Adapalene-benzoyl peroxide, a fixed-dose combination for the treatment of acne vulgaris: Results of a multicenter, randomized double-blind, controlled study

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Background: A fixed-dose combination gel with adapalene 0.1% and benzoyl peroxide (BPO) 2.5% has been developed for the once-daily treatment of acne.

Objective: To evaluate the efficacy and safety of adapalene 0.1% -BPO 2.5% fixed combination gel (adapalene-BPO) for the treatment of acne.

Methods: A total of 517 subjects were randomized in a double-blind controlled trial to receive either adapalene-BPO, adapalene, BPO, or vehicle for 12 weeks (2:2:2:1 randomization). Evaluation included success rate (subjects "clear" or "almost clear"), lesion count, cutaneous tolerability, and adverse events.

Results: The fixed-dose combination gel of adapalene and BPO was significantly more effective than corresponding monotherapies, with significant differences in total lesion counts observed as early as 1 week. Adverse event frequency and cutaneous tolerability profile for adapalene-BPO were similar to adapalene monotherapy.

Limitations: These data were generated in a controlled trial. Results obtained in clinical practice could differ.

Conclusions: The fixed-dose combination of adapalene and BPO provides significantly greater efficacy for the treatment of acne vulgaris as early as week 1 relative to monotherapies, with a comparable safety profile to adapalene. (J Am Acad Dermatol 2007;57:791-9.)

INTRODUCTION

Acne vulgaris is a complex skin disorder involving multiple abnormalities of the pilosebaceous unit, including hyperkeratinization, increased sebum production, bacterial proliferation, and inflammation.[1,2] Existing topical and systemic therapies recommended for the treatment of acne include retinoids, benzoyl peroxide (BPO), antibiotics, and

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Abbreviations used:

BPO: benzoyl peroxide
IGA: investigator's global assessment
ITT: intention-to-treat
LOCF: last observation carried forward
PP: per-protocol

hormonal therapy. Combination therapy utilizing agents with complementary mechanisms, such as a topical retinoid and an antimicrobial, is often used in the management of acne, since most anti-acne medications do not act against all 4 of the major pathophysiologic features of acne.[3]

Adapalene is a receptor-selective naphthoic acid derivative with anti-inflammatory, comedolytic, and anticomedogenic properties.[4-8] It is recognized as an effective topical retinoid with a favorable tolerability profile[9] and is therefore a rational selection for combination therapy with an antimicrobial agent. The safety and efficacy of adapalene in the treatment of acne vulgaris have been studied in numerous clinical trials.[10-19] Recent clinical studies investigating the efficacy and safety of adapalene when used in combination with several antibiotics (oral lymecycline, oral doxycycline, and topical clindamycin) for the treatment of inflammatory acne showed that the adapalene-antibiotic combinations were consistently more effective than antibiotic monotherapy.[20-23]

BPO is a safe and effective antimicrobial agent for the treatment of acne.[3] A variety of BPO formulations are available, with concentrations ranging from 1% to 10%. BPO has demonstrated activity against bacterial organisms and yeast.[3,24,25] Compared with topical antibiotics with bacteriostatic properties, BPO exhibits a potent and rapid bactericidal effect against *Propionibacterium acnes*, with no evidence for the development of bacterial resistance.[3] The enhanced efficacy and tolerability of BPO when used in combination with topical antibiotics have led to several BPO-antibiotic fixed-dose products that have met with success in the treatment of acne.[3,26-28] However, there are currently no products that combine the antibacterial efficacy of BPO with the efficacy of a retinoid in reversing the altered follicular keratinization that is key in the pathogenesis of acne.

Recently, a unique, fixed-dose combination gel with adapalene 0.1% and BPO 2.5% has been developed for the once-daily treatment of acne. Adapalene is stable when combined with BPO in the presence or absence of light.[29] A formulation containing 0.1% adapalene and 2.5% BPO was considered optimal to provide the best overall efficacy and tolerability profile.[30] The adapalene-BPO combination has an overall preclinical profile similar to the individual agents.[31] The objective of the present study was to evaluate the efficacy and safety of adapalene 0.1%—benzoyl peroxide 2.5% fixed combination topical gel (adapalene-BPO) versus adapalene 0.1% gel (adapalene), BPO 2.5% gel (BPO), and the gel vehicle (vehicle) in the treatment of acne vulgaris for up to 12 weeks.

METHODS

Study design

The efficacy and safety of a fixed combination topical gel of adapalene-BPO were compared that of adapalene, BPO, as well as the gel vehicle in a randomized, multicenter, double-blind, parallel group study conducted at 36 centers in the United States between February 17, 2004 and December 21, 2004. Subjects were randomized consecutively in a 2:2:2:1 ratio to receive either adapalene-BPO gel, adapalene gel, BPO gel, or gel vehicle for 12 weeks. (Note: the two monotherapies [adapalene and BPO] in this study are monads of the combination formulated in the same vehicle as the combination and therefore have different vehicle formulations than the available commercial products [Differin or Benzac, Galderma Laboratories]). The integrity of the blinding was ensured by packaging the topical medication in identical tubes and requiring a third party other than the investigator/evaluator to dispense the medication. Efficacy and safety evaluations were performed at baseline and at weeks 1, 2, 4, 8, and 12. A urine pregnancy test was required at baseline and at the final study visit for all female subjects of childbearing potential. Subjects were free to withdraw from the study at any time and for any reason. Subjects not completing the entire study were to be fully evaluated when possible.

This study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki and Good Clinical Practices and in compliance with local regulatory requirements. This study was reviewed and approved by an institutional review board. All patients provided their written informed consent prior to entering the study.

Subjects

Male and female subjects, 12 years of age or older, with 30 to 100 noninflammatory facial lesions, 20 to 50 inflammatory facial lesions, and no nodules or cysts were enrolled in the study. The extent of the subjects' acne for study inclusion was confirmed by a review of standardized photographs taken at the screening visit by an independent, blinded, third-party dermatologist. Specified washout periods were required for subjects taking certain topical and