



New Developments in the Topical Management of Acne

Abstract

Adapalene 0.1%/BPO 2.5% (adapalene/BPO) gel is a novel agent for acne therapy that has recently become available in Canada. This fixed-dose combination of a topical retinoid and benzoyl peroxide is efficacious in mild-moderate inflammatory acne and as an adjunct to oral antibiotics for severe acne. Adapalene 0.1%/BPO 2.5% (adapalene/BPO) gel provides synergistic efficacy, whereby efficacy of the combination exceeds the summed efficacy of individual components. Furthermore, adapalene/BPO with oral doxycycline for severe acne increases the rate of global treatment success four-fold beyond that with doxycycline alone. Practical means to abrogate the development of local intolerance have been shown to be effective.

Keywords: *acne, adapalene, benzoyl peroxide, fixed-dose gel, combination, topical acne medication, retinoids*

Of the multiple pathogenic factors involved in acne (Figure 1), three of five can be addressed by topical medications: follicular hyperkeratinization, *Propionibacterium acnes* proliferation, and inflammation (Figure 2). Androgenic stimulation and sebum hypersecretion are unaffected by currently available topical acne medications. The primary drug classes for the topical treatment of acne—retinoids, antibiotics, and benzoyl peroxide (BPO)—have recently been expanded by the addition of a fixed-dose combination gel of a retinoid and BPO.

In Canada, currently available single product combinations of these classes include retinoids and antibiotics (e.g., Stievamycin; Stiefel/GSK) and antibiotics and BPO (e.g., Clindoxyl, Stiefel/GSK; Benzamycin, Benzaclin; Dermik, Aventis). The combination of retinoid and BPO in the form of adapalene 0.1%/BPO 2.5% (adapalene/BPO)

has recently been approved in various countries, including Canada. Such a combination has been advocated by an international acne expert group as a rational standard for treating mild-moderate acne as it offers complementary mechanisms of action: adapalene, a synthetic retinoid (a naphthoic acid derivative), is comedolytic, keratolytic, antiproliferative, and anti-inflammatory; while BPO, an oxidizing agent, is keratolytic and antibacterial.^{1,2}

Adapalene 0.1%/BPO 2.5% Gel (Adapalene/BPO)

Structure and Mechanism of Action

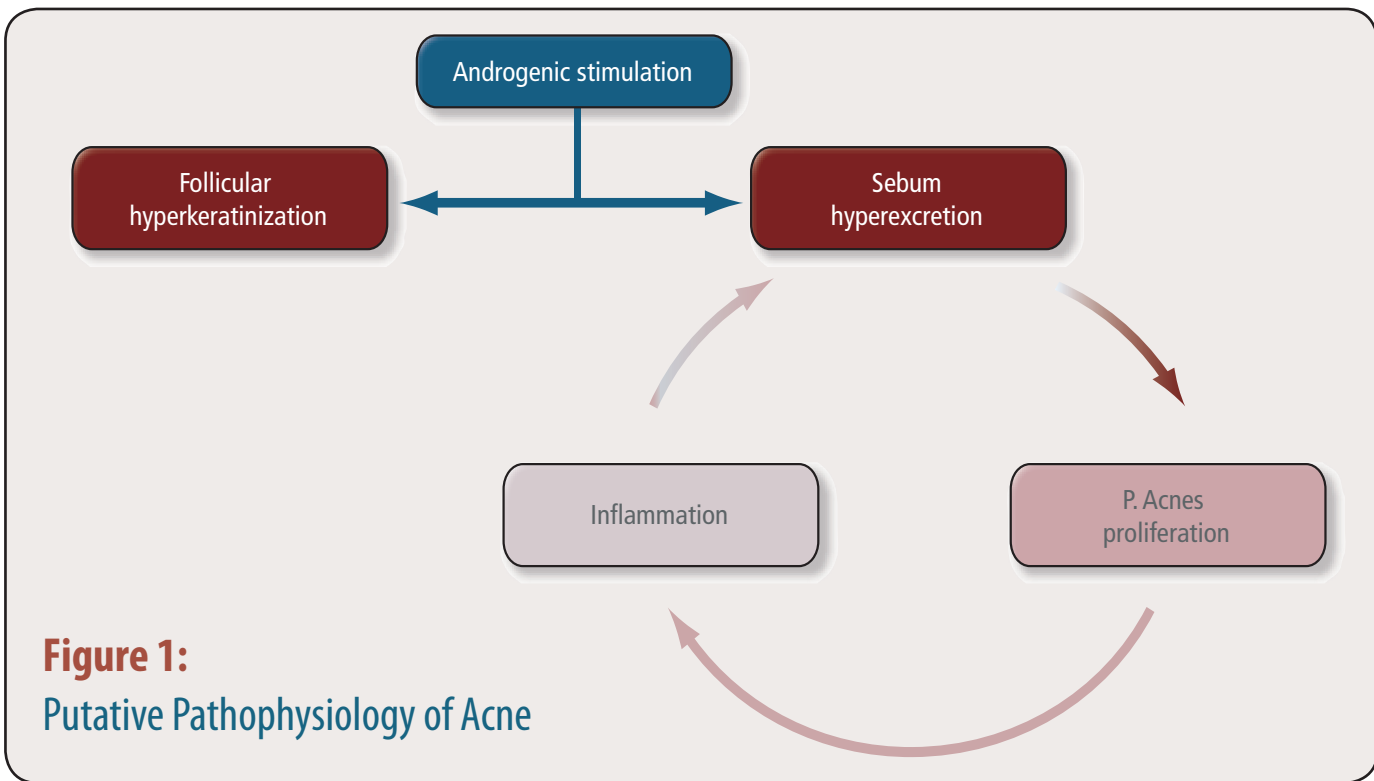
Adapalene, a synthetic retinoid derived from naphthoic acid, acts specifically on the skin processes that cause acne.

It has comedolytic, antiproliferative, and anti-inflammatory properties. The former two



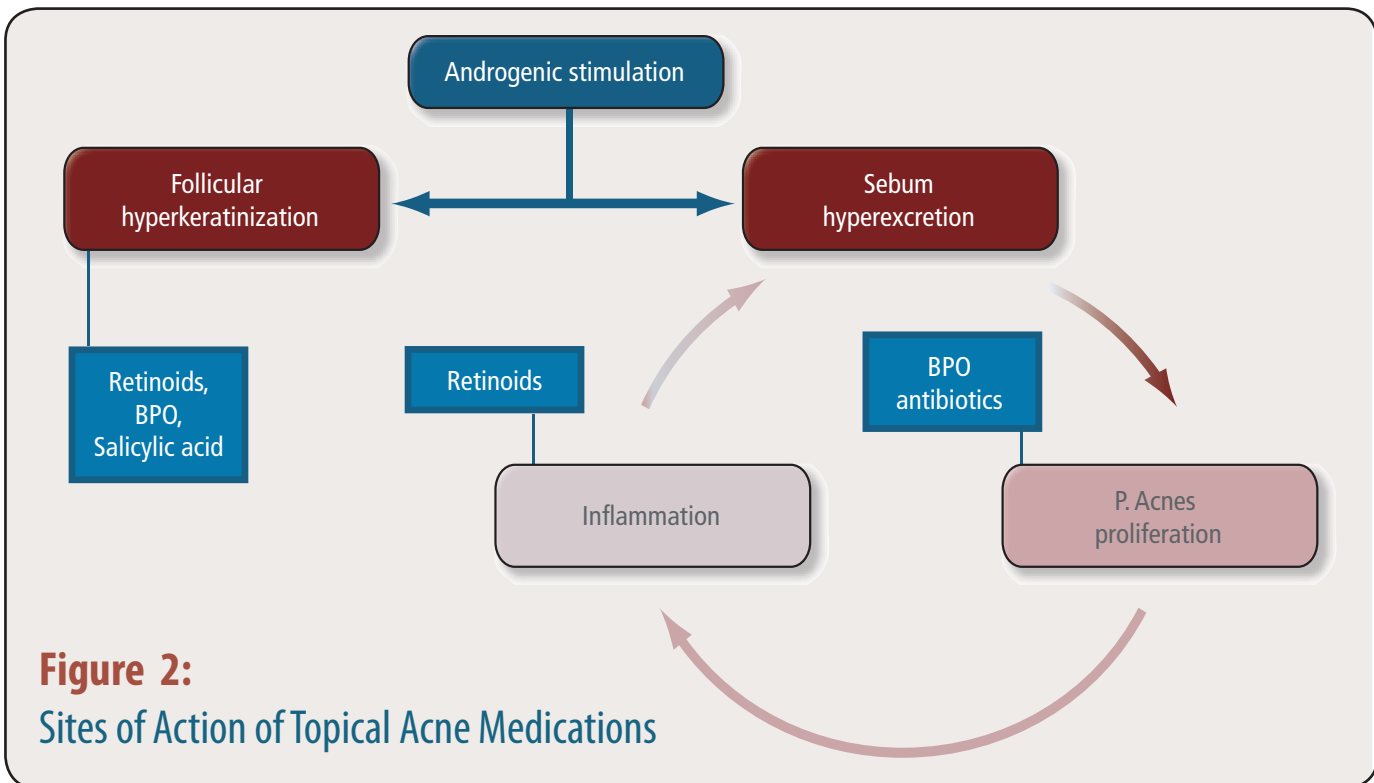
About the author

Jerry Tan, MD, FRCPC, Dept. of Medicine, Schulich School of Medicine and Dentistry, University of Western Ontario, London, ON.



actions are largely mediated through selective interaction with nuclear retinoic acid receptors while the anti-inflammatory effect is via downregulation of toll-like receptor-2 (TLR-2) *P. acnes* induced inflammation (Figure 3).³

Benzoyl peroxide is a bactericidal agent with keratolytic effects. The antibacterial effect of BPO, leading to oxidation of bacterial cell membranes, is mediated by reactive oxygen intermediates. This is a mechanism to which bacteria



have not developed mechanisms of resistance.³

Clinical Applications

Because of their comedolytic and anti-inflammatory properties, topical retinoids are a cornerstone of therapy. However, they are not specific in targeting *P. acnes*, a void filled by the bactericidal effect of BPO. Accordingly, such a combination should provide complementary mechanisms of action in addressing multiple pathogenic factors simultaneously, including hyperkeratinization, *P. acnes* proliferation, and inflammation. Additionally, combining such agents in a single product may enhance treatment adherence.

Clinical Efficacy

Moderate Acne

Double-blind, randomized, controlled trials involving 3,853 patients have been performed to evaluate the overall efficacy and tolerability of this adapalene/BPO formulation.⁴⁻⁶ Acne patients of both genders, age 12 years or older, with 20–50 inflammatory and 30–100 noninflammatory facial acne lesions were recruited. Randomization resulted in allocation into one of four 12-week treatment groups: adapalene/BPO gel, adapalene gel, BPO gel, or vehicle gel.⁷ At end of 12 weeks, adapalene/BPO provided significantly greater reduction in total lesion counts (59%); inflammatory counts (66%) and noninflammatory counts (58%). At week 12, the combination achieved significantly greater global success (33%) compared to vehicle (14%), adapalene (20%), and BPO (23%) (Table 1).

Efficacy Across Lesion Count Subgroups

While 97% of the 3,853 subjects in these three trials had moderate facial acne at baseline, there was a wide range of baseline acne counts: 14–70 inflammatory lesions, 24–115 non-inflammatory lesions and 45–166 total lesions.⁷ However, it was unclear if efficacy varied with lesion counts. A meta-analysis of the

three multicentre, randomized, double-blind, vehicle-controlled trials divided baseline lesion counts into quartiles LOW (lowest quartile of lesion counts; ≤ 23 inflammatory lesions, ≤ 36 non-inflammatory lesions, ≤ 63 total lesions); MID (middle two quartiles of lesion counts; 23–34 inflammatory lesions, 36–62 noninflammatory lesions, 63–94 total lesions); and HIGH (highest lesion count quartile; ≥ 34 inflammatory lesions, ≥ 62 noninflammatory lesions, ≥ 94 total lesions). Results demonstrated that the efficacy of adapalene/BPO was greatest in the HIGH subgroup. Specifically, the efficacy of adapalene/BPO in total lesion count reduction was 19.4%, 26.4%, and 29.1% in the LOW, MID, and HIGH subgroups, respectively. This progressive increase in relative benefit with lesion subgroups was also observed for inflammatory and noninflammatory lesions. The greater benefit with higher lesion counts was unique to adapalene/BPO across all lesion count measures and was not observed for BPO monotherapy while for adapalene monotherapy, it was observed for total and noninflammatory lesions.

Synergistic Efficacy

Combination therapies are often employed in the treatment of acne as they can address multiple pathophysiological factors concurrently.^{1,2} Beyond the convenience of using one product with combined active agents, enhanced treatment efficacy may be a further benefit. *Synergistic efficacy* can be defined as the excess benefit of the combination beyond the sum of the benefits of each of its components. This potential was recently addressed by a pooled analysis of the three large RCTs previously described. In this study efficacy measures

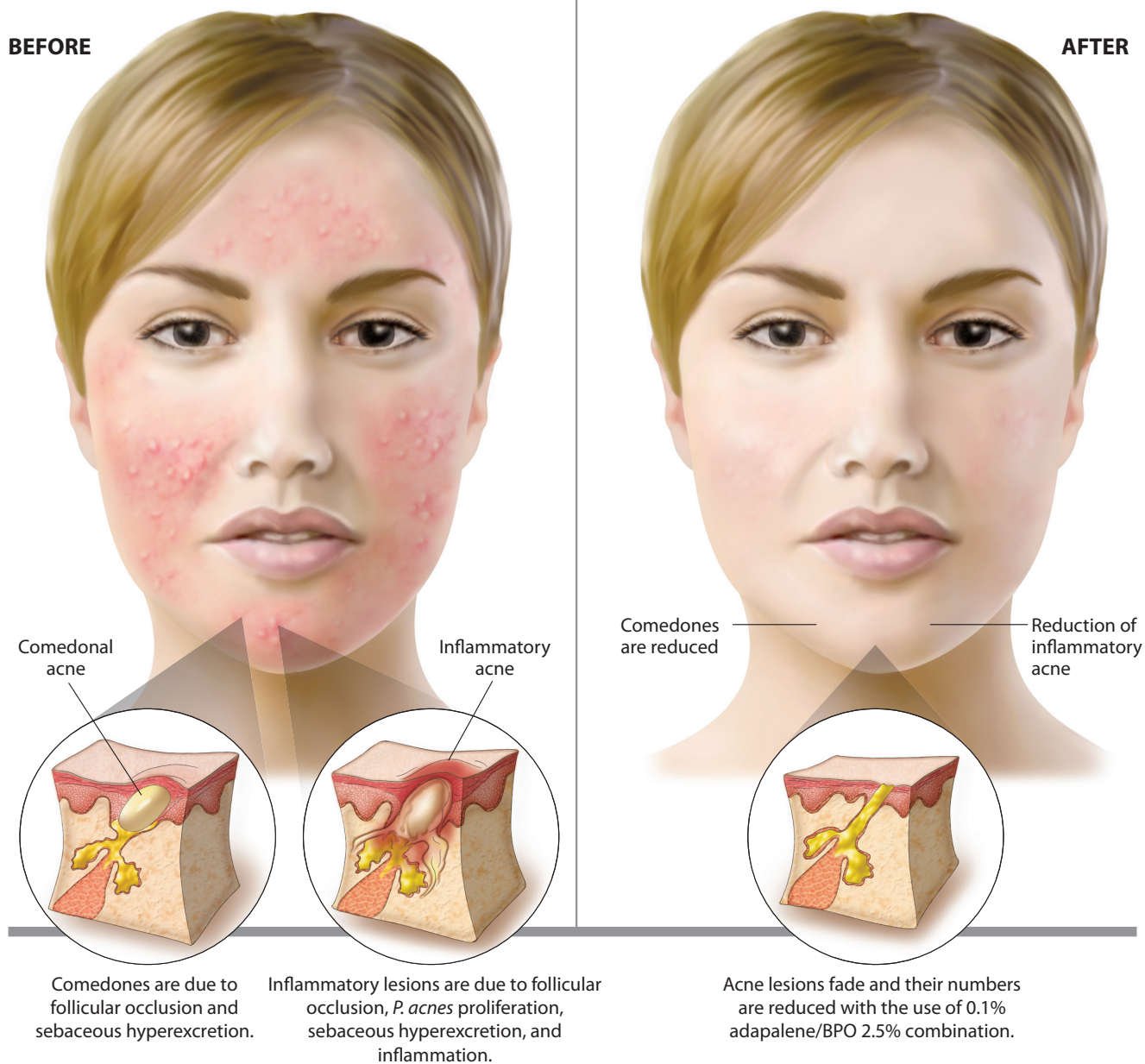
BECAUSE OF THEIR COMEDOLYTIC AND ANTI-INFLAMMATORY PROPERTIES, TOPICAL RETINOIDS ARE A CORNERSTONE OF THERAPY.



Key Point

Three of five pathogenic factors involved in acne can be addressed by topical medications: follicular hyperkeratinization, Propionibacterium acnes proliferation, and inflammation.

Figure 3: Mechanism of Action of the New Fixed-Dose Adapalene-Benzoyl Peroxide Topical Acne Treatment



A fixed-dose combination of retinoid and benzoyl peroxide in the form of adapalene 0.1%/BPO 2.5% (adapalene/BPO) has been advocated by an international acne expert group as a rational standard for treating mild-moderate acne as it offers complementary mechanisms of action. This product is indicated for the topical treatment of acne vulgaris in patients 12 years of age and older.

Adapalene, a synthetic retinoid, is comedolytic, keratolytic, antiproliferative, and anti-inflammatory; while BPO, an oxidizing agent, is keratolytic and antibacterial.

Adapalene 0.1%/BPO 2.5% targets three areas of acne pathogenesis and is:

1. comedolytic: retinoid treats existing lesions and helps to prevent the formation of new comedones.
2. anti-bacterial: benzoyl peroxide kills *P. acnes* but does not promote the development of bacterial resistance.
3. anti-inflammatory: retinoid reduces inflammation, while BPO reduces inflammation indirectly by reducing *P. acnes*.

of active treatment arms were calculated by subtracting the effect of vehicle, thereby providing a measure termed *net benefit*.^{8,9} Pooled data demonstrated progressive improvement over the course of 12 weeks in all outcome measures for all active treatment arms compared to vehicle—with the greatest benefits observed for adapalene/BPO. Calculations revealed synergistic efficacy for adapalene/BPO for all efficacy measures (total lesion counts, inflammatory counts, noninflammatory counts, global assessments) within the first week. This effect extended to week four for inflammatory counts, to week eight for total and noninflammatory counts, and to week 12 (end of study) for global assessments. However, the contribution of synergy to the net benefit of adapalene/BPO did progressively decrease with time: for inflammatory lesions declining from 62% at week one to 43% at week four; for noninflammatory lesions from 41% at week one to 14% at week eight; and for global success (achievement of global grades of *clear* or *almost clear* ratings) from 129% at week one to 22% at week 12.⁸ While the mechanism underlying this effect is unclear, current hypotheses include the combined keratolytic effect of both agents to enhance epidermal and

infundibulofollicular penetration, in addition to addressing a wider range of acne pathogenic factors. Such enhanced efficacy is enhanced patient benefit, and the convenience of a single product may translate into greater medication adherence and increased patient satisfaction.

Comparative Efficacy

The efficacy of adapalene/BPO was evaluated against clindamycin 1%/BPO 5% (C/BPO) in an investigator-blinded, randomized, controlled trial.¹⁰ Subjects with facial acne of both genders aged 12–45 years with 25–80 inflammatory lesions, 12–100 noninflammatory lesions (no nodules or cysts). Subjects were instructed to apply the study product once daily for 12 weeks and to avoid washing their face for four hours following application. The primary outcome measure was change in inflammatory lesion counts with the power calculation establishing a sample size of 200 subjects per treatment arm. However, only 190 subjects in the C/BPO arm and 192 in the adapalene/BPO arm were recruited. Success on global assessment, a secondary outcome measure, was a reduction in two grades or more, not achievement of *clear* or *almost clear* grades as for the phase III trials for adapalene/BPO.



Key Point

The combination of retinoid and BPO in the form of adapalene 0.1%/BPO 2.5% has recently been approved in Canada, and has been advocated by an international acne expert group as a rational standard for treating mild-moderate acne as it offers complementary mechanisms of action.

Table 1: Efficacy of Adapalene 0.1%/Benzoyl Peroxide 2.5% (Adapalene/BPO) from Pooled RCT Data

Efficacy measure		Adapalene (N=984)	Adapalene/BPO (N= 983)	BPO (N = 979)	Gel Vehicle (N=907)
Inflammatory lesions	Baseline	29.4±7.94	29.2±7.98	29.4±8.27	29.4±8.03
	Week 12	16.3±12.9	12.9±11.7	15.8±13.8	19.4±14.5
Noninflammatory lesions	Baseline	52.2±19.3	51.6±19.4	50.6±18.2	51.5±18.8
	Week 12	30.6±23.4	25.7±22.2	31±22.7	37.8±27.7
Global success (clear or almost clear on IGA)	Week 1	0.2%	1%	0.2%	0.35
	Week 12	20%	33%	23%	14%

**BECAUSE OF THEIR
COMEDOLYTIC AND
ANTI-INFLAMMATORY
PROPERTIES, TOPI-
CAL RETINOIDS ARE
A CORNERSTONE OF
THERAPY.**

Results demonstrated a nonsignificant trend for greater reduction in inflammatory lesions with C/BPO (77% compared to 72% with adapalene/BPO; $P=0.076$) and a significant difference in achieving global success with C/BPO (30% versus 22% with adapalene/BPO; $P=0.046$). The authors concluded that, while both combination products had similar efficacy in reducing inflammatory and noninflammatory lesions, C/BPO achieved greater global success with less cutaneous intolerance.

Limitations of this trial include inadequate details regarding study medication application in amount and duration; insufficient instruction regarding facial cleansing and moisturizer use, inadequate sample size recruitment based on the power calculation for inflammatory lesions; undefined sample size and trial power for the measure of global success. A greater rate of noncompliance in the adapalene/BPO arm (almost three times greater during the first four weeks of treatment) was observed, but the potential of this issue in affecting efficacy outcomes was not evaluated with a per-protocol subset analysis.

Severe Acne

The potential value of adapalene/BPO in treatment of severe acne as an adjunct to oral antibiotics and thereafter as a maintenance treatment to reduce recurrence has recently been evaluated. The study was randomized, double-blinded, and vehicle-controlled, comprising an initial 12-week phase whereby subjects with severe acne received an oral antibiotic (doxycycline hyclate 100 mg combined) and were randomized to either adapalene/BPO or gel vehicle.¹¹ Severe facial acne subjects aged 12–35 years with 20 inflammatory lesions minimum,

30–120 noninflammatory lesions, and maximum of three nodulocysts were enrolled ($N= 459$). Results demonstrated that doxycycline plus adapalene/BPO was significantly superior to doxycycline plus vehicle gel in lesion count reduction (total, inflammatory, and noninflammatory) as early as week two and throughout the study. At week 12, total lesion counts were reduced by 64% for doxycycline plus adapalene/BPO compared to 41% for doxycycline plus vehicle gel ($p < 0.001$). Achievement of global success (rating of clear or almost clear from severe) was observed in 32% of those subjects on doxycycline plus adapalene/BPO compared to 8% on doxycycline plus vehicle gel ($p < 0.001$).

Thus, adapalene/BPO can serve as a useful adjunct to oral antibiotic therapy in severe acne vulgaris.

Safety and Tolerability

Both topical retinoids and benzoyl peroxide can be irritating agents—and their combination may potentiate this factor. Safety and tolerability evaluation from the meta-analysis of 3,853 subjects indicated mean severity scores for dryness, erythema, scaling, and stinging/burning were greatest for adapalene/BPO.⁷ These were reported as no greater than mild, and peaked within the first two weeks of therapy, declining thereafter. A greater proportion experienced treatment-related adverse events in the adapalene/BPO group (22%) compared to adapalene (15%), BPO (8%), and vehicle (6%). The majority of these events in the adapalene/BPO group were dry skin (13%).⁷

In the study comparing adapalene/BPO against C/BPO, application site intolerance was significantly more frequent in the adapalene/BPO group ($P < 0.03$) as were treatment-related adverse events. The latter were observed in 77% on adapalene/BPO compared to 48% on C/BPO. Furthermore, missed applications were more frequently observed in the adapalene/BPO group in the first four weeks (429 versus 150) and were largely



Key Point

An adapalene/BPO formulation provides greater proportions of global success and reduction in acne lesion counts compared to the vehicle or either agent alone.

SUMMARY OF KEY POINTS

Three of five pathogenic factors involved in acne can be addressed by topical medications: follicular hyperkeratinization, *Propionibacterium acnes* proliferation, and inflammation.

The combination of retinoid and BPO in the form of adapalene 0.1%/BPO 2.5% has recently been approved in Canada, and has been advocated by an international acne expert group as a rational standard for treating mild-moderate acne as it offers complementary mechanisms of action.

An adapalene/BPO formulation provides greater proportions of global success and reduction in acne lesion counts compared to the vehicle or either agent alone.

As topical retinoids and benzoyl peroxide can be irritating, their combination may potentiate this factor. Measures to minimize intolerability include every other night application and daily moisturizer use.

attributed to tolerability issues.¹⁰

A formal study to evaluate the effect of modified application regimens on local intolerability to adapalene/BPO was recently completed.¹² In this investigator-blind study, mild-moderate facial acne subjects were randomized to one of four 4-week treatment regimens using adapalene/BPO gel: standard overnight application, standard overnight regimen with moisturiser application every morning (Cetaphil lotion), alternating night applications, or three-hour nightly applications with washing the product off prior to sleep. Results showed that local intolerability scores peaked at the first week and progressively declined thereafter. The highest mean scores for dryness (mild) and scaling were observed with both standard overnight and nightly three-hour applications. The intervention most efficacious in reducing dryness and scaling was daily morning application of moisturizer, while every other night application was most efficacious in reducing stinging/burning and worsening of erythema.

Patients should be advised that if any of the perceived side effects are difficult to bear or if any side effects

not discussed in the patient information occur, they should alert the prescribing physician or pharmacist.

Conclusion

Adapalene 0.1%/BPO 2.5% (adapalene/BPO) gel is a novel agent for acne therapy in Canada.

A fixed-dose adapalene and BPO gel combines the two agents advocated by an international acne expert group as a rational standard for treating mild-moderate acne as it offers complementary mechanisms of action. Furthermore, it has been shown to be an efficacious adjunct to oral doxycycline in treatment of severe facial acne. Judicious management by modifying treatment frequency and use of moisturisers can mitigate dryness and cutaneous irritation. This combination may be particularly valuable in enhancing overall improvement with attendant benefits in adherence and patient outcomes.

Dr. Jerry Tan has served as an advisor, consultant, and clinical trialist for Galderma.

References:

1. Gollnick H, Cunliffe W, Berson D, et

Clinical Pearls

For the treatment of mild-moderate acne, the fixed-dose adapalene and BPO gel combination may enhance treatment efficacy and adherence through improved ease of use.

Benzoyl peroxide does not induce bacterial resistance.

- al. Management of acne: a report from a Global Alliance to Improve Outcomes in Acne. *J Am Acad Dermatol* 2003;49(1 Suppl), S1–S37.
2. Thiboutot D, Gollnick H, Bettoli V, et al. New insights into the management of acne: an update from the Global Alliance to Improve Outcomes in Acne group. *J Am Acad Dermatol* 2009;60(5 Suppl):S1–S50.
3. Pariser D. Adapalene 0.1% and benzoyl peroxide 2.5% combination gel for the treatment of acne vulgaris. *Expert Rev Dermatol* 2010;5:385–91.
4. Thiboutot DM, Weiss J, Bucko A, et al. Adapalene-benzoyl peroxide, a fixed-dose combination for the treatment of acne vulgaris: results of a multicenter, randomized double-blind controlled study. *J Am Acad Dermatol* 2007;57:791–99.
5. Gold LS, Tan J, Cruz-Santana A, et al. A North American study of adapalene-benzoyl peroxide combination gel in the treatment of acne. *Cutis* 2009;84:110–16.
6. Gollnick HPM, Draelos Z, Glenn MJ, et al. Adapalene-benzoyl peroxide, a unique fixed-dose combination topical gel for the treatment of acne vulgaris: a transatlantic, randomized, double-blind, controlled study in 1670 patients. *Br J Dermatol* 2009;161:1180–9.
7. Feldman SR, Tan J, Poulin Y, et al. The efficacy of adapalene-benzoyl peroxide combination increases with number of acne lesions. *J Am Acad Dermatol* (accepted for publication Mar 29, 2010).
8. Tan J, Gollnick H, Gold LS, et al. Synergistic efficacy of adapalene 0.1%-benzoyl peroxide 2.5% in the treatment of 3855 acne vulgaris patients. *J Dermatol Treatment* (posted online 28 Jul 2010).
9. Bikowski J. A new approach to comparing efficacy results from clinical trials of topical acne vulgaris treatments. *J Drugs Dermatol* 2007;7:688–92.
10. Zouboulis CC, Fischer TC, Wohlrab J, et al. Study of the efficacy, tolerability, and safety of 2 fixed-dose combination gels in the management of acne vulgaris. *Cutis* 2009;84:223–9.
11. Gold LS, Cruz A, Elchenfield L, et al. Effective and safe combination therapy for severe acne vulgaris: a randomized, vehicle-controlled, double-blind study of adapalene 0.1%-benzoyl peroxide 2.5% fixed-dose combination gel with doxycycline hyclate 100 mg. *Cutis* 2010;85:94–104.
12. Data on file, Galderma, Inc.