Follicular hyperkeratinization,[8] sebum production,[9] *Propionibacterium acnes* bacteria colonization,[10] and resulting inflammation[11,12] all contribute to its pathogenesis. Hyperkeratinization leads to narrowing of the follicular ostium, which in turn allows for sebum accumulation beneath.[13,14] It is also thought that *P. acnes* forms a biofilm in the sebaceous gland further obstructing the follicle.[15] *P. acnes* is a commensal skin organism rather than an infection, and its lipases break down sebum triglycerides into pro-inflammatory free fatty acids[16] and activates an innate immune response through toll-like receptor 2 (TLR-2) binding with subsequent production of the pro-inflammatory cytokines TNF-α and IL-1α.[17] Collectively this inflammation promotes comedogenesis.[18]

Traditionally, acne has been categorized as having either "inflammatory" or "non-inflammatory" lesions. Inflammatory lesions include acne papules, pustules, cysts, and nodules. Non-inflammatory lesions, on the other hand, refer to open and closed comedones. The term "non-inflammatory" is still used by convention, but it is in reality a misnomer. Recent data suggest that subclinical perifollicular inflammation actually precedes formation of the microcomedone. This means that comedones are in fact inflammatory lesions. In one 2003 study, investigators took biopsies from clinically normal appearing skin in acne patients. They discovered that while no clinical lesions were observed, sub-clinical elevation of CD4+ T cells, macrophages, vascular adhesion molecules, and pro-inflammatory cytokines were present.[19] Moreover, inflammatory lesions may arise from clinically normal appearing skin. Using photographic star tracking software, investigators in another study followed acne lesions on the face during a 30-day period. Inflammatory lesions developed from comedones in 54% of patients, but from normal-appearing skin in 28% of patients.[20] Regardless of nomenclature, comendones are in fact inflammatory lesions.

Consensus guidelines recommend combination therapy for the treatment of all but the mildest comedonal acne.[21] Enhanced therapeutic benefits can be achieved by combining agents with different but complementary mechanisms of action. The following review will discuss topical medications, alone and in combination, for the treatment of AV, both traditional inflammatory lesions and inflammatory comedonal lesions.

Topical Treatment Options

An algorithmic approach may be used to select the proper acne therapy based on lesion type, severity, and extent of body surface area affected. Topical therapies may be used as a first-line approach for mild to moderate acne or in combination with orals for more severe disease. Prescription topical options include benzoyl peroxide (BPO), topical antibiotics, topical retinoids, and topical dapsone. These are frequently prescribed in various combinations to suit the specific needs of the patient. In general, simpler regimens improve outcomes, as patients

have been shown to have greater adherence to regimens with fewer steps.[22] For this reason, fixed-dose combination topical drugs have become popular options in treating acne rather than applying each of the monotherapies twice daily. Combinations include BPO-antibiotics, BPO-topical retinoids, and topical retinoids - topical antibiotics in various generic and branded formulations.

Benzoyl Peroxide

Benzoyl peroxide has at the same time anti-microbial, anti-inflammatory, and keratolytic properties. It is a recommended component of almost all combination regimens for treating acne.[21,23] BPO is directly toxic to *P. acnes*, and to date there are no reports of *P. acnes* resistance.[24] BPO is thought to work by inhibiting the metabolism of *P. acnes*' interference with protein synthesis and mitochondrial function, and lead to DNA damage.[25] It is commonly used alongside topical antibiotics to prevent the development of bacterial resistance, and acne improvement has been noted after BPO was given to patients with previously known *P. acnes* resistance.[26] By killing *P. acnes* and preventing its subsequent production of pro-inflammatory mediators, BPO is indirectly anti-inflammatory.[21] Moreover, BPO has keratolytic properties. Statistically higher concentrations of corneocytes have been shown to be removed by tape-strip analysis after application of BPO 2% cream compared with vehicle cream or untreated skin.[27]

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The most common adverse events (AEs) that patients associate with BPO are concentration-dependent irritant dermatitis. True allergic contact dermatitis is quite rare.[28,29] In fact, studies have shown that not only are lower concentrations of BPO less irritating than higher concentrations, but they also demonstrate similar efficacy to higher concentrations.[30] In one study, twice-daily application of BPO 2.5% resulted in a 97% and 99% reduction in *P. acnes* counts after 1 week and 2 weeks respectively.[31] While products are vehicle- and formulation-dependent and generalizations cannot be made blindly, in general lower BPO concentrations may be preferred because they cause less potential skin irritation.

Topical Antibiotics

Antibiotics have both anti-microbial and anti-inflammatory effects on the skin. They reduce the levels of *P. acnes* bacteria within the sebaceous follicles. Some (eg, erythromycin and tetracyclines) also have direct anti-inflammatory properties, reducing pro-inflammatory chemotactic factors and lipase levels at concentrations lower than the mean inhibitory concentrations needed for *P. acnes* killing.[32] Lipophilic antibiotics are considered best for acne because they can most easily penetrate the lipid-filled, sebaceous environment. These include macrolides (eg, erythromycin), clindamycin, tetracyclines (eg, doxycycline, minocycline), and trimethoprim.[33]

Clindamycin and erythromycin are the 2 most commonly used topical antibiotics in the United States for the treatment of acne.[34] Topical erythromycin has largely fallen out of favor with most experts because of high levels of resistance by *P. acnes*.[35] Clindamycin is widely used as an individual agent combined with a separate BPO-containing preparation or as an ingredient in one of many fixed-dose BPO/clindamycin combination products.

Besides being antimicrobial, clindamycin's anti-inflammatory properties play an important role in its therapeutic effect. Clindamycin has been shown to lower *P. acnes*-related inflammatory factors, decreasing lipase production and the subsequent release of free fatty acids. In addition, it has been shown to inhibit leukocyte chemotaxis, reducing perifollicular inflammation. Clindamycin has also been shown to reduce levels of pro-inflammatory cytokines IL1-β, IL-6, INF-ɣ, TNF-α, and GM-CSF.[36,37]

While tetracyclines are used orally, there are no topical versions currently available in the US. Minocycline, however, has been successfully stabilized in a topical foam formulation and is currently in development stages. This drug will be reviewed in a subsequent section.

With the growing awareness of bacterial resistance to antibiotics, monotherapy with topical (or oral) antibiotics is not recommended for the treatment of acne.[38] The first reports of bacterial resistance to topical clindamycin came in the 1970's and were the result of mutations in 23S ribosomal RNA, conferring cross-resistance to both erythromycin and clindamycin.[39] Resistance has been demonstrated in clinical studies. In one trial, clindamycin as monotherapy for the treatment of acne for 16 weeks resulted in *P. acnes* counts increasing by more than 1600% compared with baseline. This effect was blocked with the addition of BPO.[40] Current guidelines recommend the concurrent use of BPO with topical antibiotics to reduce the risk of developing resistance.[26]

Topical Retinoids

Retinoids are a class of drugs similar in structure to Vitamin A. Vitamin A interacts with nuclear receptors to stimulate processes related to cell growth and differentiation. Three topical retinoids are available by prescription in the US: tretinoin, tazarotene, and adapalene (ADA).[41] Collectively these drugs

have keratolytic and anti-inflammatory properties. They are also comedolytic, enhancing cellular differentiation and proliferation, normalizing desquamation and keratinization, and reducing cell cohesiveness within the follicle.[21,26] Retinoids may be used as monotherapy or in combination with other topicals for both comedonal and inflammatory disease. Moreover, they are commonly used as maintenance therapy after initial control has been obtained over the acne.[21,26] While effective, application site reactions such as dryness, peeling, redness, burning, and stinging are especially common in the first few weeks of therapy, a period known as "retinization."[42] Various approaches have been taken to minimize these AEs, including initial intermittent use and application of moisturizers.[43]

Topical Dapsone

Dapsone is a sulfone antibiotic with anti-inflammatory properties. Topical dapsone 5% gel is approved by the US Food and Drug Administration (FDA) and commercially available to treat acne. While similar in name, the sulfone dapsone is structurally different to sulfonamide antibiotics. As such there is no allergic cross reactivity with sulfonamides, and a higher likelihood of someone with a known sulfa allergy being allergic to penicillin rather than to dapsone.[44] The exact mechanism of action in treating acne is not clear. In vitro, dapsone has been demonstrated to inhibit neutrophil chemotaxis and release of lysosomal enzymes that promote inflammation and oxygen-free radicals. While dapsone is antimicrobial in treating leprosy, no activity has been shown against *P. acnes*.[45] Data from the pivotal phase 3 clinical trials revealed that twice-daily use of topical dapsone was effective in treating both inflammatory and comedonal lesions (though with greater efficacy in inflammatory lesions), and it also had an extremely favorable tolerability profile.[46] Moreover, topical dapsone has been successfully combined with other medications, such as topical retinoids and BPO.[47,48]

Newly Approved Topical Therapies

In the past year, 2 new fixed-dose combination topical products have been brought to market for the treatment of AV. Both demonstrate efficacy and tolerability across a variety of acne lesion types. The following summarizes the latest data on fixed-dose BPO 3.75%/clindamycin phosphate (CP) 1.2% gel and BPO 2.5%/ADA 0.3% gel.

Benzoyl Peroxide 3.75% /Clindamycin Phosphate 1.2% Gel

In November 2014, BPO 3.75%/CP 1.2% gel received FDA approval for the treatment of AV in patients 12 years of age and older. The vehicle is an aqueous gel with humectant properties and free from alcohol and preservatives.[49] CP is the water soluble ester of clindamycin, which is fully dissolved in the aqueous gel base and readily available when applied to the skin. BPO is both microdispersed in the gel as well as micronized. It is evenly distributed in each metered dose, and 90% of the BPO particles are less than 10 microns in diameter.[50] (As a point of reference, the hair follicle diameter for vellus hairs is estimated to be in the range of 130 microns.[51])

In the phase 3, pivotal clinical trial, 498 subjects were enrolled in a 12-week multi-center, double-blind, vehicle-controlled study. Patients were randomized 1:1 to receive either active drug or vehicle, which was applied once daily to the face. Standard washout periods for previous prescription and over-the-counter (OTC) products were enforced. Enrolled patients had a baseline Evaluator's Global Severity Score (EGSS) of moderate or severe (EGSS = 3 or 4) and mean baseline lesion counts of 27 and 37.8 inflammatory and comedonal lesions, respectively.[52]

The drug was shown to be efficacious and statistically better than vehicle for all efficacy treatment variables. At week 12, the absolute change in inflammatory lesions was -16.3 lesions compared with baseline, while the comedonal lesions were reduced by 19.2 lesions. There was a 51.8% and 60.4% mean reduction in comedonal and inflammatory lesions, respectively. 35% of patients were considered a treatment success at week 12, with a 2-grade improvement in EGSS. 29% of patients were a treatment success with a greater than 2-grade EGSS improvement. In this case, for example, a patient would have had a baseline score of a 4 (severe) and improved at least 3 grades to 1 or 0 (almost clear or clear). A severe patient (EGSS = 4) who improved 2 grades to mild (EGSS = 2) was not included in this endpoint.[52]

BPO 3.75%/CP 1.2% gel was well tolerated. The most common AEs in the study, which occurred in less than 0.5% of subjects treated with the active drug, were application site reactions including burning, contact dermatitis, pruritus, and rash. No subjects in the active treatment arm discontinued the study due to an AE or a lack of efficacy. Cutaneous tolerability was similar between the active drug and the vehicle.[49,52]

Post-hoc analyses of the phase 3 data and phase 4 studies have provided additional data on BPO 3.75%/CP 1.2% gel. In one analysis, the drug was found to be effective and well-tolerated in the severe subpopulation of acne patients in the study. 55.1% of severe patients had at least a 2 grade improvement in EGSS at week 12, and 30.6% of severe patients were clear or almost clear.[53] Additionally, it was found to be effective in adult women[54] and in adolescents.[55] Finally, BPO 3.75%/CP 1.2% gel was shown to have excellent cosmetic compatibility with facial foundation makeup in adult women.[56]

Benzoly Peroxide 2.5%/Adapalene 0.3% Gel

BPO 2.5%/ADA 0.3% fixed-dose combination gel received FDA approval for the treatment of acne in July 2015.[57] This antibiotic-free option is the next generation of BPO 2.5%/ADA 0.1% gel that was approved for acne in 2009.[58,59] An in vitro absorption study was performed comparing the fixed-dose combination gel to separate application of the monad drugs. The fixed-dose

combination gel yielded superior ADA release into the skin. Moreover, the BPO 2.5%/ADA 0.3% gel was *not* found to be bioequivalent to different regimens of monad formulations.[60]

In the pivotal phase 3 study, efficacy and safety of BPO 2.5%/ADA 0.3% gel were compared with that of vehicle gel in patients with moderate to severe acne. A subpopulation of severe patients was also evaluated. The safety and tolerability of BPO 2.5%/ADA 0.3% was compared with BPO 2.5%/ADA 0.1%. The study was not designed or powered to compare efficacy of the 0.3% vs 0.1% formulations. A total of 503 patients were enrolled in the multicenter, randomized, double-blinded, parallel-group, vehicle- and active-controlled study. Subjects were randomized 3:3:1 to receive 0.3% drug, 0.1% drug, or vehicle gel. At baseline, patients were required to have an acne severity of moderate or severe (Investigator's Global Assessment (IGA) = 3 or 4). The study medication was applied once daily for 12 weeks.[61]

BPO 2.5%/ADA 0.3% gel reached its co-primary efficacy endpoints. Treatment success rate was defined as at least a 2-grade improvement on IGA at week 12 compared with baseline. 33.5% of patients on the 0.03% drug were considered a treatment success, compared with 11.5% in the vehicle arm (P=.001). In addition, there was a 66.4% reduction in inflammatory lesions at week 12 (with a baseline mean lesion count of 39.2 lesions) in the active treatment arm. A greater degree of efficacy was observed in the severe acne subpopulation. 31.3% of patients achieved treatment success at week 12 vs 13.3% in the vehicle arm (P=.029), and there was a 71.8% reduction in inflammatory lesions vs 28.6% in the vehicle arm (P<.001).[61]

The drug was well tolerated, albeit with slightly more cutaneous AEs than reported in the BPO 2.5%/ADA 0.1% gel arm. There were a total of 15 AEs in the 0.3% drug group vs 2 AEs (both occurring in the same patient) in the 0.1% drug group. No AEs were reported in subjects on the vehicle. One subject in the 0.3% gel group discontinued from the study because of an AE (a flare of atopic dermatitis). There were no serious AEs during the study. Overall the mean tolerability scores in the 0.3% gel arm were less than mild, on a 4 point scale where 0 = none and 3 = severe.[61]

On the Horizon

While we currently have 2 new formulations of previously existing molecules, there are also several new chemical entities in development for the treatment of acne. In addition, new concentrations and novel delivery systems for some of our current medications will further add to the armamentarium of drugs available to treat acne. In the next few years there will be several new and different options available for use.

Topical Dapsone

Clinical trials for a new concentration of dapsone topical gel have been completed. This formulation is designed for once daily application.[62] Further details on the efficacy and safety of the drug are not publicly available.

DRM01

DRM01 is a new chemical entity in development for the treatment of acne. It is an inhibitor of coenzyme-A carboxylase, the enzyme responsible for the first and rate-limiting step in the production of fatty acids. In vitro, it has demonstrated a dose-dependent inhibition of lipid synthesis, and shown to decrease sebaceous gland size in an animal model.[63]

A phase 2a, first-in-human study has been completed evaluating safety, tolerability, and preliminary efficacy of the drug compared with vehicle. Patients with moderate to severe acne were enrolled in the study and randomized 1:1 to apply active drug or vehicle twice daily for 12 weeks. Patients were then followed post-therapy through week 16. Numerical improvements were noted at week 4, and statistical significance was achieved for all efficacy endpoints at week 12. A significantly greater mean reduction in both inflammatory (64% vs 46%; P=.0006) and comedonal (48% vs 29%; P=.0025) lesion counts were observed in the active drug compared with vehicle. Moreover, a statistically greater number of patients (almost 25%) in the active arm achieved a treatment success (>2 grade improvement in the IGA score) at week 12 compared with vehicle (P=.0070). The drug was well-tolerated and similar between the DRM01 and vehicle groups. Most local skin reactions were none to mild. Five subjects in the DRM01 group experienced a severe local skin reaction, which included severe erythema (1 subject) and severe burning/stinging (4 subjects).[64]

FMX101

Minocycline is commonly prescribed as an oral therapy for the treatment of AV and soft tissue infections. Because of stability issues, challenges have previously arisen in attempts to formulate it as a topical preparation. FMX101 is a topical minocycline foam currently in development for the treatment of acne. A phase 2, multicenter, randomized, double-blind trial has been completed at 3 study centers in Israel. One hundred and fifty patients with moderate to severe acne were enrolled and treated with once-daily application of either a 1% or 4% minocycline foam or vehicle. By week 12, a 72% (P<.001) and 73% (P<.05) reduction in inflammatory and comedonal lesions, respectively, were observed in the FMX101 4% group, which was statistically superior to vehicle. Moreover, 53% of patients using FMX101 4% were clear or almost clear vs 19.6% in the vehicle arm (P<.05). In addition, 36.2% of patients on the 4% drug were clear or almost clear along with a greater than 2 grades improvement, compared with 15.2% on vehicle (P<.05). There were no reported treatment-related AEs.[65]

SB204

Nitric oxide is a naturally occurring molecule in the body that possesses both anti-microbial and anti-inflammatory

properties. SB204 is a topical nitric oxide-releasing gel currently being developed. Its active ingredient, NVN1000, is anti-inflammatory, has demonstrated antimicrobial activity against *P. acnes*, and inhibited lipogenesis in an in vitro model. A phase 2, multi-center, randomized, double-blind, vehicle-controlled study treating moderate to severe acne has been completed in Latin America. Enrolled subjects were randomized to receive either SB204 1%, SB204 4%, or vehicle for 12 weeks. There was a 57% and 25% reduction in inflammatory and comedonal lesions, respectively, at week 12 in the 4% drug arm. Moreover, in a sebum analysis using sebutapes, 80% les sebum was measured from the skin in both the high and low concentration SB204 groups compared with the vehicle group. A concentration-dependent decrease in squalene and free fatty acids was observed. The drug was well tolerated, and only mild local skin reactions were reported.[66]

SEB002

Photodynamic therapy is a commonly used treatment for various skin conditions such as actinic keratoses. Its use in AV has been reported, but efficacy has been limited by the ability of the photosensitizer and light source to penetrate deep enough into the sebaceous glad where the pathology in acne occurs.[67] SEB002 is a suspension of gold-coated silica microparticles that can be delivered into the sebaceous gland using mechanical vibration. Subsequent activation using a light source leads to selective targeting and destruction of the sebaceous glands. Preliminary results are promising, with an excellent tolerability profile. In one European study, 48 patients were randomized to receive 3 treatments at 2-week intervals or to treat the skin initially with an OTC face wash for 12 weeks, then crossed over to the SEB002 treatment. At the week 28 evaluation, subjects treated initially with SEB002 experienced a 61% reduction in inflammatory lesions, while the cross-over group achieved a 50% reduction. The procedure was well tolerated. No anesthetic was used during the procedure, and most subjects reported only mild to moderate pain. Mild erythema was not uncommon, and it subsided within 30 to 60 minutes of the procedure.[68]

CONCLUSION

Acne vulgaris is a multifactorial skin condition that dermatologists treat on a daily basis. The clinical picture ranges from mild comedones to severe nodular cystic disease. However, recent data suggest that all acne lesions are in fact inflammatory despite the frequently used term "non-inflammatory" rather than "comedonal" lesions. Consensus guidelines recommend combination therapy using drugs with different, complimentary mechanisms of action. There is a variety of individual agents that may be combined to suit the individual patient's needs. The newest formulations offer enhanced efficacy with minimal irritation. These, along with several novel acne drugs in the pipeline, will continue to improve the landscape of topical anti-acne therapies.

DISCLOSURES

Dr. Zeichner has worked as an Advisory Board Member, Consultant, and Speaker for Allergan, Galderma, and Valeant and an Advisory Board Member for Foamix.

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