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ORIGINAL CONTRIBUTION

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Management of comedonal acne vulgaris with fixed-combination topical therapy

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Summary

Background: Acne vulgaris (acne) is the most common skin disease we see in dermatology practice. Clinically, it is characterized by a combination of open and closed comedones (formally referred to as noninflammatory lesions) and inflammatory papules and pustules. Comedonal acne is more typical in young adolescents, but can occur in combination with inflammatory papules and pustules at any time. Topical retinoids have long been advocated for the treatment of comedonal acne.

Aims: Given the increasing recognition of the inflammatory nature of acne and the synergistic benefits seen with fixed combinations we review the latest clinical data to provide guidance on optimal management of comedonal acne.

Methods: An English language literature search of Medline, EMBASE, and the Web of Science using key terms (acne, comedonal, noninflammatory, clinical trials) was conducted, and relevant articles reviewed.

Results: Comparative data is sparse, but we show the importance of fixed combinations with and without retinoids, where treatment benefits are comparable. Adapalene 0.1%-benzoyl peroxide 2.5% gel has been shown to be comparable to clindamycin 1%-benzoyl peroxide 5% gel, and adapalene 0.3%-benzoyl peroxide 2.5% gel. A meta-analysis suggested that clindamycin 1.2%-benzoyl peroxide 2.5% gel was more effective than clindamycin-benzoyl peroxide 5% gel in noninflammatory lesions, and two equivalent clinical programs suggest additional benefits of higher doses of benzoyl peroxide (3.75% vs 2.5%) in this fixed combination.

Conclusions: Clindamycin 1.2%-benzoyl peroxide 3.75% gel may afford similar benefits to adapalene 0.3%-benzoyl peroxide 2.5% gel in this sometimes difficult to treat patient population.

KEYWORDS
acne, comedones, fixed combinations, topical

1 | INTRODUCTION

Acne vulgaris (acne) is a common chronic inflammatory disease of the skin. It is found in about 80% of young adults and adolescents, and increasingly seen in older adults. It consists of open and closed comedones, and lesions with visually apparent inflammation such as nodules, pustules, and papules typically affecting areas with a high proportion of sebaceous follicles, such as the face, chest, and back.[1]

A mixture of comedonal (formally referred to as noninflammatory lesions) and inflammatory lesions can occur at any time. Studies have

shown that prevalence and severity of acne increase with pubertal maturation and comedonal acne predominates in preteens, with increasing inflammatory acne developing during the teen years.[2,3] Adult acne is most common in women,[4] and its clinical presentation may be more similar to that seen in adolescents than was previously thought.[5]

While comedonal acne is typically the mildest form of the disease, it can be the hardest to treat as comedones are usually firmly seated within the follicle. Treatment is selected based on severity; assessed in terms of lesion site, type and number, the development of scars, the effect on the patient emotionally, and whether the lesions undermine confidence and self-esteem, or interfere with work/school or relationships.

Treatment guidelines have traditionally advocated the use of topical retinoids to treat comedonal acne.[1,6] Indeed, all topical retinoids effectively reduce the number of comedones as well as inflammatory lesions in mild-to-moderate facial acne.[7]

Consideration of acne as a chronic inflammatory disease,[8] with early inflammatory events important in the development of the microcomedo, has led to several studies evaluating the response of comedonal acne to combination treatment with topical retinoids and other topical agents having additional direct (eg, dapsone) or indirect (ie, antibacterial) anti-inflammatory properties.[9-11] Such combination therapy appears to enhance the efficacy against comedonal acne relative to the use of the retinoid alone. With the emergence of antibiotic resistance to *Propionibacterium acnes*, benzoyl peroxide (BP) is considered an important component in combination therapy, as it reduces the development and emergence of antibiotic-resistant strains.[10,12]

The purpose of this article was to review the latest data on the use of fixed-combination topical therapy in comedonal acne. English language literature review was performed using Medline, EMBASE, and the Web of Science, and relevant articles reviewed for inclusion. As well as summarizing the key data, we also calculated where possible treatment benefit (active minus vehicle) as comparative data are sparse.

2 | TOPICAL RETINOID AND BENZOYL PEROXIDE FIXED COMBINATIONS

The most widely studied topical retinoid/benzoyl peroxide fixed combination is adapalene 0.1% and BP 2.5% gel. Treatment benefit ranged from 18% to 25%, and the most common adverse event (AE) was dry skin. It was compared to individual monads and vehicle in 2 pivotal phase 3 studies of 2185 patients with moderate facial acne.[13-15] Following 12 weeks' daily treatment, the mean percent change in comedonal lesions was 45.9% and 48.1%, compared with 29.6% and 40.8% with adapalene 0.1% gel, 32.2% and 37.2% with BP, and 27.8% and 23.3% with vehicle (Epiduo Pl). Treatment benefit (active minus vehicle) was 18.1% and 24.8%, respectively, and smaller in patients with a small number of baseline lesions (Figure 1). During the clinical trials in 564 patients, AEs were reported in 14%, the most common being dry skin (7%), contact dermatitis (3%), and application site burning and irritation (2%).

Adapalene 0.1%-BP 2.5% gel was also studied in 2453 adolescent acne patients (aged 12-17 years).[16] Mean percent reduction data are not available, but median reductions in comedonal lesion counts at Week 12 were 54.5%, compared with 45.2% for adapalene 0.1% gel, 40.9% for BP 2.5% gel and 29.1% for vehicle (all $P < .05$ vs adapalene). Treatment benefit based on median data (25.4%) was slightly higher than that seen in the pivotal studies. Again, dry skin was the most common AE with the fixed combination (13.4% of patients compared with 9.6% and 3.9% with adapalene and BP, respectively). In a small pediatric study (N = 285) comparing adapalene 0.1%-BP 2.5% gel and vehicle, the mean percent change in comedonal lesions counts was similar (54.7%, Epiduo Pl).

Few direct comparative studies are available with fixed combinations. Adapalene 0.1%-BP 2.5% gel (which contains glycerin) was compared with clindamycin 1%-BP 5% gel (with a hydrating excipient) in 382 patients with mild-to-moderate acne. There was no significant difference between the 2 groups in treating comedonal lesions. After 12 weeks' daily treatment, the mean percent change from baseline

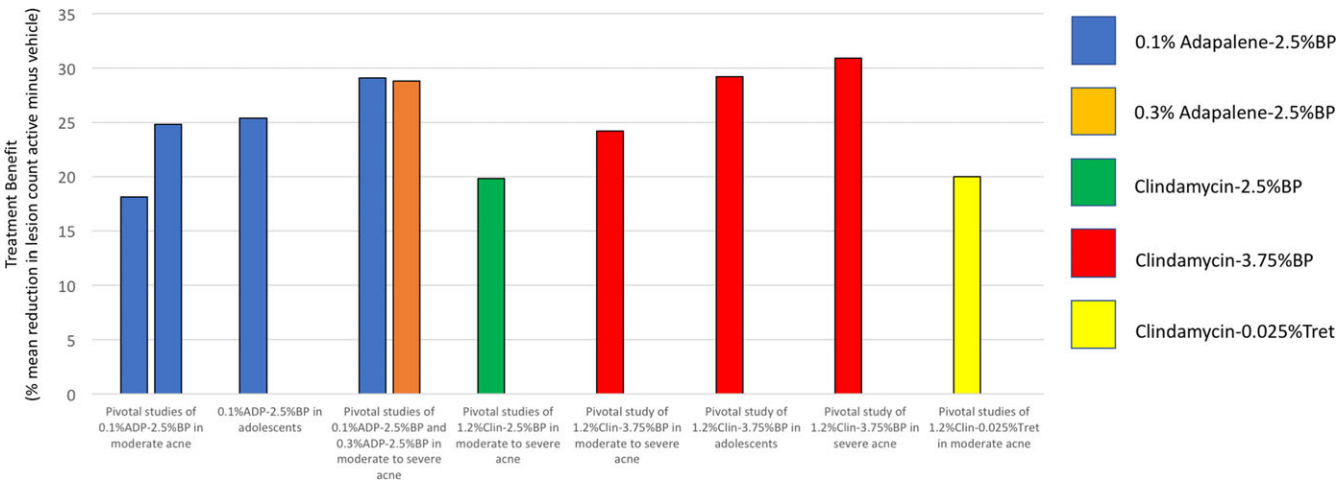

FIGURE 1 Treatment benefit of fixed-combination therapy in comedonal acne (mean percent reduction in noninflammatory lesions active minus vehicle at Week 12)

was 62.2% and 61.5%, respectively. As this was not a vehicle-controlled study, treatment benefit cannot be calculated. Tolerability of the clindamycin 1%-BP 5% gel combination was significantly better over the duration of the study ($P < .03$), and treatment-related AEs were mostly mild-to-moderate application site pain.[17]

Adapalene 0.1%-BP 2.5% gel and adapalene 0.3%-BP 2.5% gel were compared in a study of 503 patients with moderate-to-severe acne.[18] At Week 12, mean percent reductions in comedonal lesions were 68.0% and 68.3%, respectively, compared to 37.4% with vehicle ($P < .001$).[19] Treatment benefit (30.6% and 30.9%, respectively) was higher than that seen in the adapalene 0.1%-BP 2.5% gel pivotal studies, and this finding might be reflective of acne severity. In the severe population subgroup, there was an efficacy trend in favor of adapalene 0.3%-BP 2.5% gel; efficacy of adapalene 0.1%-BP 2.5% gel did not reach statistical significance in comparison with vehicle. Most common treatment-related AEs were skin irritation and skin burning sensation (2.8% and 0.9% of patients treated with adapalene 0.3%-BP 2.5% gel). Local tolerability profile was similar across the 2 active treatment groups.

3 | TOPICAL CLINDAMYCIN AND BENZOYL PEROXIDE FIXED COMBINATIONS

Many studies have reported the synergistic benefits of clindamycin/BP combinations, and more recently, formulation has been developed with lower concentrations of BP to minimize any irritant affects. A combination of clindamycin 1.2% and BP 2.5% gel was compared to individual monads and vehicle in 2 pivotal phase 3 studies of 2813 patients with moderate-to-severe acne.[20] Following 12 weeks' daily treatment, the mean percent change in comedonal lesions was 43.2%, compared with 36.2% with clindamycin 1.2% gel, 37.4% with BP and 24.0% with vehicle, giving a treatment benefit of 19.2%. Incidence of AEs was low and similar across treatment groups, and application site reactions were rare (0.1%).

A meta-analysis of 16 randomized controlled trials compared the efficacy of clindamycin 1.2%-BP 2.5% gel with clindamycin-BP 5% gel, individual monads and vehicle in reducing comedonal lesions.[21] At weeks 10 through 12, the percent reduction in comedonal lesion count was statistically greater with clindamycin 1.2%-BP 2.5% gel than any of the other treatments, with nonoverlapping 95% confidence intervals. Weighted mean reductions in comedonal lesions were 43.4% compared with 38.2%, 34.2%, 27.9% and 14.9% for clindamycin-BP 5% gel, BP, clindamycin and vehicle, respectively. The authors suggested the better efficacy with clindamycin 1.2%-BP 2.5% gel in comedonal lesions may be due to the formulation itself, or better adherence due to decreased irritation.

Clindamycin 1.2%-BP 3.75% gel achieved a 51.8% mean percent reduction in comedonal lesions follow 12 weeks' daily treatment of patients with moderate-to-severe acne, compared with 27.6% with vehicle (Onexton PI). There appeared to be a dose-dependent treatment benefit compared with clindamycin 1.2%-BP 2.5% gel (24.2% vs 19.2%). There were 4 treatment-related AEs (1.6%) with clindamycin 1.2%-BP 3.75% gel (burning sensation, contact dermatitis, pruritus and rash) and seven with vehicle. There were no treatment discontinuations. The benefits of active treatment (active minus vehicle) were more noticeable in the adolescent subpopulation (29.2%),[22] and the patients with severe acne (30.9%).[23]

4 | TOPICAL CLINDAMYCIN AND TRETINOIN

A combination of clindamycin 1.2% and tretinoin 0.025% gel was compared to individual monads and vehicle in a pooled analysis of three pivotal phase 3 studies in mild-to-severe acne.[24] Efficacy, in terms of median percent change from baseline comedonal lesion count, was statistically greater than tretinoin ($P < .02$), clindamycin and vehicle (both $P < .0001$) in those patients with mild/moderate acne, but only significant when compared with vehicle in severe acne. In the first 2 studies, 2340 patients were enrolled and mean percent reduction in comedonal lesions at Week 12 was 36% compared with 27%, 31%, and 16%, respectively, for clindamycin, tretinoin, and vehicle, giving a treatment benefit of 20% (Ziana PI). In the third study of 2010 patients with moderate-to-severe acne, comedonal lesions were reduced by 50%, compared with 41% for clindamycin. AEs in the active and vehicle groups were similar, with dry skin being reported in 1% of cases.

5 | ADDITIVE EFFECT OF DAPSONE AND CLINDAMYCIN/BENZOYL PEROXIDE TO RETINOID THERAPY

Although no fixed dapsone-retinoid combination exists, a combination of dapsone 5% gel (twice daily) and tazarotene 0.1% cream (daily) resulted in significantly greater reductions ($P < .001$) in comedonal lesion counts compared with tazarotene monotherapy at Week 12.[9] Similarly, clindamycin-BP 5% gel when used in combination with tazarotene cream 0.1% resulted in significant treatment benefits compared with tazarotene monotherapy in comedonal lesion reduction in patients with moderate-to-severe acne.[25] The combination of clindamycin-BP 5% gel and adapalene 0.1% gel also resulted in significantly greater reductions in comedonal lesion counts at Week 12 ($P = .05$).[11] Added treatment benefits over monotherapy ranged from 13% to 20%.[9,11,25]

6 | CONCLUDING REMARKS

Topical retinoids alone have been recommended for the treatment of comedonal acne lesions. Fixed-combination therapy has been shown to be more effective than individual monads. Given the importance of inflammation in the pathogenesis of acne, combining

a topical retinoid with agents that also have direct or indirect anti-inflammatory properties has been found to be more effective in reducing comedonal acne. This suggests that combination therapy is the best choice.

Few comparative studies exist. Adapalene 0.1%-BP 2.5% gel has been shown to be comparable to clindamycin 1%-BP 5% gel, and adapalene 0.3%-BP 2.5% gel. A meta-analysis suggested that clindamycin 1.2%-BP 2.5% gel was more effective than clindamycin-benzoyl peroxide 5% gel in noninflammatory lesions, and 2 equivalent clinical programs suggest additional benefits of higher doses of BP (3.75% vs 2.5%) in this fixed combination.

Comparison across studies is also complicated through study design and disease severity. However, treatment benefit (active minus vehicle) provides some insights (see Figure 1) and suggests clindamycin 1.2%-BP 3.75% gel may afford similar benefits to adapalene 0.3%-BP 2.5% gel in this sometimes difficult-to-treat patient population.

DISCLOSURES

Dr. Gold is a consultant and investigator for Galderma. Dr Baldwin is an advisor, investigator, and/or speaker for Allergan, Galderma, Encore, BiopharmX, Sun, La Roche Posay, Valeant, Foamix, Dermira, and Novan. Tina Lin is an employee of Valeant Pharmaceuticals.

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