REVIEW

Profile of clindamycin phosphate 1.2%/benzoyl peroxide 3.75% aqueous gel for the treatment of acne vulgaris

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Abstract: Acne vulgaris is a common and chronic skin disease, and is a frequent source of morbidity for affected patients. Treatment of acne vulgaris is often difficult due to the multifactorial nature of this disease. Combination therapy, such as that containing clindamycin and benzoyl peroxide, has become the standard of care. Several fixed formulations of clindamycin 1% and benzoyl peroxide of varying concentrations are available and have been used with considerable success. The major limitation is irritation and dryness from higher concentrations of benzoyl peroxide, and a combination providing optimal efficacy and tolerability has yet to be determined. Recently, a clindamycin and benzoyl peroxide 3.75% fixed combination formulation was developed. Studies have suggested that this formulation may be a safe and effective treatment regimen for patients with acne vulgaris. Here, we provide a brief review of acne pathogenesis, benzoyl peroxide and clindamycin, and profile a new Clindamycin-BP 3.75% fixed combination gel for the treatment of moderate-to-severe acne vulgaris.

Keywords: acne vulgaris, benzoyl peroxide, clindamycin

Introduction

Acne vulgaris is a common and chronic skin disease affecting millions of people worldwide. It is the most common skin disorder in the USA and is the number one reason for visiting a dermatologist.[1] It is a common source of morbidity, and a variety of topical and systemic medications have been developed to treat acne. However, because of the multifactorial nature of acne, effective treatment is often difficult to obtain. Combination therapies targeting different aspects of acne pathogenesis have become the standard of care.[2] Treatment with topical clindamycin in combination with benzoyl peroxide (BP) has been found to be superior to either medication alone.[3] This combination appears to target both inflammatory and noninflammatory acne, and as such, has become a major treatment option for patients with acne. Several fixed formulations of clindamycin 1% and BP (varying concentrations) have been used with considerable success.[4–7] The major limitation associated with many fixed combinations is irritation and dryness from higher concentrations of BP.[8] Here, we will provide a brief overview of acne pathogenesis, background on the use of BP and clindamycin, and profile a new clindamycin–BP 3.75% fixed combination gel for the treatment of moderate-to-severe acne vulgaris.

Background on acne vulgaris

Acne vulgaris is the most common cutaneous disorder worldwide. It is particularly common in adolescents and young adults and is often a significant source of anxiety,

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embarrassment, and psychosocial morbidity for affected patients.[9] Although most cases of acne vulgaris are self-limited or responsive to topical medications alone, severe cases may last well into adulthood and may be associated with scarring, persistent hyperpigmentation, and significant psychosocial consequences.[2] Clinically, acne is characterized by a combination of noninflammatory open and closed comedones and inflammatory papules and pustules, typically affecting areas with a high proportion of sebaceous follicles, such as the face, chest, and back.

The pathogenesis of acne vulgaris is a multifactorial process, involving follicular hyperkeratinization and obstruction, increased sebum production, *Propionibacterium acnes* colonization, and inflammation.[10] One of the major factors in the early formation of acne appears to be sebaceous follicle obstruction caused by follicular hyperkeratinization and deposition of keratinocytes in the follicle orifice leading to microcomedones.[10,11] The cause and pathogenesis of follicular hyperkeratinization is still not completely understood. It is thought to be associated with changing hormonal influences during puberty. Higher levels of dihydrotestosterone have been found to act on infundibular keratinocytes, contributing to the hyperkeratinzation seen in acne pathogenesis.[12] Additionally, increased expression of IL-1α, K16, and filaggrin has been found in conjunction with follicular hyperkeratinization, and they are thought to be contributing factors.[13,14] It is still unclear why follicular hyperkeratinization and increased keratinocyte proliferation occur in some individuals, but not others.

Increased sebum production during puberty is also a major contributing factor in the pathogenesis of acne vulgaris. During puberty, androgens play an important role in altering the sebaceous unit expression in the skin. Sebaceous units have been found to contain enzymes that are capable of synthesizing androgens from precursor molecules.[12] Additionally, androgens can have a stimulatory effect on sebocyte proliferation.[15] Interestingly, increased levels of lipoperoxides and decreased levels of vitamin E have been found in the sebum of acne patients, indicating that there is not only excessive sebum production in acne patients, but also altered sebum composition.[16] Therefore, sebaceous gland growth, increased sebum excretion, and altered sebum composition likely predispose certain patients toward acne pathogenesis.

Follicular obstruction caused by hyperkeratinization in conjunction with increased sebum production during puberty provides an excellent environment for bacterial growth, particularly *P. acnes*. *P. acnes* is an anaerobic, Gram-positive bacteria that is typically present in normal skin flora, but

can grow rapidly in areas of obstruction or increased sebum production. *P. acnes* has been found to be highly associated with acne and has been found to induce proinflammatory and antimicrobial factors, leading to the characteristic inflammation seen in acne vulgaris.[17,18] Because *P. acnes* is part of the body's natural flora, it is likely that only certain strains with the ability to induce changes in immune response predispose patients to acne vulgaris.

Another important feature in the pathogenesis of acne vulgaris is inflammation. The presence of increased inflammatory cytokines is common to all patients with acne vulgaris. Inflammation is believed to play an important role in acne progression and increases the risk of scarring.[19] Follicular hyperkertinization, abnormal sebum properties, and the presence of *P. acnes* all appear to contribute to the production of an inflammatory response in acne patients.[17] Alterations in the immune response and the increased presence of inflammatory mediators in acne patients suggest that acne is an inflammatory skin disorder, and targeting the inflammatory response may improve acne symptoms.

Benzoyl peroxide

BP is often a mainstay in acne treatment regimens today. BP has known bactericidal properties.[20] An in vitro study by Waller et al[21] demonstrated that the minimum inhibitory concentrations against *P. acnes* was 128 μg/mL, making it an effective agent for targeting *P. acnes* in the pathogenesis of acne vulgaris. The second mechanism of action by which BP targets acne is through its keratolytic effects. BP has been found to be more effective in disrupting stratum corneum cohesion compared to salicylic acid, retinoic acid, and vehicle.[21] Additionally, it also has been found to have mild anti-inflammatory properties.[22] Interestingly, bacterial resistance to BP has not been reported, and use of BP in combination with topical antibiotics may even reduce the risk of *P. acnes* resistance to these agents as well.[2,23,24] Although BP can be associated with some dryness and irritation, and occasional allergic contact dermatitis, it is generally a well-tolerated, safe, and effective topical medication for the treatment of acne vulgaris.[24]

Topical antibiotics

The most common topical antibiotics used for the treatment of acne include clindamycin and erythromycin. These antibiotics are used for acne treatment because they target *P. acnes* colonization and proliferation.[25] Clindamycin and erythromycin are antibiotics that work by targeting the 50s subunit of bacterial ribosomes and interfering with protein synthesis, thereby exerting antibacterial effects. In

addition to antibacterial activities, clindamycin also has anti-inflammatory properties. It is well known that *P. acnes* can induce an inflammatory response. Clindamycin has been shown to inhibit this *P. acnes*-driven inflammatory response as well as inhibit the expression of proinflammatory cytokines, such as IL-1β, IL-6, INF-γ, TNF-α, and GM-CSF.[26] Additionally, studies have demonstrated that clindamycin use can also lead to increased phagocytosis and opsonization and an improved inflammatory response.[26] Although these topical antibiotics have been shown to display considerable success in the treatment of acne vulgaris, they are rarely used as a monotherapy because of the risk for antimicrobial resistance.[25,27]

Combination therapy: benzoyl peroxide and topical antibiotics

Although topical antibiotics have been shown to be efficacious in the treatment of acne vulgaris, a major limitation for their use as monotherapy is the associated risk of antimicrobial resistance.[25,27] Before the introduction of combination therapy, the emergence of erythromycin-resistant and clindamycin-resistant *P. acnes* in patients receiving topical or systemic antibiotics alone was a significant problem.[28] Therefore, combination therapy utilizing at least two medications is currently the gold standard for treatment of acne vulgaris because it targets more than one factor in acne pathogenesis and prevents antimicrobial resistance.[2] Topical combination therapy can involve the use of several medications together, such as BP, antibiotics, and retinoids, or may be available as fixed-dose combination therapies.

Benzoyl peroxide and erythromycin

The first studies combining BP with a topical antibiotic were performed using erythromycin rather than clindamycin. In 1983, Chalker et al[29] sought to determine the efficacy of a combination erythromycin 3% and BP 5% gel in comparison to either medication alone and vehicle. They found that the combination of erythromycin and BP therapy had superior efficacy to vehicle and to either medication alone. There was also a significant improvement in mean pustule, papule, and inflammatory lesion count in the combination therapy group compared to vehicle, BP alone, or erythromycin alone.[29] Eady et al[28] also confirmed that combination of BP and erythromycin is superior to either product alone, and a checkerboard titration of BP and erythromycin at varying concentrations was used to determine whether this finding was due to synergistic antibacterial effects. They concluded that the improved efficacy of this combination therapy was not due to a synergistic effect, but rather a result of reducing both antibiotic-sensitive

and -resistant strains of bacteria as well as its ability to prevent selection of antibiotic-resistant variants on the skin of acne patients maintaining the efficacy of topical antibiotics.[28,30]

The mechanism of action of the combination of topical antibiotics and BP is likely multifactorial. The combination of keratolytic, bactericidal, and anti-inflammatory properties of BP and the antibacterial and anti-inflammatory properties of topical antibiotics make this treatment useful for both inflammatory and noninflammatory acne.

Clindamycin 1.2% and benzoyl peroxide 5%

Similar to erythromycin, several studies involving topical combinations of clindamycin and BP demonstrated efficacy in treating acne vulgaris and have been found to be superior to monotherapy with either medication alone.[4–7,31,32] In 1997, Lookingbill et al[32] performed two double-blind controlled clinical trials to determine the efficacy and safety of a combination clindamycin 1.2% and BP 5% gel (clindamycin–BP 5%) compared to either agent alone and vehicle. Efficacy and safety were evaluated at baseline and again at weeks 2, 5, 8, and 11. Efficacy was evaluated using inflammatory and noninflammatory lesion counts, and safety was evaluated using scores for facial erythema, peeling, burning, dryness, and pruritus. At week 11, clindamycin–BP 5% had a 66% mean reduction in inflammatory and noninflammatory lesions compared to 41% reduction in BP-treated patients, 36% reduction in clindamycin-treated patients, and 10% reduction in those patients treated with the vehicle. Clindamycin–BP 5% also had a statistically significant improvement in global improvement scores. Overall, combination therapy was fairly well tolerated, but was associated with mild erythema, peeling, and irritation. The rate of these adverse events was comparable to BP alone.[32]

Clindamycin 1.2% and benzoyl peroxide 2.5%

Because of concerns for decreased compliance, fixed combinations of clindamycin and BP 2.5% have been developed to decrease the side effects associated with higher concentrations of BP. The major concern regarding reducing or changing the concentration of BP was the possibility that lower concentrations may be associated with reduced efficacy. However, several studies have demonstrated the clinical efficacy of clindamycin–BP 2.5% for the treatment of acne vulgaris, indicating that it may be just as effective as 5% and 10% concentrations for the treatment of acne vulgaris.[4,5,31,33] Additionally, in an in vitro penetration study, Bucks et al[34] found that reducing the BP concentration from 5% to 2.5% still maintained a similar amount of total BP delivered to the

skin, while also leading to a 33% reduction in local irritation, thus increasing patient compliance.

A meta-analysis by Seidler and Kimball[3] examined the efficacy of fixed combination treatments containing clindamycin–BP 5% vs clindamycin–BP 2.5%. A Cochrane review identified 126 randomized controlled trials in which subjects were treated with BP 2.5% or 5% and 1% or 1.2% clindamycin. A total of 5,737 patients were included. Of them, 1,069 patients were in the clindamycin–BP 5% group and 872 patients were in the clindamycin–BP 2.5% group. The remainder of the patients received either BP alone, clindamycin alone, or vehicle. They found that the combination of clindamycin and BP in any concentration was superior to either single agent alone in treating inflammatory lesions. Clindamycin–BP 2.5% was comparable to clindamycin–BP 5% in treating acne vulgaris. Interestingly, clindamycin–BP 2.5% led to a significantly greater absolute reduction in lesion count for both inflammatory and noninflammatory lesions compared to clindamycin–BP 5%.[3] Weighted absolute reductions in inflammatory and noninflammatory lesion counts for clindamycin–BP 5% were 14.81 and 16.83, respectively. Weighted absolute reduction in inflammatory and noninflammatory lesion counts for clindamycin–BP 2.5% were 25.37 and 20.83, respectively. It is unclear whether this advantage is due to increased efficacy or increased compliance due to decreased localized irritation from a lower concentration of BP. However, this combination is an effective treatment for mild-to-moderate acne vulgaris. Despite the various combinations of clindamycin and BP available, the concentration of BP for optimal efficacy and tolerability is still unknown.

Clindamycin phosphate 1.2% and benzoyl peroxide 3.75%

Recently, a clindamycin phosphate 1.2% and BP 3.75% fixed combination aqueous gel was created as a novel intervention for the treatment of moderate-to-severe acne vulgaris. At BP 3.75%, the combination was designed to have improved efficacy over the clindamycin–BP 2.5%, with increased tolerability over the clindamycin–BP 5% combination. Pariser et al[35] evaluated the safety and efficacy of clindamycin–BP 3.75% aqueous gel in a study involving 498 patients with moderate-to-severe acne. Patients with moderate-to-severe acne were randomized to clindamycin–BP 3.75% or vehicle.

Results

After 12 weeks of treatment, Pariser et al[35] found that clindamycin–BP 3.75% was statistically superior to vehicle for the treatment of moderate-to-severe acne vulgaris. The mean percentage reduction in lesion counts was significantly higher in the clindamycin–BP 3.75% group compared to vehicle. The mean percentage change from baseline to week 12 for inflammatory and noninflammatory lesion counts on clindamycin–BP 3.75% was 60.6% and 51.6%, respectively. The mean percentage change from baseline to week 12 for inflammatory and noninflammatory lesion counts on vehicle was 31.4% and 27.4%, respectively. Treatment success, defined as at least a 2-grade improvement in Evaluator Global Severity Score, occurred in 34.3% vs 15.6% in patients treated with clindamycin–BP 3.75% compared to patients treated with vehicle by the end of the study.

Subjective assessment of efficacy included assessment of subject self-assessment (SSA), patient satisfaction survey (PSS), degree of oiliness and shininess, and acne-specific quality of life questionnaires.

At the end of the study, an SSA of "clear" or "almost clear" was reported in 34.9% of cases in the clindamycin–BP 3.75% group compared to 17.4% in the vehicle group. More importantly, over 96% of patients reported some improvement in their acne on SSA following 12 weeks of treatment. Mean PSS scores at the end of the study increased from baseline by 56% in the clindamycin–BP 3.75% group compared to 41% in the vehicle group. Additionally, the percent of patients reporting "none" to "mild" oiliness and shininess increased by week 12 by 22.6% vs 15.6% for clindamycin–BP 3.75% and vehicle, respectively. This corresponded with a decrease in patients reporting "moderate" to "severe" oiliness or shininess. Interestingly, the results of the acne quality of life assessment did not show a meaningful difference between the two groups at the end of the study.

Limitations

Despite the improvement associated with clindamycin–BP 3.75% gel, this trial only evaluated this fixed combination gel to the vehicle. Therefore, it is impossible to determine whether it is superior or inferior to the existing 2.5% or 5% combination therapies. In this study, mean improvement after 12 weeks of treatment with clindamycin–BP 3.75% or vehicle was 60.6% vs 31.4% in inflammatory lesions and 51.6% vs 27.4% in noninflammatory lesions, respectively.[35] In a similar study using clindamycin–BP 2.5%, the reported reduction was 64.1% vs 34.3% in inflammatory lesions and 48.7% vs 26.0% in noninflammatory lesions with clindamycin–BP 2.5% and vehicle, respectively.[31] Comparative effectiveness studies of the BP–clindamycin combination therapies have not been performed. Further studies evaluating clindamycin–BP 3.75% efficacy and tolerability compared

to clindamycin monotherapy, BP monotherapy, and other fixed combination medications could be useful.

Clindamycin phosphate 1.2% and benzoyl peroxide 3.75% in women

Unlike males who typically outgrow acne with time, a subset of female patients may experience acne into adulthood, and this may include as much as half of all adult females between the ages of 20–29 years.[36,37] In this subset of patients, hormonal dysregularities such as polycystic ovarian syndrome and hyperandrogenism are more common.[36] For this reason, these patients tend to not respond as robustly to standard acne treatments, and gynecological follow-up is often required. It is generally accepted that acne in adult females typically presents as mild-to-moderate inflammatory acne that is usually limited to the jawline, chin, and neck, otherwise known as the "U-zone".[36,37] However, in a recent large-scale international study, researchers found that almost 90% of women with acne did not have it limited to the "U-zone", and a mixed inflammatory and noninflammatory acne was the most common presentation.[38] These results suggested that the presentation of facial acne in adult females might be more similar to adolescent acne than once believed.

A subgroup analysis performed by Pariser et al[35] in their study suggested a slightly greater efficacy for clindamycin–BP 3.75% in female patients compared to males. The mean percentage reduction of noninflammatory lesions at the end of the study was 55.7% vs 48.1% in female and male patients, respectively. The mean percentage reduction of inflammatory lesions at the end of the study was 65.3% vs 55.8% in female and male patients, respectively.[35] Although this information suggests that the response of male and female patients to clindamycin–BP 3.75% may differ, it is unclear whether there is a distinction between acne in different sexes or different age groups. Additionally, the female patients included in this analysis were not limited to those with "U-zone" distributed acne. Further clinical trials are necessary to determine whether clindamycin–BP 3.75% is more effective in female patients and whether the pathogenesis of acne in this subset of patients is different from other patients.

Conclusion

Acne vulgaris is the most common skin disease worldwide and is a frequent source of morbidity for affected patients. A significant proportion of treatment options exist for acne vulgaris, and combination therapy is commonly employed to combat the various causes of acne pathogenesis. Clindamycin in conjunction with BP has become part of the mainstay of treatment for patients with inflammatory and noninflammatory acne. However, the optimal combination of efficacy and tolerability has yet to be determined. Pariser et al[35] demonstrated that clindamycin–BP 3.75% is safe and effective for the treatment of acne vulgaris, suggesting that this formulation may be an effective treatment regimen for affected patients. It is clear that this specific combination has the ability to reduce both inflammatory and noninflammatory acne lesions and to be well tolerated. Further studies would be useful to assess comparative effectiveness to other BP–clindamycin products and monotherapy antibiotics and BP.

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Disclosure

The authors report no conflicts of interest in this work.

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