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Is a once daily topical application of fixed-dose combination gel containing adapalene 0.1%-benzoyl peroxide (BPO) 2.5%(adapalene-BPO) effective at treating mild to moderate acne?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements for

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 19th, 2014

ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not a once daily topical application of fixed-dose combination gel containing adapalene 0.1%-benzoyl peroxide (BPO) 2.5% (adapalene-BPO) is effective at treating mild to moderate acne.

STUDY DESIGN: Three multi-center double blind randomized control studies published in the English language between 2007-2013.

STUDY SOURCES: Three peer-reviewed RCTS were found using Pubmed. These studies compared the same fixed-dose combination gel adapalene-BPO against placebo vehicles. Two studies also compared to additional groups receiving monotherapies.

OUTCOMES MEASURED: Outcomes measured were improvement of participant's acne according to the Investigator's Global Assessment of Acne Severity (IGS), percentage change in acne lesions from baseline to post treatment, safety and tolerability assessment scales, participants' assessment of their acne improvement, and Children's Dermatology Life Quality Index.

RESULTS: The fixed-dose combination gel of adapalene-BPO demonstrated significant differences with total lesion counts and treatment efficacy. It was significantly more effective than monotherapies or a placebo vehicle for the treatment of mild to moderate acne. Adverse events were similar to those experienced with the monotherapies and mainly consisted of dryness and erythema that primarily occurred early in the studies.

CONCLUSIONS: A once daily topical application of adapalene-BPO is effective at treating mild to moderate acne. Adapalene-BPO demonstrated superior efficacy, increased lesion count reduction, and a faster onset of action compared to monotherapies consisting of adapalene or benzoyl peroxide as well as a placebo vehicle.

KEY WORDS: adapalene, benzoyl peroxide (BPO), adapalene-BPO, acne

INTRODUCTION

Acne vulgaris is an inflammatory skin condition that is characterized by comedones, papules, pustules, nodules, and cysts.¹ Acne is the most common skin disorder in the US affecting 40-50 million Americans. It is also the most commonly treated skin disease in the U.S. and has been estimated to affect approximately 85% of the population between ages 12 and 26 years of age.^{1,3} Acne is one of the many multi-factorial variables highly associated with depression and other psychiatric processes. Balkrishnan et al (2006) found patients with acne demonstrated “a consistent relationship with anxiety, self-consciousness, inhibition of social interactions, and dissatisfaction with appearance”.² Acne has been shown to affect patient quality of life in a way that is comparable to the psychological effects of other chronic diseases.^{2,4} With an estimated 5-6 million visits, acne continues to be an economic burden on many families with the total episode cost across age groups averaging \$689.06 per episode.^{2,4} In 2004 the direct cost associated with treatment of acne in the U.S. alone was \$2.2 billion^{2,4}

The course can be self-limiting but the sequelae can be life long with risks of hypertrophic scarring. In twin studies 81% of the acne population variance was found due to genetic factors (vs. 19% environmental factors).¹ The pathogenesis includes multiple processes such as follicular epidermal hyperproliferation, excess sebum production, inflammation, and the presence of *Propionibacterium acnes* (*P acnes*) species on the skin.⁹ *P acnes* antagonizes the toll-like receptor 2 in the skin to induce the production of inflammatory cytokines.⁵

The intensity of medical treatment is based off of the amount of cystic lesions, open and closed comedones, and inflammatory lesions. For mild to moderate acne, topical treatments such as antibacterials (clindamycin), salicylic acid, benzoyl peroxide, and retinoids (adapalene, retin-a) are typically employed.¹ For moderate to severe acne, oral antibiotics (tetracycline, doxycycline,

erythromycin, Bactrim) combined with topicals are prescribed. ¹ Isotretinions (Accutane) are effective for severe cases or acne that is refractory to other treatment. ¹

Benzoyl peroxide is a safe and effective broad-spectrum bactericidal with no potential for inducing bacterial resistance. ^{5,4} Due its potency, BPO is more effective than topical antibiotics against *P. Acnes*. ^{5,4} Its mechanism of action releases free-radical oxygen molecules that oxidize bacterial proteins located in the sebaceous follicles. This process eliminates *P. Acnes* and decreases fatty acids that irritate the sebaceous follicles. ^{5,4}

Topical retinoids such as adapalene decrease inflammation by targeting the body's immune system response to inflammation. ^{6,7} Their mechanism of action involves down regulating the surface toll-like receptors, cell differentiation, inflammatory mediators, migration of inflammatory cells, and cellular keratinization. ⁷

Objective

The objective of this selective EBM review is to determine whether or not a once daily topical application of fixed-dose combination gel containing adapalene 0.1%-benzoyl peroxide (BPO) 2.5% (adapalene-BPO) is effective at treating mild to moderate acne.

Methods

Criteria used for selection included; males and females with mild to moderate acne and an inflammatory lesion count ranging from 20-100. The intervention used in all three studies was a once daily topical application of adapalene 0.1%-benzoyl peroxide (BPO) 2.5% (adapalene-BPO). The adapalene-BPO gel was applied to the intent to treat groups in all three studies once daily in the evening for 12 weeks. The control groups received a visually matched placebo gel. Comparisons in the pediatric population study consisted of a visually matched placebo vehicle in

the control group.⁸ Two studies utilized comparison groups that received monotherapies of either adapalene 0.1% or benzoyl peroxide 2.5% in addition to the controlled placebo group.^{5,7}

Outcomes measured included success rate of the treatment based on the improvement of participants' acne, the percentage change in lesions from the baseline to the end of the study, safety, tolerability, and the subjects' personal assessments of their acne improvement. Pubmed was the primary data source utilized for this meta-analysis and all of the articles selected were published in peer-reviewed journals. The articles were selected based on their relevance to the objective and content consisting of patient-oriented evidence that matters (POEMS). All three articles were published in English and consisted of multi-center randomized double-blind controlled studies. Keywords used in the searches included "acne vulgaris", "adapalene", and "benzoyl peroxide".

Inclusion criteria included males and females ages 9 and older, mild to moderate acne, and 20-100 inflammatory lesions (Table 1). An IGA score of 3 or less was required for participants to qualify for the study and this same IGA scale was utilized to evaluate the efficacy of treatment.⁸ Specific washout periods were enforced in all three studies for participating subjects previously taking topical or systemic acne treatment medications.^{5,7,8} Exclusion criteria included individuals with severe nodular cystic acne, pregnant women, men with facial hair, and patients requiring oral therapy treatment (Table 1). Summary statistics were reported using p-values, NNT, NNH, RBI, ABI (Table 2).

Outcomes measured in all three studies assessed POEMS. The Investigator's Global Assessment (IGA) of acne severity was used to evaluate treatment efficacy and success in all three studies. IGA specifically defines the qualifications for a patient to receive a score of 0 – 4 (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, and 4 = severe).^{5,7,8} The change in IGA was

assessed on a weekly basis throughout all three studies as well as the percentage change in lesion count from baseline, cutaneous tolerability, and adverse events. Compliance with intervention was not reported.

Summary statistics were reported in all three studies using p-values. Success rate and percentage lesion count reduction were systematically analyzed in all three studies using the Cochran-Mantel Haenzel (CMH) test. The CMH test was then “stratified by analysis center using general association for success rates and row mean differences by relative to identified distribution transformed scores for percentage lesion changes.”^{5,7,8} These analyses were repeated for the per-protocol groups. CMH was also used to analyze the subject’s assessment of their acne improvement. In all three studies, the outcomes tests were two-sided and used a .05 level to declare significance. Safety and tolerability were assessed weekly by investigators using a scale to rate erythema, dryness, stinging, burning with scores ranging from 0 (none) to 3 (severe).^{5,7,8} Eichenfield et al (2013) also investigated quality of life utilizing the Children’s Dermatology Life Quality Index (C-DLQI) at baseline and week 12.⁸

1.) Table 1: Demographics and Characteristics of included studies

Study	Type	# pts	Age (yr)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Eichenfield (2013) ⁸	Double blind RCT	283	9 – 11	- Males and females with mild to moderate acne vulgaris (score of 3 or less on IGA scale) -20-100 lesions on face	-nodule or cystic acne lesions - severe acne that requires systemic treatment - use of hormonal contraceptives	42	Fixed dose combination gel of adapalene 0.1% and benzoyl peroxide (BPO) 2.5% (adapalene-BPO) once daily in the evening for up to 12 weeks
Gollnick (2009) ⁵	Double blind RCT	1670	12 +	- males and females with mild to moderate acne	- severe acne requiring isotretinoin therapy	146	Fixed dose combination gel of adapalene 0.1%

				- 20-50 inflammatory lesions - IGA score of 3 - no more than 1 active nodule	- pregnant women - men with facial hair that would interfere with visual assessments		and benzoyl peroxide (BPO) 2.5% (adapalene-BPO) once daily in the evening for up to 12 weeks
Thiboutot (2007) ⁷	Double blind RCT	517	12+	- Males and females with acne - 30-100 noninflammatory facial lesions, 20-50 inflammatory facial lesions - no nodules or cysts	- Severe acne requiring isotretinoin therapy - women who were pregnant, nursing, or planning pregnancy - men with facial hair that would interfere with visual assessments	47	Fixed dose combination gel of adapalene 0.1% and benzoyl peroxide (BPO) 2.5% (adapalene-BPO) once daily in the evening for up to 12 weeks

RESULTS

The studies in this meta-analysis were multi-center randomized double-blind controlled studies conducted in a clinical setting. All three studies required participants with an IGA scale of 3 (moderate acne) with slight variations in the inclusions criteria. Thiboutot et al (2007) confirmed their inclusion sample by having blinded third party dermatologists review photos taken of participants at the selection screening.⁷ Eichenfield et al (2013) modified the IGA scale to apply to the pediatric population.⁸ Gollnick et al (2009) and Thiboutot et al (2007) included males and females ages 12 and older, while Eichenfield et al (2013) included only male and female children ages 9 to 11 years old.^{5,7,8} Gollnick et al (2009) and Thiboutot et al (2007) also included additional experimental groups that solely received either adapalene or benzoyl peroxide as a monotherapy treatment in addition to a controlled placebo vehicle group.^{7,8} Exclusion criteria in all three studies included the presence of cystic acne lesions or severe acne

requiring isotretinoin or systemic therapy. Gollnick et al (2009) and Thiboutot et al (2007) excluded pregnant or nursing women and men with facial hair that interfered with assessment of their skin.^{7,8} All three studies defined efficacy and success of treatment based on the percentages of patients with ‘clear’ or ‘almost clear’ ratings on the IGA score.

For success rate and efficacy of treatment, Gollnick et al (2009) found the adapalene-BPO combination (37.9%) superior to all other treatment and placebo groups (17.9%, $p < .05$) (Table 2). The numbers needed to treat are 3 (Table 2). The adapalene-BPO also demonstrated the greatest reductions in inflammatory lesions counts relative to the other treatments by as early as week 1 in the study ($p < .05$) and continued to remain superior by week 12 ($p < .05$).

Eichenfield et al (2013) also utilized the IGA scale and total lesion count to assess the efficacy the adapalene-BPO in the ITT group.⁸ Since they focused on a specific population of children they also utilized the C DLQI at baseline and week 12. At week 12, 71.0% of the intent to treat (ITT) group reported their acne had no effect on their quality of life vs. 57.5% in the control group. At week 12, the efficacy and success of adapalene-BPO was significantly superior to the vehicle.⁸ Approximately half of the subjects (49.3%) were rated ‘clear’ or ‘almost clear’ compared to 15.9% of the placebo group ($p < .05$). The numbers needed to treat were 3 (Table 2). According to Eichenfield et al (2013), while the adapalene-BPO ITT group presented with decreased lesion counts as early as week 1 ($p < .05$), the vehicle percentage change in total and non-inflammatory lesions “plateaued and worsened for inflammatory lesions between weeks 8 and 12.”⁸

Thiboutot et al (2007) had similar findings with the success rate and efficacy of the adapalene-BPO combination (27.5%) compared to the placebo group (9.9%, $p < .05$) (Table 2).⁷ The numbers needed to treat were 6 (Table 2). The lesion counts on participants including total,

inflammatory, and non-inflammatory after 12 weeks of treatment also revealed a significantly greater response to the combination therapy relative to placebo and monotherapy groups (p values < 0.05).

Overall, statistically significant findings using the combination gel were observed across all studies.^{5,7,8} Not only did the studies demonstrate adapalene-BPO to be effective at treating acne compared to groups receiving a placebo vehicle, but Gollnick et al (2009) also found the adapalene-BPO (37.9%) superior and statistically significant to the groups that received the monotherapy of only adapalene (21.8%, p <.05) or BPO (26.7%, p <.05).⁵ Thiboutot et al (2007) reported similar statistically significant findings when comparing the adapalene-BPO treatment group (27.5%) to the monotherapy groups receiving either adapalene (15.5%, p <.05) or benzoyl peroxide (15.4%, p <.05).⁷

SAFETY

All three studies assessed safety based on tolerability and adverse events such as erythema, dryness, scaling, and burning. In the study performed by Gollnick et al (2009), the overall incidence of participants experiencing at least one adverse event was 48% for the adapalene-BPO and 28% for the vehicle (Table 3). The numbers needed to harm were 5 (Table 3). No serious adverse events were deemed related to the study treatments and the adverse events that appeared to be related were primarily dermatological in nature consisting of erythema and dry skin.⁵ According to Gollnick et al (2009) these adverse events “occurred early in the study, and resolved without residual effects.”⁵

According to Thiboutot et al (2007) the overall incidence of subjects experiencing at least one adverse event was 38% for the adapalene-BPO group and 26.8% for the vehicle (Table 3).⁷ The numbers needed to harm were 9 (Table 3). No serious adverse events were deemed related

to the study treatments. Some of the incidents that were deemed “un-related” to the study included illicit drug overdose and social circumstances. The most frequently reported adverse event was dry skin.⁷

According to Eichenfield et al (2013) mean scores for adverse side effects did not exceed a score of 1 (mild) for both the ITT population and vehicle group.⁸ There were 29 subjects (20%) who experienced treatment-related AE and 1 subject (0.7%) in the vehicle group. The numbers needed to harm were 8 (Table 3). The incidence of adverse side effects peaked for the adapalene-BPO in the first two weeks of treatment. However, Eichenfield et al (2013) reported these adverse side effects such as redness and irritation “remained mild and then disappeared over time to reach a tolerability level comparable to vehicle as week 4”.⁸ The most common adverse effect was skin burning sensation (9.2%) and skin irritation (5.6%).⁸

Table 2. Efficacy of adapalene-BPO in the treatment of acne (dichotomous data) - NNT

Study	Control Event Rate (CER)	Experimental Event Rate (EER)	P value	Relative benefit increase (RBI)	Absolute benefit increase (ABI)	Numbers needed to treat (NNT)
Gollnick et al (2009) ⁵	17.9%	37.9%	P < 0.05*	1.12	0.2	5
Eichenfield et al (2013) ⁸	15.9%	49.3%	P < 0.05*	2.10	0.334	3
Thiboutot et al (2007) ⁷	9.9%	27.5%	P < 0.05*	1.8	0.176	6

*statistically significant differences

Table 3. Adverse effects of adapalene-BPO in the treatment of acne (dichotomous data) – NNH

Study	EER	CER	RRI	ARI	Numbers needed to harm (NNH)
Gollnick et al (2009) ⁵	48%	28%	0.71	0.2	5
Eichenfield et al (2013) ⁸	20%	7%	1.9	0.13	8
Thiboutot et al (2007) ⁷	38.3%	26.8%	0.4	0.12	9

Discussion

Adapalene-BPO is marketed and sold under the brand name Epiduo.⁶ There is currently no generic available, limiting the availability to consumers until the patent expires. The average cost of a 45 g tube of Epiduo gel is \$376.20.⁶ Although some insurances may cover the prescription, the Epiduo drug manufacturer offers coupons enabling consumers to pay \$25 for their first prescription, \$15 for the first refill, and \$10 for following refills.⁹ However, without adequate insurance or access to these coupons, the expense of the product limits its availability. An alternative for consumers is to buy adapalene (0.1%) topical gel and benzoyl peroxide (BPO) separately.⁶

Current research trials have not demonstrated any long-term effects aside from increased photosensitivity while on the medication.⁶ The FDA has not issued any black box warnings although Epiduo remains in pregnancy category C and excretion in breast milk is unknown.⁶ Other adverse effects such as dryness, scaling, erythema, burning/stinging, are commonly experienced in the first four weeks of treatment and usually decrease with continued use.⁶

All three studies were controlled research trials that cannot precisely reflect the efficacy and safety in the general population.⁸ Eichenfield et al (2013) performed one of the few clinical studies focusing on the treatment of pediatric acne. However, a major limitation affecting the reliability of their study is a lack of diversity in their participants: 76.1% of their subjects were females and 81% of their subjects were Caucasian.⁸ Another limitation found in all three studies is the limited time frame of 12 weeks. Although this is a common length of time to evaluate efficacy and safety of dermatological FDA-approved medications, it is possible for adverse side effects to manifest after this three month period.

Overall, all three studies found adapalene-BPO to be superior and statistically significant compared to the placebo groups at treating acne.^{5,7,8} Adapalene-BPO was found to have a significantly greater and faster onset of action at improving acne as well as the greatest reductions in inflammatory lesions compared to the placebo group or those receiving monotherapies.^{5,7,8} The numbers needed to treat in all three studies were low, supporting the efficacy of the treatment in terms of patient oriented medicine (Table 2). The numbers needed to harm were higher than the numbers needed to treat, but they still remained within a close range to those needed to treat (Table 3). Higher numbers need to harm would be preferable to support the efficacy and success of adapalene-BPO, but it is important to note that the incidence of reported adverse effects in patients receiving the monotherapies solely BPO or adapalene remained comparable or higher to those receiving the combination therapy.^{7,8}

CONCLUSION

This meta-analysis has demonstrated that a once daily topical application of a combination gel containing adapalene 0.1%-benzoyl peroxide (BPO) 2.5% is effective at improving acne. Gollnick et al (2009) and Thiboutot et al (2007) found adapalene-BPO to be significantly more effective and to have a faster onset of action than adapalene or BPO used as monotherapies.^{5,7}

Retinoids such as adapalene have been found to permanently alter the toll-like receptors on the skin.⁷ Future study is warranted to evaluate if patients continue to experience long-term clearer skin effects after completing a treatment with adapalene-BPO. These studies could help determine an adequate treatment time required to permanently change the toll-receptors and enable patients to maintain clearer skin indefinitely. These future studies can also investigate adverse effects experienced by patients using adapalene-bpo longer than 12 weeks.

With the concerning and increasing incidence of antibiotic resistance, adapalene-BPO may become a vital treatment resource in the future of medicine. Future studies could investigate if adapalene-BPO has a decreased incidence of bacterial resistance compared to oral and topical antibiotics used to treat acne. Patient adherence to treatment with once daily Adapalene-BPO could also be compared to those patients treated with multiple daily dosing of antibiotics. It is possible the once daily dosing of adapalene-BPO could shorten the time for visible signs of acne improvement if patients are more likely to adhere to the treatment routine.

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