A PEER-REVIEWED JOURNAL

The Journal of Clinical and Aesthetic Dermatology

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A PEER-REVIEWED JOURNAL PROVIDING EVIDENCE-BASED INFORMATION TO PRACTICING CLINICIANS

VOL. 5, NO. 5 • MAY 2012

The Tolerability Profile of Clindamycin 1%/ Benzoyl Peroxide 5% Gel vs. Adapalene 0.1%/ Benzoyl Peroxide 2.5% Gel for Facial Acne

Results of Two Randomized, Single-Blind, Split-Face Studies

•

Safety and Effectiveness of a New Blue Light Device for the Self-treatment of Mild-to-moderate Acne

•

Over-the-counter Acne Treatments

A Review

•

Presentation of Reticulate Acropigmentation of Kitamura and Dowling-Degos Disease Overlap

•

A Treatment Protocol for Vascular Occlusion from Particulate Soft Tissue Augmentation

FOR PATIENTS WITH GRADE I OR II ACTINIC KERATOSES OF THE FACE OR SCALP

1 Therapy → 2 Steps → 3 Reasons to use

High Clearance[1*]

Low Down Time[**]

Physician-Controlled Therapy

*At 8 weeks, 77% of patients treated with Levulan PDT experienced 75% clearance of AK lesions vs 23% of the control group. 83% of the patients treated with Levulan PDT had 75% clearance of face lesions and 60% of the patients had 75% clearance of scalp lesions. 66% of patients treated with Levulan PDT experienced 100% clearance of AK lesions vs 13% of the control group. 70% of the patients treated with Levulan PDT had 100% clearance of face lesions and 55% of the patients had 100% clearance of scalp lesions.

Important Risk Information

The Levulan® Kerastick® for Topical Solution plus blue light illumination using the BLU-U® Blue Light Photodynamic Therapy Illuminator is indicated for the treatment of minimally to moderately thick actinic keratoses of the face or scalp.

Contraindicated in patients with cutaneous photosensitivity at wavelengths of 400-450 nm, porphyria, or known allergies to porphyrins, and in patients with known sensitivity to any of the components of the Levulan Kerastick for Topical Solution.

The most common adverse events include scaling/crusting, hypo/hyperpigmentation, itching, stinging and/or burning, erythema and edema. Severe stinging and/or burning at one or more lesions being treated was reported by at least 50% of patients at some time during the treatment.

Following treatment, the treated AKs and to some degree the surrounding skin may redden, and swelling and scaling may also occur. However, these effects are temporary and should completely resolve by 4 weeks after treatment.

**Patients treated with Levulan PDT should avoid exposure of the photosensitized lesions to sunlight or prolonged or intense light for at least 40 hours.

1. Levulan® Kerastick® Prescribing Information, DUSA Pharmaceuticals, Inc.®

Please see safety information on adjacent page.

Levulan® Kerastick®
(aminolevulinic acid HCl)
for Topical Solution, 20%

Levulan® Kerastick®

(aminolevulinic acid HCl) for Topical Solution, 20%

For Topical Use Only • Not for Opthalmic Use

Brief Summary (For full prescribing information, see physician's insert)

INDICATIONS AND USAGE

The LEVULAN KERASTICK for Topical Solution, 20% plus blue light illumination using the BLU-U® Blue Light Photodynamic Therapy Illuminator is indicated for the treatment of minimally to moderately thick actinic keratoses (Grade 1 or 2, see table 2 for definition) of the face or scalp.

CONTRAINDICATIONS

The LEVULAN KERASTICK for Topical Solution, 20% plus blue light illumination using the BLU-U Blue Light Photodynamic Therapy Illuminator is contraindicated in patients with cutaneous photosensitivity at wavelengths of 400-450 nm, porphyria or known allergies to porphyrins, and in patients with known sensitivity to any of the components of the LEVULAN KERASTICK for Topical Solution, 20%.

WARNINGS

The LEVULAN KERASTICK for Topical Solution, 20% contains alcohol and is intended for topical use only. Do not apply to the eyes or to mucous membranes. Excessive irritation may be experienced if this product is applied under occlusion.

PRECAUTIONS

General: During the time period between the application of LEVULAN KERASTICK Topical Solution, 20% and exposure to activating light from the BLU-U Blue Light Photodynamic Therapy Illuminator, the treatment site will become photosensitive. After LEVULAN KERASTICK Topical Solution, 20% application, patients should avoid exposure of the photosensitive treatment sites to sunlight or bright indoor light (e.g., examination lamps, operating room lamps, tanning beds, or lights at close proximity) during the period prior to blue light treatment. Exposure may result in a stinging and/or burning sensation and may cause erythema and/or edema of the lesions. Before exposure to sunlight, patients should, therefore, protect treated lesions from the sun by wearing a wide-brimmed hat or similar head covering of light-opaque material. Sunscreens will not protect against photosensitivity reactions caused by visible light. It has not been determined if perspiration can spread the LEVULAN KERASTICK Topical Solution, 20% outside the treatment site to eye or surrounding skin.

Application of LEVULAN KERASTICK Topical Solution, 20% to perilesional areas of photodamaged skin of the face or scalp may result in photosensitization. Upon exposure to activating light from the BLU-U Blue Light Photodynamic Therapy Illuminator, such photosensitized skin may produce a stinging and/or burning sensation and may become erythematous and/or edematous in a manner similar to that of actinic keratoses treated with LEVULAN KERASTICK PDT. Because of the potential for skin to become photosensitized, the LEVULAN KERASTICK Topical Solution, 20% should be used by a qualified health professional to apply drug only to actinic keratoses and not perilesional skin.

The LEVULAN KERASTICK for Topical Solution, 20% has not been tested on patients with inherited or acquired coagulation defects.

Information for Patients:

LEVULAN KERASTICK Photodynamic Therapy for Actinic Keratoses. The first step in LEVULAN KERASTICK photodynamic therapy (PDT) for actinic keratoses is application of the LEVULAN KERASTICK Topical Solution, 20% to actinic keratoses located on the patient's face or scalp. After LEVULAN KERASTICK Topical Solution, 20% is applied to the actinic keratoses in the doctor's office, the patient will be told to return the next day. During this time the actinic keratoses will become sensitive to light (photosensitive). Care should be taken to keep the treated actinic keratoses dry and out of bright light. After LEVULAN KERASTICK Topical Solution, 20% is applied, it is important for the patient to wear light-protective clothing, such as a wide-brimmed hat, when exposed to sunlight or sources of light. Fourteen to eighteen hours after application of LEVULAN KERASTICK Topical Solution, 20% the patient will return to the doctor's office to receive blue light treatment, which is the second and final step in the treatment. Prior to blue light treatment, the actinic keratoses will be rinsed with tap water. The patient will be given goggles to wear as eye protection during the blue light treatment. The blue light is of low intensity and will not heat the skin. However, during the light treatment, which lasts for approximately 17 minutes, the patient will experience sensations of tingling, stinging, prickling or burning of the treated lesions. These feelings of discomfort should improve at the end of the light treatment. Following treatment, the actinic keratoses and, to some degree, the surrounding skin, will redden, and swelling and scaling may also occur. However, these lesion changes are temporary and should completely resolve by 4 weeks after treatment.

Photosensitivity

After LEVULAN KERASTICK Topical Solution, 20% is applied to the actinic keratoses in the doctor's office, the patient should avoid exposure of the photosensitive actinic keratoses to sunlight or bright indoor light (e.g., from examination lamps, operating room lamps, tanning beds, or lights at close proximity) during the period prior to blue light treatment. If the patient feels stinging and/or burning on the actinic keratoses, exposure to light should be reduced. Before going into sunlight, the patient should protect treated lesions from the sun by wearing a wide-brimmed hat or similar head covering of light-opaque material. Sunscreens will not protect the patient against photosensitivity reactions.

If for any reason the patient cannot return for blue light treatment during the prescribed period after application of LEVULAN KERASTICK Topical Solution, 20% (14 to 18 hours), the patient should call the doctor. The patient should also continue to avoid exposure of the photosensitized lesions to sunlight or prolonged or intense light for at least 40 hours. If stinging and/or burning is noted, exposure to light should be reduced.

Drug Interactions: There have been no formal studies of the interaction of LEVULAN KERASTICK Topical Solution, 20% with any other drugs, and no drug-specific interactions were noted during any of the controlled clinical trials. It is, however, possible that concomitant use of other known photosensitizing agents such as griseofulvin, thiazide diuretics, sulfonylureas, phenothiazines, sulfonamides and tetracyclines might increase the photosensitivity reaction of actinic keratoses treated with the LEVULAN KERASTICK Topical Solution, 20%.

Carcinogenesis, Mutagenesis, Impairment to Fertility: No carcinogenicity testing has been carried out using ALA HCl. No evidence of mutagenic effects was seen in four studies conducted with ALA HCl to evaluate this potential. In the *Salmonella-Escherichia coli*/mammalian microsome reverse mutation assay (Ames mutagenicity assay), no increases in the number of revertants were observed with any of the tester strains. In the *Salmonella-Escherichia coli*/mammalian microsome reverse mutation assay in the presence of solar light radiation (Ames mutagenicity assay with light), ALA HCl did not cause an increase in the number of revertants per plate of any of the tester strains in the presence or absence of simulated solar light. In the L5178Y TK± mouse lymphoma forward mutation assay, ALA HCl was evaluated as negative with and without metabolic activation under the study conditions. PpIX formation was not demonstrated in any of these in vitro studies. In the in vivo mouse micronucleus assay, ALA HCl was considered negative under the study exposure conditions. In contrast, at least one report in the literature has noted genotoxic effects in cultured rat hepatocytes after ALA HCl exposure with PpIX formation. Other studies have documented oxidative DNA damage in vivo and in vitro as a result of ALA exposure.

No assessment of effects of ALA HCl on fertility has been performed in laboratory animals. It is unknown what effects systemic exposure to ALA HCl might have on fertility or reproductive function.

Pregnancy Category C: Animal reproduction studies have not been conducted with ALA HCl. It is also not known whether LEVULAN KERASTICK Topical Solution, 20% can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. LEVULAN KERASTICK Topical Solution, 20% should be given to a pregnant woman only if clearly needed.

Nursing Mothers: The levels of ALA or its metabolites in the milk of subjects treated with LEVULAN KERASTICK Topical Solution, 20% have not been measured. Because many drugs are excreted in human milk, caution should be exercised when LEVULAN KERASTICK Topical Solution, 20% is administered to a nursing woman.

ADVERSE REACTIONS

In Phase 3 studies, no non-cutaneous adverse events were found to be consistently associated with LEVULAN KERASTICK Topical Solution, 20% application followed by blue light exposure.

Photodynamic Therapy Response: The constellation of transient local symptoms of stinging and/or burning, itching, erythema and edema as a result of LEVULAN KERASTICK Topical Solution, 20% plus BLU-U treatment was observed in all clinical studies of LEVULAN KERASTICK Topical Solution, 20% Photodynamic Therapy for actinic keratoses treatment. Stinging and/or burning subsided between 1 minute and 24 hours after the BLU-U Blue Light Photodynamic Therapy Illuminator was turned off, and appeared qualitatively similar to that perceived by patients with erythropoietic protoporphyria upon exposure to sunlight. There was no clear drug dose or light dose dependent change in the incidence or severity of stinging and/or burning.

In two Phase 3 trials, the sensation of stinging and/or burning appeared to reach a plateau at 6 minutes into the treatment. Severe stinging and/or burning at one or more lesions being treated was reported by at least 50% of the patients at some time during treatment. The majority of patients reported that all lesions treated exhibited at least slight stinging and/or burning. Less than 3% of patients discontinued light treatment due to stinging and/or burning.

The most common changes in lesion appearance after LEVULAN KERASTICK Topical Solution, 20% Photodynamic Therapy were erythema and edema. In 99% of active treatment patients, some or all lesions were erythematous shortly after treatment, while in 79% of vehicle treatment patients, some or all lesions were erythematous. In 35% of active treatment patients, some or all lesions were edematous, while no vehicle-treated patients had edematous lesions. Both erythema and edema resolved to baseline or improved by 4 weeks after therapy. LEVULAN KERASTICK Topical Solution, 20% application to photodamaged perilesional skin resulted in photosensitization of photodamaged skin and in a photodynamic response. (see Precautions).

Other Localized Cutaneous Adverse Experiences: Table 5 depicts the incidence and severity of cutaneous adverse events, stratified by anatomic site treated.

Adverse Experiences Reported by Body System: In the Phase 3 studies, 7 patients experienced a serious adverse event. All were deemed remotely or not related to treatment. No clinically significant patterns of clinical laboratory changes were observed for standard serum chemical or hematologic parameters in any of the controlled clinical trials.

TABLE 1 Post-PDT Cutaneous Adverse Events - ALA-018/019

	FACE				SCALP			
	LEVULAN (n=139)		Vehicle (n=41)		LEVULAN (n=42)		Vehicle (n=21)	
Degree of Severity	Mild/ Moderate	Severe	Mild/ Moderate	Severe	Mild/ Moderate	Severe	Mild/ Moderate	Severe
Scaling/ Crusting	71%	1%	12%	0%	64%	2%	19%	0%
Pain	1%	0%	0%	0%	0%	0%	0%	0%
Tenderness	1%	0%	0%	0%	2%	0%	0%	0%
Itching	25%	1%	7%	0%	14%	7%	19%	0%
Edema	1%	0%	0%	0%	0%	0%	0%	0%
Ulceration	4%	0%	0%	0%	2%	0%	0%	0%
Bleeding/ Hemorrhage	4%	0%	0%	0%	2%	0%	0%	0%
Hypo/hyper-pigmentation	22%		20%		36%		33%	
Vesiculation	4%	0%	0%	0%	5%	0%	0%	0%
Pustules	4%	0%	0%	0%	0%	0%	0%	0%
Oozing	1%	0%	0%	0%	0%	0%	0%	0%
Dysesthesia	2%	0%	0%	0%	0%	0%	0%	0%
Scabbing	2%	1%	0%	0%	0%	0%	0%	0%
Erosion	14%	1%	0%	0%	2%	0%	0%	0%
Excoriation	1%	0%	0%	0%	0%	0%	0%	0%
Wheal/Flare	7%	1%	0%	0%	2%	0%	0%	0%
Skin disorder NOS	5%	0%	0%	0%	12%	0%	5%	0

OVERDOSAGE

LEVULAN KERASTICK Topical Solution Overdose: LEVULAN KERASTICK Topical Solution, 20% overdose have not been reported. In the unlikely event that the drug is ingested, monitoring and supportive care are recommended. The patient should be advised to avoid incidental exposure to intense light sources for at least 40 hours. The consequences of exceeding the recommended topical dosage are unknown.

BLU-U Light Overdose: There is no information on overdose of blue light from the BLU-U Blue Light Photodynamic Therapy Illuminator following LEVULAN KERASTICK Topical Solution, 20% application.

HOW SUPPLIED

The LEVULAN KERASTICK for Topical Solution, 20%, is a single-unit dosage form, supplied in packs of 6. Each LEVULAN KERASTICK for Topical Solution, 20% applicator consists of a plastic tube containing two sealed glass ampoules and an applicator tip. One ampoule contains 1.5 mL of solution vehicle. The other ampoule contains 354 mg of aminolevulinic acid HCl. The applicator is covered with a protective cardboard sleeve and cap.

Product Package	NDC number
Individual LEVULAN KERASTICK for Topical Solution, 20%	67308-101-01
Carton of 6 LEVULAN KERASTICKS for Topical Solution, 20%	67308-101-06

Storage Conditions: Store between 20° - 25 °C (68° - 77 °F); excursions permitted to 15°- 30 °C (59° - 86 °F) [See USP Controlled Room Temperature].The LEVULAN KERASTICK for Topical Solution, 20% should be used immediately following preparation (dissolution). Solution application must be completed within 2 hours of preparation. An applicator that has been prepared must be discarded 2 hours after mixing (dissolving) and a new LEVULAN KERASTICK for Topical Solution, 20% used, if needed.

US Patents: 5,079,262 5,211,938 5,422,093, 5,954,703, 6,710,666Manufactured for: DUSA Pharmaceuticals, Inc.® 25 Upton Drive, Wilmington, MA 01887

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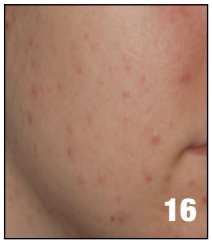

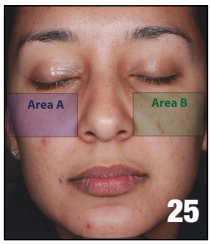

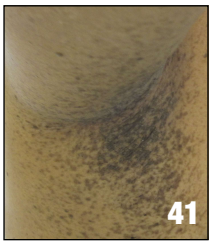

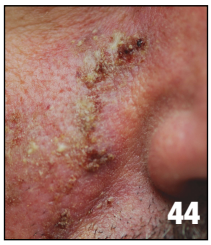

EDITORIAL MESSAGE

May Highlights

James Q. Del Rosso, DO, FAOCD
Editor-in-Chief, Clinical Dermatology
The Journal of Clinical and Aesthetic Dermatology

Wm. Philip Werschler, MD, FAAD, FAACS
Editor-in-Chief, Aesthetic Dermatology
The Journal of Clinical and Aesthetic Dermatology

Dear Colleagues:

Welcome to the May 2012 issue of *The Journal of Clinical and Aesthetic Dermatology.* This month, we lead with an original research article entitled, "The Tolerability Profile of Clindamycin 1%/Benzoyl Peroxide 5% Gel vs. Adapalene 0.1%/Benzoyl Peroxide 2.5% Gel for Facial Acne: Results of Two Randomized, Single-Blind, Split-Face Studies," by Green et al. The objective of the study was to compare the first two weeks of tolerability of clindamycin/benzoyl peroxide (C/BPO) gel versus adapalene/benzoyl peroxide (A/BPO) gel followed by six weeks of open-label C/BPO gel therapy in subjects with mild-to-moderate acne who participated in two eight-week, identically designed, clinical studies. The study found that C/BPO gel had better tolerability with regard to erythema, dryness, and peeling than A/BPO gel during the first two weeks of treatment.

Next, we present, "Safety and Effectiveness of a New Blue Light Device for the Self-Treatment of Mild-to-Moderate Acne," by Wheeland and Koreck. The purpose of this study was to assess the safety and effectiveness of treating acne for eight weeks using a new blue light device at a dose of ~2J/cm^2/day (representing typical full-face treatment) or ~29J/cm^2/day (representing the typical dose after localized spot treatment of acne). The authors found that the blue light treatment is effective and well tolerated and offers rapid, gentle, and convenient treatment of inflammatory acne. It also offers a valuable alternative to other therapies and can be used adjunctively to complement other therapies.

In the literature review entitled, "Over-The-Counter Acne Treatments: A Review," by Decker and Graber, the authors review the acne therapies available over the counter, as use of these treatments is a mainstay in our society and it is important that dermatologists are knowledgeable about the different options, including potential benefits and limitations. The authors assert that many over-the-counter products are not well supported by clinical studies, with a conspicuous absence of double-blind or investigator-blind, randomized, vehicle-controlled studies and that these types of studies that provide clinically relevant data that support the recommendation of over-the-counter products are needed.

In the case report, "Presentation of Reticulate Acropigmentation of Kitamura and Dowling-Degos Disease Overlap," Tang et al, present the interesting case of a 57-year-old woman with two rare genodermatoses. The authors assert that when encountering reticulated hyperpigmentation disorders, it is important to recognize the distress they may impart on the patient. Unfortunately, these disorders are difficult to manage due to limited therapeutic options.

Finally, we present the case series entitled, "A Treatment Protocol for Vascular Occlusion from Particulate Soft Tissue Augmentation," by Beer et al. In this article, the authors present two cases of vascular occlusion with particulate fillers and suggest a protocol of optimal treatments for this type of adverse event.

If you have any comments regarding any of these articles, please contact us. We would appreciate hearing from you. ●

The Journal of Clinical and Aesthetic Dermatology

INFORMATION FOR AUTHORS

Submission requirements for *The Journal of Clinical and Aesthetic Dermatology* are in accordance with the International Committee of Medical Journal Editors (ICMJE). See "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" at www.icmje.org.

EDITORIAL PURPOSE

The mission of *The Journal of Clinical and Aesthetic Dermatology (JCAD)* is to provide dermatologists with up-to-date, evidence-based information on the latest treatment options, new techniques, and practice management issues; thus, helping them improve their daily practice. *JCAD* is a peer-reviewed medical journal that publishes original research and practical information on a broad range of pertinent topics relating to both clinical and aesthetic dermatology.

SCOPE OF MANUSCRIPTS

Manuscripts that meet our editorial purpose include but are not limited to: (1) reports of preclinical and clinical research studies that expand existing knowledge; (2) case studies and reports that stimulate research and the exchange of information; (3) in-depth reviews of clinical practice, management, reimbursement, education, ethics, and legal issues; (4) reviews and reports of contemporary topics in dermatology and dermatology practice that may affect the delivery, reimbursement, or practice of dermatologic care.

Original Research. Reports of investigations that address questions about clinical care or expand existing knowledge. References and illustrative material are recommended. Must include abstract. Recommended length: up to 6000 words, not including references.

Review Articles. Comprehensive articles summarizing basic strategies to facilitate the dermatologist's approach to diagnosis and treatment and articles highlighting emerging diagnostic and therapeutic modalities. May also include in-depth reviews of clinical practice, management, reimbursement, educational, ethical, and legal issues. At least 25 current references are recommended. Illustrative material is preferred. Must include abstract. Recommended length: up to 6000 words, not including references.

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Brief Reports. Short reports of original studies or evaluations or unique, first-time reports of clinical case series. Must include abstract. Recommended length: 1000 to 1500 words (not including references).

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3. Heller T. Promoting healthy aging and community inclusion of adults with developmental disabilities. Presented at: The National Association for the Dually Diagnosed; October 24, 2003; Chicago.

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A quick look at the noteworthy articles in dermatology research May 2012

By Angela Hayes and Laura Alexander

CLINDAMYCIN 1%/BENZOYL PEROXIDE 5% GEL VS. ADAPALENE 0.1%/BENZOYL PEROXIDE 2.5% GEL FOR FACIAL ACNE

Study of the efficacy, tolerability, and safety of two fixed-dose combination gels in the management of acne vulgaris.
Zouboulis CC, Fischer TC, Wohlrab J, Barnard J, Alió AB. *Cutis.* 2009;84(4):223–229.
Synopsis: This study investigated the efficacy, tolerability, and safety of two fixed-dose combination gels for the treatment of facial acne: clindamycin 1%/benzoyl peroxide 5% gel with hydrating excipients (C/BPO HE) and adapalene 0.1%/benzoyl peroxide 25% gel (A/BPO). The authors concluded that C/BPO HE and A/BPO have similar efficacy in treating inflammatory and noninflammatory acne lesions, but C/BPO HE achieves better overall treatment success in less time coupled with a significantly better tolerability profile and notably better safety profile.
PMID: 19911678

Prospective, open-label, comparative study of clindamycin 1%/benzoyl peroxide 5% gel with adapalene 0.1% gel in Asian acne patients: efficacy and tolerability.
Ko HC, Song M, Seo SH, et al. *J Eur Acad Dermatol Venereol.* 2009;23(3):245–250.
Synopsis: The researchers conducted a 12-week prospective, randomized, open-label study to compare the efficacy and tolerability of combination clindamycin phosphate 1% with benzoyl peroxide 5% (CDP/BPO) CDP/BPO in comparison with adapalene 0.1% (ADA) in Asian patients with mild-to-moderate acne vulgaris. A total of 69 patients, including 31 patients for CDP/BPO group and 38 for ADA group, with mild-to-moderate acne vulgaris were enrolled. The researchers concluded that combination formulation of CDP/BPO and ADA were shown to be both effective in decreasing total, inflammatory, and noninflammatory lesion counts along with well tolerability in Asian patients with mild-to-moderate acne vulgaris.
PMID: 19438817

A randomized, single-blind comparison of topical clindamycin + benzoyl peroxide and adapalene in the treatment of mild to moderate facial acne vulgaris.
Langner A, Chu A, Goulden V, Ambroziak M. *Br J Dermatol.* 2008;158(1):122–129. Epub 2007 Nov 28. Comment in: *Br J Dermatol.* 2008;159(2):480–481.
Synopsis: In this article, the authors conducted an assessor-blind, randomized study to compare the clinical effectiveness of two treatments for facial acne: 1) a ready-mixed once-daily gel containing clindamycin phosphate 10mg/mL(-1)/benzoyl peroxide 50mg/mL(-1) (CDP plus BPO) and 2) a once-daily gel containing adapalene (ADA) 0.1%. CDP plus BPO showed an earlier onset of action with a faster significant reduction in inflammatory and total lesion counts than ADA. A between-group comparison of the percentage change from baseline showed that CDP plus BPO was statistically significantly superior to ADA from Week 1 onward both for inflammatory lesions ($P \leq 0.001$) and for total lesions ($P \leq 0.004$). The authors concluded that CDP plus BPO and ADA are both effective treatments for acne, but CDP plus BPO has a significantly earlier onset of action, is significantly more effective against inflamed and total lesions and is better tolerated, which should improve patient compliance.
PMID: 18047518

BLUE LIGHT DEVICE FOR THE SELF-TREATMENT OF MILD-TO-MODERATE ACNE

Clinical efficacy of home-use blue-light therapy for mild-to-moderate acne.
Gold MH, Sensing W, Biron JA. *J Cosmet Laser Ther.* 2011;13(6):308–314.

Synopsis: The authors conducted an institutional review board (IRB)-approved, randomized, self-control study to evaluate the efficacy of a home use, blue-light, light-emitting diode (LED) application in improving lesions and shortening their time to clearance. For each patient (n=30), two similar lesions, one on each side of the face, were chosen for treatment with either a blue-light LED hand-held or sham device. Treatments (n=4) were conducted twice daily in the clinic and lesions were followed up until resolution. Both the physician and the patients evaluated reduction in blemish size and erythema and the overall improvement. Time to lesion resolution was recorded. There was a significant difference in the response of lesions to the blue-light LED application as opposed to the placebo in terms of reduction in lesion size and lesion erythema as well as the improvement in the overall skin condition (p<0.025). The authors concluded that the results support the effectiveness of using blue-light LED therapy on a daily basis for better improvement and faster resolution of inflammatory acne lesions.
PMID: 22091799

Evaluation of self-treatment of mild-to-moderate facial acne with a blue light treatment system.
Wheeland RG, Dhawan S. *J Drugs Dermatol.* 2011;10(6):596–602.
Synopsis: This study evaluated the efficacy and tolerability of treating mild-to-moderate facial acne using a new, hand-held, light-emitting diode blue light device in conjunction with a foam cleanser containing 5% glycolic acid and 2% salicylic acid plus a skin rebuilding serum containing 1.25% salicylic acid, 0.5% niacinamide, 0.08% liposomal-based azelaic acid and superoxide dismutase. Volunteers with mild-to-

moderate facial inflammatory acne used the blue light device twice daily for eight weeks, plus the cleanser before treatments and the serum after each evening treatment. Among 33 subjects aged 25 to 45 years old, 28 completed the study. In a 3x5cm target area receiving a daily dose of approximately 29 J/cm^2, treatment was associated with significant reductions from Baseline in the inflammatory lesion count from Week 1 onward ($P \leq 0.01$) and in the noninflammatory lesion count from Week 4 onward ($P \leq 0.05$). The number of flares was significantly reduced from Baseline from Week 2 onward ($P \leq 0.05$), and flare severity and flare redness were significantly reduced from Baseline from Week 4 onward ($P \leq 0.01$ and $P \leq 0.05$, respectively). At Week 8, more than 90 percent of subjects reported improvements in their skin's overall appearance, clarity, radiance, tone, texture, and smoothness. In addition, 82 percent were satisfied, very satisfied, or extremely satisfied with the blue light treatment system and 86 percent agreed the treatment system was much gentler than traditional acne treatments. The researchers concluded that the blue light treatment system offers effective, rapid, convenient, and well-tolerated treatment of inflammatory and noninflammatory acne lesions. The blue light treatment system and blue light therapy alone are attractive treatment options for acne vulgaris, both as alternatives to traditional acne treatments and as adjunctive treatments to complement existing therapies.
PMID: 21637900

OVER THE COUNTER ACNE TREATMENTS

Effective over-the-counter acne treatments.
Bowe WP, Shalita AR. *Semin Cutan Med Surg.* 2008;27(3):170–176.
Synopsis: The researchers discuss the large and expanding market for over-the-counter (OTC) medications, many of which,they say, are not only effective but also well tolerated and cosmetically elegant. The authors advise dermatologists to be aware of OTC products as their patients will be acutely aware of them and will have questions. The authors discuss combinations of OTC acne medications in treatment regimens or "kits," which have gained popularity and appear to have increased patient adherence. Quality-of-life outcomes from OTC medication use, in at least one study, have demonstrated good benefit. The most common OTC ingredients include benzoyl peroxide, a potent antibacterial agent, and salicylic acid, a mild comedolytic and antiinflammatory medication. Other, less-common OTC ingredients include sulfur, sodium sulfacetamide, and alpha hydroxy acids. Zinc, vitamin A, tea tree oil, and ayurvedic therapies also are available OTC for acne. The authors concluded that additional and better studies are needed to clarify the benefit of these latter medications.
PMID:18786494

Botanicals in dermatology: an evidence-based review.
Reuter J, Merfort I, Schempp CM. *Am J Clin Dermatol.* 2010;11(4):247–267.
Synopsis: In this article, the authors discuss controlled clinical trials with botanicals in the treatment of acne, inflammatory skin diseases, skin infections, ultraviolet (UV)-induced skin damage, skin cancer, alopecia, vitiligo, and wounds. Experimental research on botanicals was considered to a limited extent when it seemed promising for clinical use in the near future. In acne therapy, Mahonia, tea tree oil, and *Saccharomyces* may have the potential to become standard treatments. *Mahonia, Hypericum, Glycyrrhiza,* and some traditional Chinese medicines appear promising for atopic dermatitis. Some plant-derived substances like dithranol and methoxsalen (8-methoxypsoralen) [in combination with UVA] are already accepted as standard treatments in psoriasis; Mahonia and Capsicum (capsaicin) are the next candidates suggested by present evidence. Oral administration and topical application of antioxidant plant extracts (green and black tea, carotenoids, coffee, and many flavonoids from fruits and vegetables) can protect skin from UV-induced erythema, early aging, and irradiation-induced cancer. Hair loss and vitiligo are also traditional fields of application for botanicals. The authors concluded that according to the number and quality of clinical trials with botanicals, the best evidence exists for the treatment of inflammatory skin diseases, (i.e. atopic dermatitis and psoriasis). However, many more controlled clinical studies are needed to determine the efficacy and risks of plant-derived products in dermatology.
PMID: 20509719

RETICULATE ACROPIGMENTATION OF KITAMURA AND DOWLING-DEGOS DISEASE

Dowling-Degos disease.
Georgescu EF, Stanescu L, Popescu CF, et al. *Rom J Morphol Embryol.* 2010;51(1):181–185.
Synopsis: In this article, the researchers discuss the case of a 35-year-old woman with Dowling-Degos disease (DDD), a rare autosomal dominant inherited pigmentary disorder of the flexures with a reticulate aspect and with presence of prominent comedone-like lesions and pitted scars. The patient presented with flexural hyperpigmentation considerate as acanthosis nigricans. At a close clinical and histopathological examination, the researchers obtained sure data for DDD, with a possible familial history of this disease in her son.
PMID: 20191141

Reticulate acropigmentation of Kitamura: report of a familial case.
Kocatürk E, Kavala M, Zindanci I, et al. *Dermatol Online J.* 2008;14(8):7.
Synopsis: The authors report cases of Reticulate Acropigmentation of Kitamura (RAPK), a condition reported primarily among patients of Asian ethnic groups, in a mother and daughter who were from a non-Asian ethnic group. Patients with RAPK present with angulated, slightly atrophic, hyperpigmented macules that are arranged in a reticulate pattern and are typically found on the dorsal hands and feet. The authors concluded that the condition is inherited in an autosomal dominant fashion and skin changes begin to develop during childhood.
PMID:19061567

Section Editors: Dr. Brian Berman, MD, PhD, is Professor of Dermatology and Internal Medicine at the University of Miami Miller School of Medicine, Miami, Florida. Dr. Paolo Romanelli, MD, is Associate Professor, Department of Dermatology and Cutaneous Surgery at the University of Miami Miller School of Medicine, Miami, Florida. Contributor: Ms. Alexander is a freelance writer and editor who lives in New Orleans, Louisiana.

The Tolerability Profile of Clindamycin 1%/Benzoyl Peroxide 5% Gel vs. Adapalene 0.1%/Benzoyl Peroxide 2.5% Gel for Facial Acne

Results of Two Randomized, Single-Blind, Split-Face Studies

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ABSTRACT

Objective: To compare the first two weeks of tolerability of clindamycin/benzoyl peroxide gel versus adapalene/benzoyl peroxide gel followed by six weeks of open-label clindamycin/benzoyl peroxide gel therapy in subjects with mild-to-moderate acne who participated in two eight-week, identically designed, clinical studies. **Methods:** Using a split-face method, patients received both clindamycin/benzoyl peroxide gel and adapalene/benzoyl peroxide gel once daily for two weeks (allocation to the right or left side of the face was randomized) in an investigator-blinded fashion. Patients then went on to receive a further six weeks of open-label, full-face clindamycin/benzoyl peroxide gel. The primary outcome was to compare signs and symptoms of tolerability during the first two weeks of treatment using an investigator-assessed 4-point rating scale. Secondary endpoints included assessment of acne severity (Investigator Static Global Assessment and lesion counts), quality of life, product acceptability/preference, and patient assessments of tolerability and safety. **Results:** Of the 76 subjects enrolled in the two studies, 72 completed them. Overall both products were well tolerated, but mean scores for erythema, dryness, and peeling were significantly higher with adapalene/benzoyl peroxide gel than with clindamycin/benzoyl peroxide gel at both Weeks 1 and 2 ($p<0.03$). Patients also rated clindamycin/benzoyl peroxide gel significantly more tolerable than adapalene/benzoyl peroxide gel for redness, dryness, burning, itching, and scaling at Weeks 1 and 2 ($p\leq0.0073$). Mean Investigator Static Global Assessment score improved with both products during the first two weeks of treatment and continued to show significant improvement versus baseline when treatment with clindamycin/benzoyl peroxide gel was continued for a further six weeks ($p<0.001$ at Week 8). Lesion counts improved throughout the study with significant reductions from baseline occurring at Weeks 5 and 8 ($p<0.0001$ for both time points for total lesion counts). Clindamycin/benzoyl peroxide gel and adapalene/benzoyl peroxide gel were well tolerated, with most adverse events of mild-to-moderate severity. **Conclusion:** Clindamycin/benzoyl peroxide gel had better tolerability with regard to erythema, dryness, and peeling than adapalene/benzoyl peroxide gel during the first two weeks of treatment. (*J Clin Aesthet Dermatol.* 2012;5(5):16–24.)

Acne is a multifactorial disease with the following four primary pathogenic features: sebum production *Propionibacterium acnes* colonization, altered keratinization, and release of inflammatory mediators.[1] Topical combination therapy can target multiple pathogenic mechanisms and therefore is currently recommended as the standard of care in the treatment of mild-to-moderate acne, particularly in patients with an inflammatory component.[1] The Global Alliance to Improve Outcomes in Acne recommends the combination of a retinoid with an

DISCLOSURE: Dr. Green was paid by Stiefel as an investigator for this study. Dr. Cirigliano and Ms. Gwazdauskas are employees of Stiefel. Dr. Gonzalez serves as a researcher and/or speaker for GSK. These studies were sponsored by Stiefel, a GSK company.
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antimicrobial, preferably the nonantibiotic benzoyl peroxide (BPO), as first-line therapy for mild-to-moderate acne.[1] Topical antibiotics also have a role in acne management, but they should be used in combination with BPO to limit the development of *P. acnes* resistance.[1] Fixed-combination products are reported to be effective, well tolerated, and more convenient for patients than multiple individual agents,[2] and by reducing the number of medications and applications, fixed-combination products may improve patient adherence and treatment outcomes.[2]

A number of fixed-combination topical products are available for the treatment of acne, including clindamycin-BPO combinations and adapalene-BPO combinations. The fixed combination of adapalene and BPO (A/BPO) is a retinoid-antimicrobial combination that has proven to be more effective than monotherapy with either component or placebo.[3] Local irritation, including erythema, peeling, dryness, burning, and itching, is the most common adverse effect of topical retinoids, although the potential for irritation appears to be lower with adapalene than with other retinoids such as tretinoin.[4–6] BPO can also cause local irritation,[7] but combining adapalene and BPO has a comparable safety and tolerability profile relative to adapalene alone.[3,8] The combination of clindamycin and BPO (C/BPO) has been shown to more rapidly reduce the number of total and inflammatory lesions compared with adapalene monotherapy,[9] erythromycin and zinc combination,[10] and A/BPO.[11] C/BPO has a good tolerability profile, minimizes irritation, and does not have the early flare effect characteristic of topical retinoids.[12] Levels of hydrating excipients have been increased in a combination formulation of C/BPO to improve tolerability.[13] Both C/BPO and A/BPO are once-daily formulations, making them convenient for patients to use. In a 12-week comparative study, A/BPO and C/BPO proved to be similarly effective in reducing inflammatory and noninflammatory acne lesions, but C/BPO had a more rapid effect on lesion counts, particularly inflammatory lesions, and was better tolerated.[11]

The authors present pooled data from two similarly designed studies using C/BPO and A/BPO in subjects with acne. A randomized, investigator-blind, split-face design was used to compare the agents during the first two weeks of treatment, followed by six weeks of open-label treatment with C/BPO over the entire face. The primary objective of the study was to compare the tolerability of C/BPO and A/BPO during the first two weeks of treatment in subjects with acne, using a study design that minimized the potential for variation by having patients act as their own control.

PATIENTS AND METHODS

Study design. Two multicenter, eight-week studies were conducted, one in the United States (study 410) and one in Argentina (study 401). The study designs were identical and therefore suitable for pooling, but there were some slight differences in patient inclusion criteria and endpoint analyses. For example, study 401 enrolled subjects aged ≥18 years and included investigator assessments of tolerability while study 410 enrolled subjects aged ≥21 years and included both investigator- and subject-rated assessments of tolerability.

For the first two weeks of the study, a randomized, single-blind, split-face study design was conducted. Subjects applied C/BPO (Duac® or Clindoxyl®, Stiefel, a GSK Company, Research Triangle Park, North Carolina) and A/BPO (Epiduo®, Galderma Laboratories, Fort Worth, Texas) in a bilateral split-face fashion (allocation to the left or right side of the face was randomized). Investigators were blinded during the first two weeks of treatments. For the remaining six weeks, subjects applied C/BPO to the entire face, in an open-label, full-face fashion.

Both studies were approved by their local Institutional Review Boards and Ethics Committees and conducted in accordance with the guidelines of the International Conference on Harmonisation Good Clinical Practice (ICH GCP).

Patients. Subjects were eligible for study entry if they were ≥18 years of age (study 401) or ≥21 years of age (study 410), were in good health, had documented acne vulgaris (15–60 inflammatory and noninflammatory facial lesions excluding nose, nasolabial fold, and upper and lower eyelids), and were willing to avoid all other topical or systemic acne therapies for the duration of the studies. Female subjects who were pregnant, planning to become pregnant, or breastfeeding were excluded, and sexually active female subjects had to be using a medically acceptable form of contraception (oral contraception, injectable or implantable methods, or intrauterine devices); barrier methods were considered acceptable in study 410 but not in study 401.

Hormonal treatments, initiated before entry to the trial, including contraceptives (those containing estrogen, androgens, or anti-androgens), were allowed as long as there was no expected change to the dose or drug or discontinuation during the study. Other exclusion criteria were severe systemic disease or diseases of the facial skin other than acne; presence of facial hair that could interfere with the accurate assessment of acne severity; history or presence of regional enteritis, inflammatory bowel disease or photosensitivity; recent use of topical antibiotics (in the preceding 2 weeks) or systemic antibiotics (in the preceding 4 weeks), topical corticosteroids (in the preceding 4 weeks), systemic retinoids (preceding 6 months), or other topical anti-acne medications (preceding 2 weeks); concomitant use of photosensitizing or neuromuscular blocking agents or medications known to exacerbate acne, including vitamins; current use of facial products that could potentially affect results (e.g., astringents, toners, peels, hair removal wax, cleansers, washes or soaps containing BPO, sulfacetamide sodium or salicylic acid, or moisturizers containing retinol, salicylic, or hydroxyl acids); facial procedure (peel, dermabrasion, or ultraviolet light therapy) within the past four weeks; use of an investigational drug or treatment within the previous four weeks; and/or sharing a household with another study participant. All subjects provided written

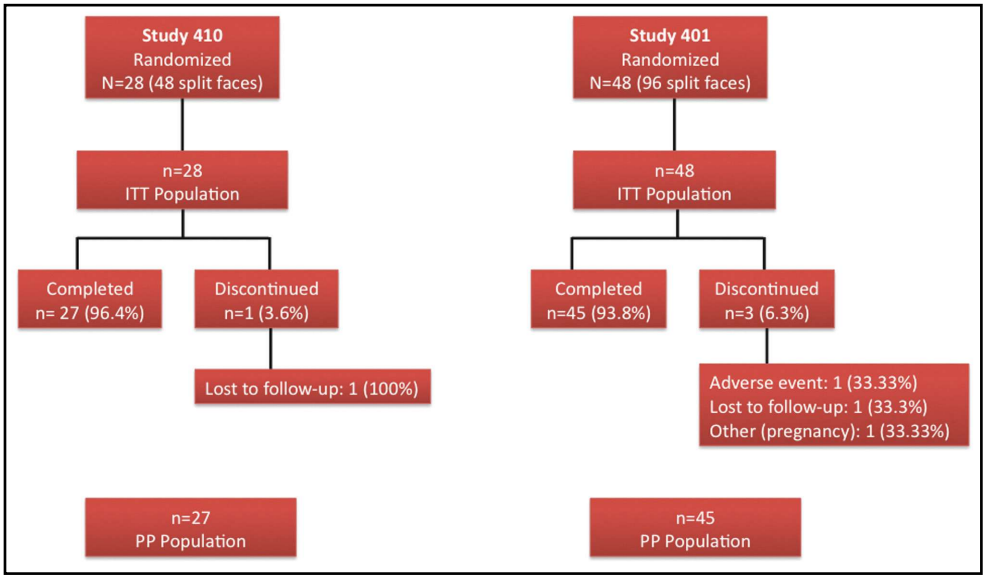


Figure 1. Flow chart of subject disposition in each of the two studies

informed consent before entering the study.

Procedures and study endpoints. Data collected during the baseline study visit included information about patient demographics, medical/medication histories, and lesion counts. A number of assessment procedures were also performed including an Investigator Static Global Assessment (ISGA; face only), SKINDEX-29, local tolerability assessments, and a pregnancy test. Patients were then dispensed one 45g tube of C/BPO and one 45g tube of A/BPO. Subjects were instructed to wash their face in the evening with soap-free cleanser (Physiogel®, Stiefel, a GSK Company, in study 401), rinse thoroughly, and pat dry with soft towel before applying a thin film of each study product to either side of the face (as per the randomization schedule). Each gram of C/BPO gel contained 10mg (1%) clindamycin as clindamcyin phosphate and 50mg (5%) BPO and each gram of A/BPO gel contained 1mg (0.1%) adapalene and 25mg (2.5%) BPO in an aqueous gel.

Subjects were instructed not to wash their skin for at least four hours, and preferably to leave the study product on for eight hours. In the morning, subjects washed their face with the same cleanser and applied moisturizer/sunscreen. This was undertaken daily for two weeks. At the end of Week 2, subjects applied C/BPO to the entire face each evening for the next six weeks and undertook the same procedures for cleansing and moisturizer/sunscreen application as used in the first two weeks.

Following the Baseline visit, subsequent study visits were performed at Weeks 1, 2, 5, and 8. At each visit, subjects returned used product tubes for weighing and provided updated information about concomitant medication, and investigators undertook ISGAs, lesion counts after Week 5 and 8, and tolerability assessments. Adverse events (AEs) were also monitored at each visit.

Diary cards were collected at Weeks 1 and 2 and SKINDEX-29 quality-of-life (QOL) assessments were undertaken at Baseline, Week 2, and Week 8 in study 401 and at Baseline plus Week 8 in study 410. Product acceptability and preference questionnaires were also completed by subjects at Weeks 1, 2, and 8 in both studies.

The primary endpoint for both studies was the investigator assessment of the signs and symptoms of local tolerability (erythema, peeling, and dryness) during the first two weeks of treatment. Investigators measured erythema, peeling, and dryness using a 4-point scale for each where 0=no signs/symptoms and 3=intense signs/symptoms. Secondary endpoints were signs of local tolerability (erythema, peeling, and dryness) at Weeks 5 and 8, ISGA assessments of acne severity using a 6-point scale from 0 (clear) to 5 (very severe), SKINDEX-29 QOL assessments, product acceptability, and preference.

As part of the Product Acceptability and Preference questionnaire, subjects in both studies assessed local tolerability for each product individually as a secondary endpoint. Assessments were undertaken for each side of the face separately at Weeks 1 and 2, using a 6-point scale from 0 (none) to 5 (very severe) to describe any redness, dryness, burning, itching, or scaling.

Safety was determined by recording all AEs that were observed or spontaneously reported throughout the study by subjects, investigators, or designees. The main safety outcomes investigated were the frequency of treatment-emergent events, treatment-related events (all AE reports were reviewed by the investigator to determine causality), events leading to discontinuation, and serious events.

Data analysis and statistical methods. Assuming a standard deviation (SD) of 2 in tolerability scores, it was estimated that 45 subjects per treatment arm (sides of face) would detect a 1.2 difference with 80 percent power using a 2-sided type I error rate of 0.05. Once subjects gave informed consent and were found to have met the inclusion criteria, their treatment was randomly allocated to either side of their face by a computer-generated randomization schedule (generated by the sponsor). To maintain the single blind during the initial two weeks, subjects and study-center staff were instructed not to reveal the treatment allocation to the investigator and subjects were instructed not to apply the product in their presence. Subjects were enrolled and assigned their interventions by a study coordinator, nurse, or pharmacist.

Analysis was undertaken on pooled endpoint data from the intent-to-treat (ITT) populations in the two studies (i.e., all patients who received ≥1 application of study

medication). At Weeks 1 and 2, the individual differences between both sides of the face in terms of investigator and subject tolerability scores, ISGA, and each question of the Product Acceptability and Preference questionnaire were analyzed using the Wilcoxon signed-rank test at an alpha level of 0.05. No adjustments were made for multiplicity. The assumption of the normality was tested using a Shapiro-Wilk test at an alpha of 0.01, and if not verified, a nonparametric method (Wilcoxon signed-rank test) was used. All endpoint data at Weeks 5 and 8 were presented in a descriptive fashion and AE data were analyzed in terms of frequencies and percentages.

RESULTS

Subjects. Seventy-six subjects were enrolled in the two studies: 28 in study 410 and 48 in study 401. Enrollment for the 401 study began in February 2009 and the last subject completed the trial in April 2009. For the 410 study, enrollment began in July 2009 and the study was completed in December 2009. A total of 72 subjects completed the studies and four discontinued (Figure 1). Demographic characteristics were generally similar at Baseline (Table 1). Most subjects (82%) were female and the median age was 26 to 27 years. There was a clear difference between the studies in the ethnic/racial mix. In study 401, all subjects were white and of these, 69 percent were of Hispanic or Latino ethnicity, whereas in study 410, 54 percent of subjects were white (the rest were African American or Asian) with only 11 percent Hispanic or Latino. Subjects in study 410 also tended to have more severe disease compared with subjects in study 401. Approximately 93 percent of subjects in study 410 had moderate-to-severe scores on ISGA compared with 71 percent in study 401. Likewise, mean baseline lesion counts (inflammatory, noninflammatory, and total) were higher in the 410 than the 401 population. The mean (SD) number of days subjects were exposed to treatment was 52.3 (9.2) days in study 401 and 58.4 (4.2) days in study 410.

Local tolerability. During the split-face study, both C/BPO and A/BPO were well tolerated, with low investigator-rated scores for erythema, dryness, and peeling (primary endpoint; Figure 2). However, mean scores for these parameters were significantly higher after application of A/BPO than C/BPO at Weeks 1 and 2 ($p<0.03$ vs. C/BPO; Figure 2). Mean subject ratings for signs and symptoms of local tolerability (redness, dryness, burning, itching, and scaling) were also significantly lower with C/BPO than with A/BPO at Weeks 1 and 2 ($p\leq0.0073$; Figure 3).

The incidence and ratings as assessed by investigators for erythema, dryness, and peeling continued to decline from Week 2 when C/BPO therapy only began, such that at Week 8 mean scores for each of these signs were negligible and, in each case, nearly two thirds or more of patients had no signs present (Table 2). Subject ratings for tolerability parameters also continued to decrease during full-face treatment with C/BPO, such that at Week 8, the mean (SD) score for each parameter was <1, very minimal (Table 3).

Acne severity. Mean ISGA improved for both sides of the face and there was no significant difference between the scores for C/BPO and A/BPO during the split-face portion of the study. Specifically, mean (SD) ISGA scores were 2.42 (0.83) and 2.48 (0.78) for C/BPO and A/BPO, respectively, at Week 1 (p=0.4850), and 2.16 (0.87) and 2.17 (0.86), respectively, at Week 2 (p=1.0). Over the course of the entire study, there was a significant improvement in full-face

TABLE 1. Baseline demographics and disease characteristics

	STUDY 401 (n=48)	STUDY 410 (n=28)
Age, years		
Mean (SD)	27.6 (5.5)	29.6 (9.5)
Median	26	27.6
Range	21.6–45.6	18.6-48.4
Sex, n (%)		
Male	10 (20.8)	4 (14.3)
Female	38 (79.2)	24 (85.7)
Race, n (%)		
White	48 (100)	15 (53.6)
African American	0	11 (39.3)
Asian	0	2 (7.1)
Ethnicity, n (%)		
Hispanic or Latino	33 (68.8)	3 (10.7)
No Hispanic or Latino	15 (31.3)	25 (89.3)
ISGA score, n (%)		
2 – Mild	14 (29.2)	2 (7.1)
3 – Moderate	31 (64.6)	20 (71.4)
4 – Severe	3 (6.3)	6 (21.4)
Lesion count, mean (SD)		
Inflammatory	14.2 (9.1)	21.5 (9.3)
Noninflammatory	24.8 (12.8)	33.0 (24.7)
Total	39.1 (13.0)	54.5 (27.1)

Figures 2A–2E. Visual examples of outcomes following 2 weeks of split-face application.

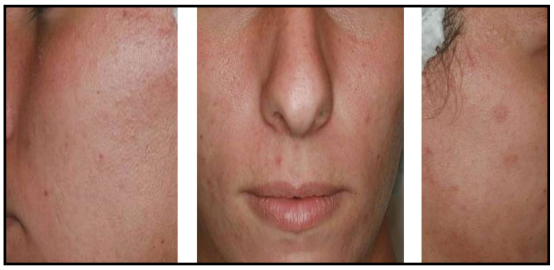


Figure 2A. Left = Epiduo; Right = Duac
Argentina study, Dr. Pablo Gonzalez; TAN 0038–R-V

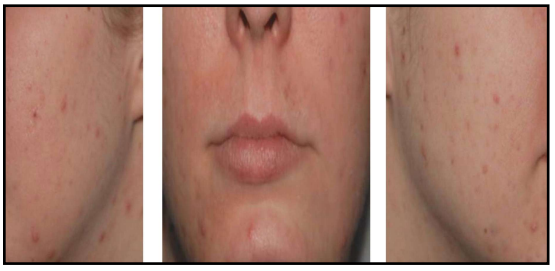


Figure 2B. Left = Epiduo; Right = Duac
United States study

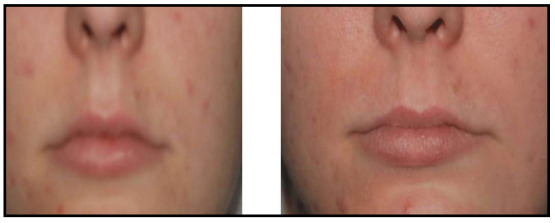


Figure 2C. Left = Baseline—1008 HMP;
Right = Week 3; 1008 HMP; split-face—primary endpoint

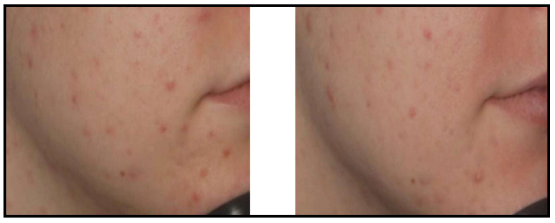


Figure 2D. Left = Baseline—1008 HMP;
Right = Week 3; 1008 HMP; split-face—primary endpoint

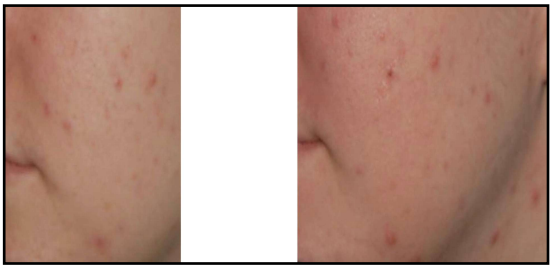


Figure 2E. Left = Baseline—1008 HMP;
Right = Week 3; 1008 HMP; split-face—primary endpoint

ISGA ratings ($p<0.001$) (Figure 4).

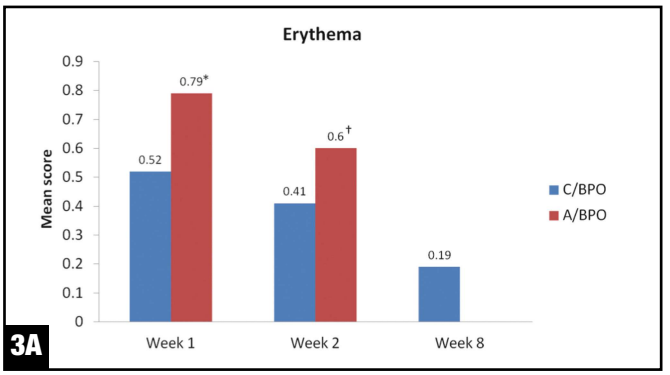
In terms of lesion counts, pooled data showed a significant reduction in the number of inflammatory, noninflammatory, and total lesions at Weeks 5 and 8 compared with baseline ($p<0.0001$; Figure 5). No comparative analysis was undertaken for lesion counts during the split-face phase of the study because baseline lesion counts were undertaken on the full face (not separately for each side) in study 401.

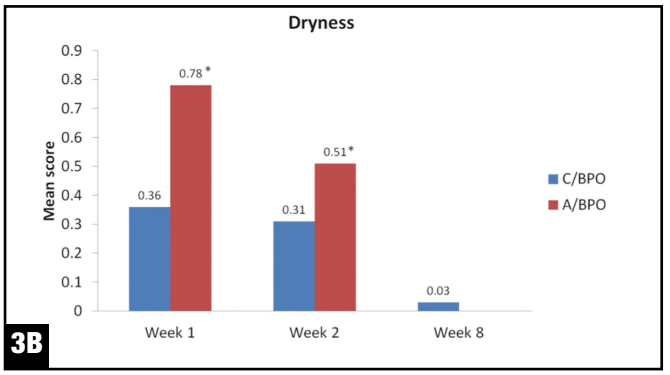
Patient preference and QOL. Patient QOL improved over the course of the study, with reductions in scores for all domains of the Skindex-29 quality-of-life questionnaire, as well as the total score (Figure 6). During the split-face portion of the study, almost all subjects (95–98%) rated C/BPO and A/BPO as "easy" or "very easy" to use, even with make-up, and there were no between-group differences. Similarly, both treatments were rated equally effective at reducing acne breakouts. However, A/BPO had significantly worse scores for skin comfort compared with C/BPO at Week 1 ($p<0.02$) and Week 2 ($p=0.0036$), and more subjects reported being more satisfied with C/BPO than with A/BPO at Week 1 (65.3% vs. 31.9% of patients; 2.8% of patients were equally satisfied with both treatments) and at Week 2 (56.2% vs. 42.5% of patients; 1.4% of patients were equally satisfied with both treatments).

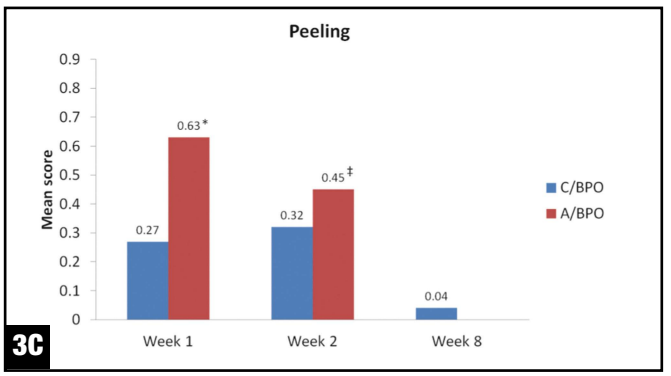
Neither product rated well in terms of leaving the skin moisturized or hydrated with fewer than 50 percent in each group reporting a sensation of hydration at Week 1 or Week 2 (45–46% with C/BPO and 38–40% with A/BPO). At the end of Week 1, 63/76 subjects (88.7%) said they would choose to use C/BPO again and 41/76 (56.9%) said they would use A/BPO again. The corresponding number of subjects responding in this way at the end of Week 2 was 55/76 (76.4%) for C/BPO and 50/76 (68.5%) for A/BPO. At the end of Week 8 (after 6 weeks of full-face treatment with C/BPO), 61/76 subjects (83.6%) said they would choose to use this product again. Overall treatment satisfaction was high; 54/73 subjects (74%) rated being "satisfied" or "very satisfied" with C/BPO and 48/76 (66%) with A/BPO at Week 1. The corresponding rates at Week 2 were 61/74 (82.4%) with C/BPO and 56/74 (76%) with A/BPO. The between-group differences were not significant. After an additional six weeks of full-face C/BPO treatment, 55/73 (75%) of subjects were "satisfied" or "very satisfied."

Compliance with both agents was reported to be high; 93 percent of patients in each group reported they were 80 to 100 percent compliant with treatment during the first week and 89 percent in each group reported the same at Week 2. During the full-face portion of the study, 92 percent of subjects reported that they used C/BPO every day.

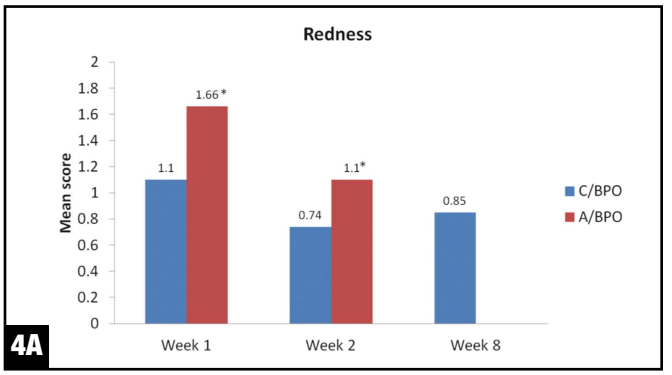
Adverse events. Three subjects in study 410 developed an AE (10.7%). One had diarrhea, one dizziness, and one erythema. None of these was considered treatment related or serious and no subject discontinued treatment because of AEs. In contrast, 41/48 subjects in study 401 (85.4%) developed a treatment-related AE. Almost all of these events (in 40/41 subjects with an AE) occurred during the split-face portion of the study and

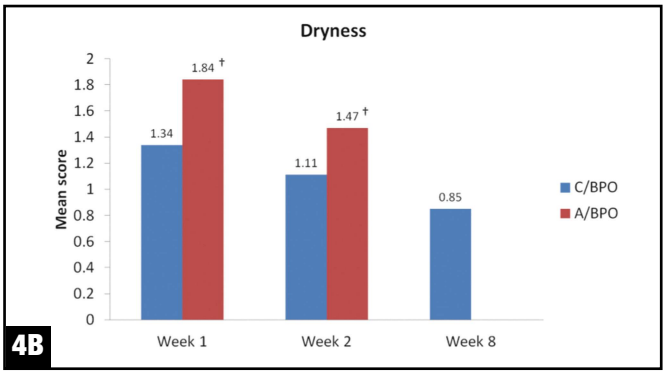


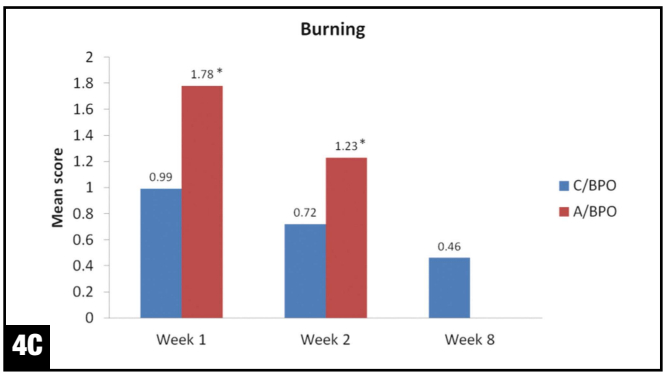


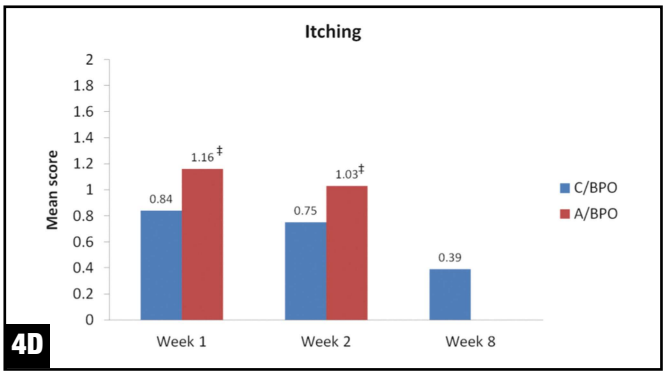


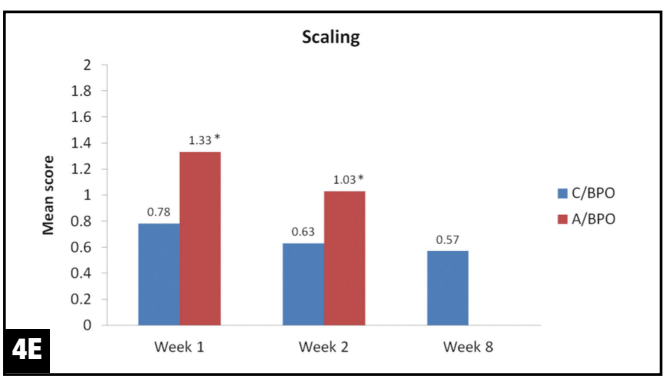
Figures 3A–3C. Mean scores for (A) erythema, (B) dryness, and (C) peeling, as rated by investigators using a 4-point scale at Weeks 1, 2, and 8. *p<0.0001 vs. C/BPO, †p=0.002 vs. C/BPO and ‡p<0.03 vs. C/BPO











Figures 4A–4E. Mean scores for (A) redness, (B) dryness, (C) burning, (D) itching, and (E) scaling as rated by subjects using a 6-point scale at Weeks 1, 2, and 8. *p<0.0001 vs. C/BPO, †$p\leq$0.0006 vs. C/BPO; ‡p<0.0073 vs. C/BPO

TABLE 2. Investigator assessments of C/BPO local tolerability at Weeks 2 and 8

	INVESTIGATOR ASSESSMENTS (n=76) WEEK 2		INVESTIGATOR ASSESSMENTS (n=76) WEEK 8	
	NO. (%) WITH NO SIGN/SYMPTOM PRESENT	MEAN (SD) SCORE ON 4-POINT SCALE*	NO. (%) WITH NO SIGN/SYMPTOM PRESENT	MEAN (SD) SCORE ON 4-POINT SCALE*
Redness	47 (62.7)	0.41 (0.57)	62 (83.8)	0.19 (0.46)
Dryness	54 (72.0)	0.31 (0.52)	73 (98.6)	0.03 (0.23)
Peeling	54 (72.0)	0.32 (0.55)	71 (95.9)	0.04 (0.20)
Irritant/allergic contact dermatitis	73 (97.3)	0.03 (0.16)	74 (100.0)	0.00 (0.00)

*0=none, 1=slight, 2=moderate, and 3=intense

TABLE 3. Subject assessments of C/BPO local tolerability at Weeks 2 and 8

	SUBJECT ASSESSMENTS (n=76) WEEK 2		SUBJECT ASSESSMENTS (n=76) WEEK 8	
	NO. (%) WITH NO SIGN/SYMPTOM PRESENT	MEAN (SD) SCORE ON 6-POINT SCALE*	NO. (%) WITH NO SIGN/SYMPTOM PRESENT	MEAN (SD) SCORE ON 6-POINT SCALE*
Redness	34 (46.6)	0.74 (0.83)	39 (52.7)	0.85 (1.11)
Dryness	24 (33.3)	1.11 (1.01)	37 (50.0)	0.85 (1.06)
Burning	37 (51.4)	0.72 (0.89)	52 (70.3)	0.46 (0.83)
Itching	39 (54.2)	0.75 (0.98)	52 (70.3)	0.39 (0.74)
Scaling	39 (54.2)	0.63 (0.78)	51 (68.9)	0.57 (1.02)

*0=none, 1=very minimal, 2=mild, 3=moderate, 4=severe, and 5=very severe

involved application-site conditions (Table 4). A *post-hoc* analysis indicated that irritation, dryness, and erythema were significantly more common with A/BPO than with C/BPO ($p<0.015$; Table 4). Eleven subjects (22.9%) reported an AE during full-face treatment with C/BPO. Most events were of mild or moderate severity, but three subjects developed serious severe cutaneous AEs and one of these withdrew from the study.

DISCUSSION

These studies have demonstrated that topical C/BPO is better tolerated than A/BPO during the initial two weeks of treatment for acne, with significantly lower overall scores for all investigator- and subject-rated tolerability parameters ($p<0.05$). These data are consistent with a previous randomized study comparing these two agents.[11] Zouboulis et al[11] reported a significantly greater incidence of local reactions

with A/BPO than with C/BPO from Weeks 1 through 12 and that, among patients who experienced tolerability reactions, C/BPO was significantly better tolerated than A/BPO at all grades from Week 1 onward.[11] This was true for both investigator-rated (erythema, dryness, peeling) and participant-rated (pruritus, burning/stinging) outcomes. The study by Zouboulis et al[11] also showed that both treatments effectively reduced inflammatory, noninflammatory, and total lesion counts over the 12-week treatment period. A similarly effective reduction was observed in these three parameters at both five and eight weeks in the current study, although subjects in the current study received two weeks of split-face C/BPO and A/BPO followed by full-face C/BPO, whereas subjects in the study by Zouboulis et al[11] received 12 weeks' treatment with each therapy. It should be noted that the use of A/BPO for just two weeks during the comparative phase of the current study is insufficient to assess this agent's efficacy in treating acne; rather, the study was designed primarily to assess short-term tolerability differences.

Although there was no difference in the overall incidence of AEs occurring with C/BPO or A/BPO use in one of the studies (410), the other (401) showed a significantly higher rate of local AEs with A/BPO than C/BPO, albeit in a *post-hoc* analysis.

In addition to the improvement of local irritation and reduction in acne lesions, the authors' study also demonstrated that continued use of C/BPO was associated with improvements in QOL. Moreover, QOL parameters also improved throughout the studies with subjects reporting improvements in emotional distress and ability to function as well as symptomatic improvement in physical signs and symptoms.

As with most clinical trials, this study is not without limitations. The authors pooled data from two almost identical studies, allowing for a larger study population and greater statistical power. However, this meant there were some slight differences in the study populations and in the way that endpoint data were collected. Nevertheless, the authors believe that these factors are unlikely to have demonstrably impacted the results. Another limitation is that the authors' study was a single-blind analysis, and the fact that patients were not blinded to treatment allocation may have introduced some bias. However, the primary endpoint was the investigator rating of local tolerability, and investigators were blinded to treatment allocation, minimizing the impact of any bias on the primary results. The last limitation is that this study was of eight weeks' duration with only two weeks of direct comparison and therefore no conclusions should be drawn about the comparative efficacy of the two products at 12 weeks where maximal benefit of acne treatment is achieved. The results from this study do not allow statements about therapeutic equivalence or noninferiority of A/BPO and C/BPO to be made as the study was not powered to address such issues. However, the focus of this study was the evaluation of acute tolerability, and since irritation potential is highest during the first two weeks of treatment, the study duration was deemed appropriate.

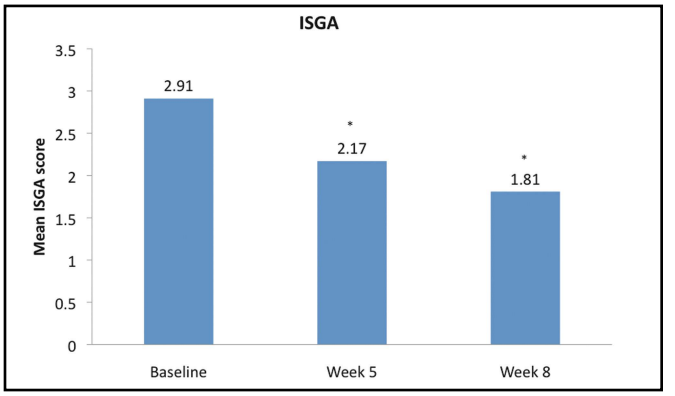


Figure 5. Mean Investigator Static Global Assessment scores at baseline, Week 5 and Week 8. *$p<0.0001$ vs. baseline

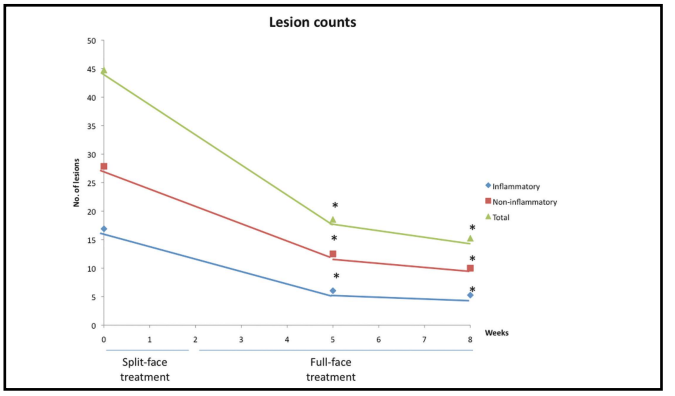


Figure 6. Lesion counts over the course of the 8-week studies. *$p<0.0001$ vs. baseline

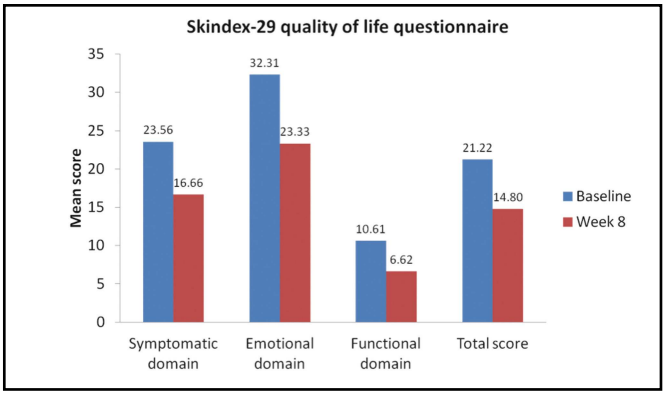


Figure 7. Mean Skindex-29 scores for all patients (n=76) at Baseline and Week 8. A reduction in score reflects improvement in quality of life.

CONCLUSION

In conclusion, C/BPO gel has demonstrated a better tolerability profile than A/BPO during the first two weeks of treatment. Both agents are effective in reducing overall acne severity and achieving high levels of patient satisfaction, and continued use of C/BPO for a further six weeks may be associated with better adherence to therapy, clinical improvement in acne, and QOL.

TABLE 4. Adverse events occurring during the course of the split-face portion (Weeks 1 and 2) of the 401 study

	SUBJECTS WITH AEs, n (%)		*P*-VALUE
	C/BPO (N=48)	A/BPO (N=48)	
Any AE			
	31 (64.6)	40 (83.3)	0.0067
Application site conditions			
Irritation	23 (47.9)	33 (68.8)	0.0124
Erythema	13 (27.1)	19 (39.6)	0.0143
Dryness	10 (20.8)	18 (37.5)	0.0114
Exfoliation	8 (16.7)	10 (20.8)	0.1573
Pruritus	8 (16.7)	10 (20.8)	0.3173
Dermatitis	2 (4.2)	1 (2.1)	0.3173

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Safety and Effectiveness of a New Blue Light Device for the Self-treatment of Mild-to-moderate Acne

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ABSTRACT

Objective: To assess the safety and effectiveness of treating acne for eight weeks using a new blue light device at a dose of ~2J/cm^2/day (representing typical full-face treatment) or ~29J/cm^2/day (representing the typical dose after localized spot treatment of acne). **Design:** Prospective, single-center, open-label study evaluating two levels of blue light in each subject. **Setting:** Subjects were recruited from the local community for self-treatment at home. **Participants:** Thirty-two subjects with mild or moderate facial acne vulgaris. **Measurements:** Inflammatory lesion count; number, severity, and redness of flares; improvement in skin characteristics (overall appearance, clarity, radiance, tone, texture, and smoothness); tolerability; subject satisfaction. **Results:** The blue light treatment was associated with significant reductions from baseline in inflammatory lesion count as early as Week 1 with ~29J/cm^2/day and Week 3 with ~2J/cm^2/day ($P \leq 0.01$). It was also associated with significant reductions in the number, severity, and redness of flares and with improvements in the skin's appearance, clarity, radiance, tone, texture, and smoothness. Overall, 53 percent of subjects considered the treatment much gentler than traditional acne treatments and 61 percent were satisfied. Three adverse events were probably related to treatment—minimal transient skin dryness (2) and minimal transient hyperpigmentation (1). **Conclusion:** The blue light treatment is effective and well tolerated, offering rapid, gentle, and convenient treatment of inflammatory acne. The blue light device offers a valuable alternative to antibiotics and potentially irritating topical treatments and can also be used adjunctively to complement other therapies.

(*J Clin Aesthet Dermatol.* 2012;5(5):25–31.)

A new, handheld, blue light device for the self-treatment of mild-to-moderate inflammatory acne was cleared by the United States Food and Drug Administration (FDA) in January 2010.[1] Blue light is effective in the treatment of inflammatory acne because it results in photoexcitation of porphyrins within *Propionibacterium acnes* and this generates free radicals that are bactericidal to *P. acnes*.[2] Blue light treatment also appears to have anti-inflammatory effects on keratinocytes.[3]

The first blue light-emitting devices for acne therapy required patients to attend their physician's office for treatment once or twice weekly, and compliance suffered as a result. The new handheld device offers both the convenience of self-treatment at home and lower costs than in-office blue light therapy.

A study has been performed to evaluate the safety and effectiveness of using the blue light device—which emits blue light at ~412nm from light-emitting diodes—to self-treat mild-to-moderate inflammatory acne at two different doses in the home setting.

METHODS

Study design. This was a prospective, single-center, open-label study.

Subjects. Subjects were eligible for enrollment into the study if they had mild or moderate facial acne vulgaris, were 13 to 45 years of age, and were generally in good health. Mild-to-moderate facial acne was considered to consist of

DISCLOSURE: Dr. Wheeland has been an investigator for TRIA Beauty, Inc., and Dr. Koreck is a consultant for TRIA Beauty, Inc. This study was supported by TRIA Beauty, Inc., Dublin, California.

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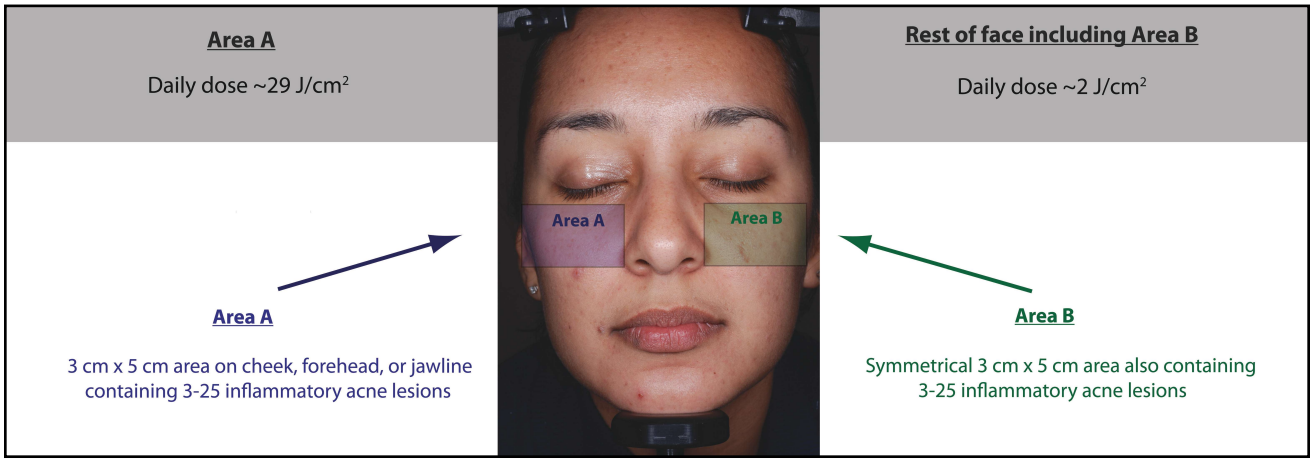

Figure 1. Blue light dosing

small (1–3mm) diffusely scattered inflammatory lesions (papules or pustules) together with noninflammatory lesions and no more than one small (2–4mm) nodular lesion.

They were also required to have one 3cm x 5cm target area on their cheek, forehead, or jawline containing 3 to 25 inflammatory lesions (Area A) and another 3cm x 5cm target area containing 3 to 25 inflammatory lesions located symmetrically on the other side of the face (Area B).

Exclusion criteria included the following: cystic acne; the use of prescription acne medication other than oral contraceptives; known light sensitivity; history of phototoxicity; sensitivity or allergic reaction to over-the-counter topical facial products; need to spend excessive time in the sun; psoriasis, vitiligo, or other conditions affecting the visual appearance of the face; history of herpes simplex virus or cold sores on the treatment area; and pregnancy, nursing, or planning to become pregnant. A washout period of eight weeks was required for previous facial cosmetic procedures (e.g., laser resurfacing, chemical peels, and dermabrasion) and six months for oral isotretinoin.

The protocol (TRIA-AC-030) was approved by the relevant institutional review board and conducted in accordance with the principles of the 2004 version of the Declaration of Helsinki. All subjects were recruited from the local community and signed informed consent (except if they were minors in which case they signed an assent and their parents or guardians signed informed consent).

Treatment regimen. Subjects were instructed to use the blue light device in a sweeping "paint the face" motion, twice daily for eight weeks. Treatment was given at two different doses—the higher dose on Area A and the lower dose on the rest of the face, which included Area B (Figure 1). The higher dose used on Area A (~29J/cm²/day) is representative of the dose that may occur during treatment of a localized outbreak of acne. The lower dose used on the rest of the face (~ 2J/cm²/day) is representative of the typical full-face treatment dose. After these treatments, and during the first two weeks of treatment only, subjects were additionally allowed to spot-treat by dwelling (holding the device) on one or more areas of acne to deliver an additional dose of 12J/cm² to such areas.

Subjects were instructed to cleanse their face before each treatment with an unscented soap or nonirritating facial cleanser provided by the sponsor. They were also instructed to apply a moisturizing noncomedogenic sunscreen with sun protection factor (SPF) 32 provided by the sponsor after each morning treatment as needed (for sun protection and to mitigate potential dryness and/or irritation).

Subjects were required to adopt the specified facial skin care regimen and avoid using any other facial skin care products for the duration of the study. Continued use of noncomedogenic make-up, perfume, and body spray was allowed, but the use of nonstudy facial astringents, cleansers, creams, and lotions was prohibited.

Outcome measures. Subjects were evaluated at Baseline and Weeks 1, 2, 3, 4, 6, and 8. The investigator assessed the inflammatory lesion count in Area A and Area B at all timepoints.

At the Baseline visit only, the subjects evaluated their level of frustration with flares and their level of concern over skin texture and skin tone and radiance (Table 1). At Baseline and/or Weeks 2, 3, 4, 6, and 8, the subjects also evaluated the number, severity, and redness of their flares; the improvement in the frequency and severity of their flares; the improvement in their skin's overall appearance, clarity, radiance, tone, texture, and smoothness; the improvement in their acne relative to their prior skin care regimen; and the speed of improvement in their acne relative to their prior skin care regimen (Table 1).

At all post-baseline timepoints, subjects were also asked to rate their level of agreement or disagreement with the following statements about the blue light treatment and its results: "it clears flares better than any other skin care product I've used," "it prevents flares better than any other skin care product I've used," "it is much gentler than traditional acne treatments," "it leaves my skin looking and feeling healthier than with any other skin product I've used," "my skin looks better than ever," and "my skin looks

TABLE 1. Scales used for evaluations

FRUSTRATION WITH FLARES	CONCERN OVER SKIN TEXTURE, SKIN TONE, AND RADIANCE	NUMBER OF FLARES	SEVERITY OF FLARES	REDNESS OF FLARES	IMPROVEMENT IN FREQUENCY OF FLARES, SEVERITY OF FLARES	IMPROVEMENT IN SKIN'S OVERALL APPEARANCE, CLARITY, RADIANCE, TONE, TEXTURE, AND SMOOTHNESS	IMPROVEMENT IN ACNE RELATIVE TO PRIOR SKIN CARE REGIMEN	SPEED OF IMPROVEMENT IN ACNE RELATIVE TO PRIOR SKIN CARE REGIMEN	SATISFACTION WITH THE BLUE LIGHT TREATMENT
Not frustrated at all	Not concerned at all	A few	Minimal flares	No redness	Dramatic improvement	Dramatic improvement	Significantly better	Significantly faster	Extremely satisfied
Somewhat frustrated	Somewhat concerned	Some	Mild flares	Minimal redness	Significant improvement	Significant improvement	Slightly better	Slightly faster	Very satisfied
Moderately frustrated	Moderately concerned	Quite a few	Moderate flares	Mild redness	Moderate improvement	Moderate improvement	As well as	As fast as	Satisfied
Very frustrated	Very concerned	Large number	Severe flares	Moderate redness	Slight improvement	Slight improvement	Worse than	Slower than	Slightly satisfied
—	—	—	—	Severe redness	No improvement	No improvement	—	—	Not satisfied

so much better that I reduced the amount of makeup I wear." Each of these was evaluated as strongly agree, moderately agree, neither agree or disagree, moderately disagree, or strongly disagree. Subjects also reported their level of satisfaction with the acne treatment at all post-baseline timepoints (Table 1).

Statistical analysis. Determinations of sample size were not based on a power analysis approach. Instead, using the results from previous clinical studies, the sample size was selected based on what was thought to be sufficient to demonstrate a statistically significant reduction in inflammatory lesion count in Area B at Week 8 relative to baseline.

All 32 subjects who enrolled and received at least one treatment with the blue light device were included in the intent-to-treat and safety analyses. A p value of <0.05 was considered statistically significant and p values were not adjusted for multiplicity. Within-group differences in lesion count reduction were evaluated using a paired t-test or Wilcoxon signed rank test. Changes from baseline in the number, severity, and redness of flares were analyzed using a Wilcoxon signed rank test.

RESULTS

Subjects. Of 32 subjects enrolled, 31 (97%) completed and one discontinued for nonstudy-related reasons. The majority of subjects were female (66%), of Fitzpatrick skin type III (44%) or IV (25%), and Caucasian (65% Caucasian, 7% Hispanic/Latino, 3% black/African descent, 26% other). Their mean age was 22 (±SD of 6.7) years. Areas A and B were located on the forehead in 47 percent of subjects, on the jawline in 28 percent of subjects, and on the cheek in 25 percent of subjects.

At Baseline, subjects had a median of five inflammatory lesions in each of Areas A and B. Overall, 97 percent of subjects were frustrated with acne flares—38 percent were very frustrated, 31 percent were moderately frustrated, and 28 percent were somewhat frustrated. In addition, 72 percent were concerned about their skin texture (22% very concerned, 34% moderately concerned, and 16% somewhat concerned) and 75 percent were concerned about the tone and radiance of their skin (25% very concerned, 22% moderately concerned, and 28% somewhat concerned). Other anti-acne treatments that subjects had tried previously were topical over-the-counter products (78% of subjects),

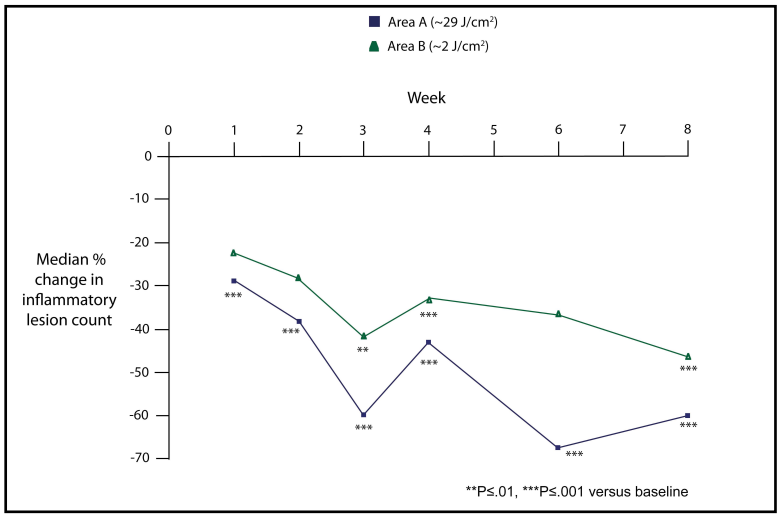

Figure 2. Reduction in inflammatory lesion count. Reproduced with permission from Wheeland RG, Dhawan S. Evaluation of self-treatment of mild-to-moderate facial acne with a blue light treatment system. *J Drugs Dermatol.* 2011;10:596–602

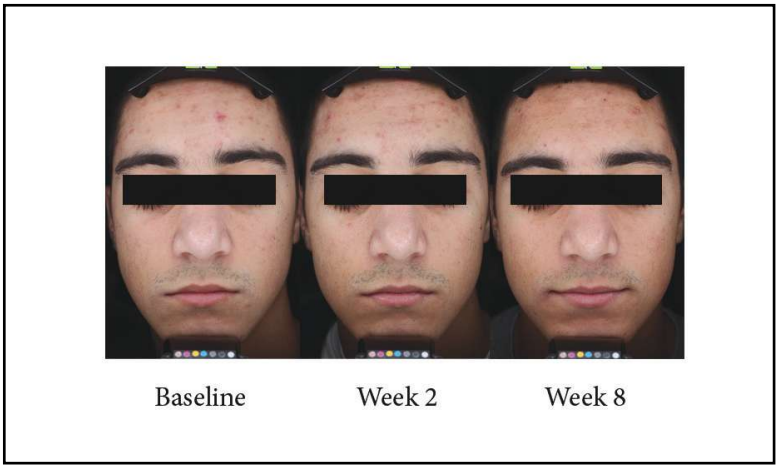

Figure 3. Clinical improvement after treatment with the blue light device. Area A was on the upper middle right forehead and received ~29J/cm²/day from the blue light device. The rest of the face received ~2J/cm²/day.

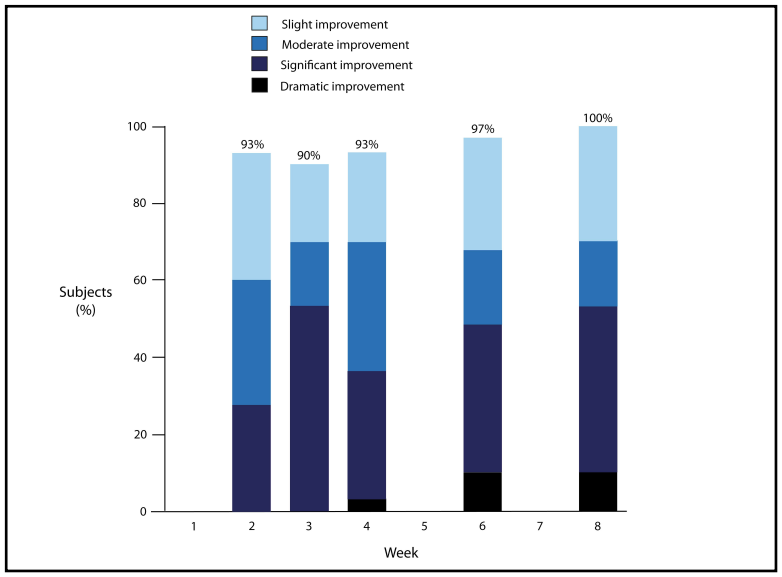

Figure 4. Proportion of subjects reporting improvement in severity of flares

topical prescription products (22%), oral medications (19%), oral contraceptives (6%), microdermabrasion (3%), and other (13%). The first subject started the study on May 26, 2009, and the last subject exited the study on August 26, 2009.

Investigator evaluations. The blue light treatment was associated with significant ($P \leq 0.01$) percentage reductions from baseline in inflammatory lesion count as early as Week 1 in Area A and Week 3 in Area B (Figure 2). The median reductions in inflammatory lesion count at Weeks 1, 4, and 8 were 29, 43, and 60 percent, respectively, in Area A, and 23, 33, and 46 percent, respectively, in Area B. Photographic documentation is shown in Figure 3.

Subject evaluations. Overall, 100 percent of subjects reported improvement in the frequency and severity (Figure 4) of their flares at Week 8 compared with baseline. The median number of flares declined from "some to quite a few" to "a few," the median severity declined from moderate to minimal, and the median redness declined from mild to minimal. The number of flares was significantly ($P \leq 0.05$) reduced from baseline from Week 3 onward, and the severity and redness of flares were significantly reduced from baseline from Week 4 onward. Also at Week 8, 53 percent of subjects agreed that the blue light treatment both cleared and prevented their flares better than any other skin care products they had used.

At Week 8, 100 percent of subjects considered their overall appearance was improved (Figure 5). High rates of improvements were also reported for clarity (97%), radiance (73%), tone (80%), texture (80%), and smoothness (83%) (Figure 5). At Week 8, the majority of subjects also reported better improvement than with their prior skin care regimen (77%) and "significantly faster" improvement than with their prior regimen (56%). In addition, 57 percent reported that their skin looked and felt healthier than with any other skin product they had used before, 37 percent reported that their skin looked better than ever, and 48 percent reported that their skin looked so much better that they had reduced the amount of makeup they wore. Overall, 61 percent were satisfied, very satisfied, or extremely satisfied with the blue light treatment.

Tolerability. At Week 8, 53 percent of subjects agreed that the blue light treatment was much gentler than traditional acne treatments (Figure 6). Three adverse events were probably related to treatment—minimal and transient skin dryness (2) and minimal and transient hyperpigmentation (1).

DISCUSSION

The results of this study demonstrate the effectiveness of the blue light device in reducing

the inflammatory acne lesion count and the frequency, severity, and redness of flares. Furthermore, the majority of subjects considered their blue light treatment achieved better and significantly faster improvement than their prior skin care regimen. Of additional benefit was the improvement in several other appearance-related skin parameters that are of great importance to many individuals—clarity, radiance, tone, texture, smoothness, and overall appearance. At baseline, a high incidence of subjects reported frustration with flares and concern over the tone, radiance, and texture of their skin. Therefore, the subsequent improvements in the frequency, severity, and redness of flares, and in the tone, radiance, texture, and other appearance-related characteristics of the skin were likely to be highly relevant and clinically meaningful.

The inflammatory lesion counts were statistically significantly lower than baseline at all timepoints for Area A and at Weeks 3, 4, and 8 for Area B. Even though the reductions in Area B were not *statistically* significant at some timepoints, the degree of reduction at these visits (23–37%) suggests that they were, nevertheless, *clinically* significant. The lower of the two dose levels of blue light used in this study was selected to investigate the effectiveness of treatment under recommended conditions of usage. The higher dose used (for treating Area A) was selected to investigate the safety and effectiveness of treatment when the device is also used to "spot treat" flares. Although it is not specifically recommended that users dwell on individual lesions, it is anticipated that they may tend to use a longer blue light exposure on their more troublesome areas of acne than on less affected areas of their face. The lack of troublesome adverse events suggests that the higher dose does not cause any additional safety concerns.

A similar study has been performed using the same blue light device as part of a treatment system (i.e., in conjunction with a proprietary cleanser and a proprietary serum, both of which contain salicylic acid).[4] It is not possible to make a meaningful comparison of results across two studies and a direct comparative study would be needed to make definitive comparisons. Nevertheless, the results from the two studies suggest that using the blue light device as part of a treatment system may further enhance the effectiveness of treatment, the appearance of the skin, and the likelihood of achieving subject satisfaction (Table 2).

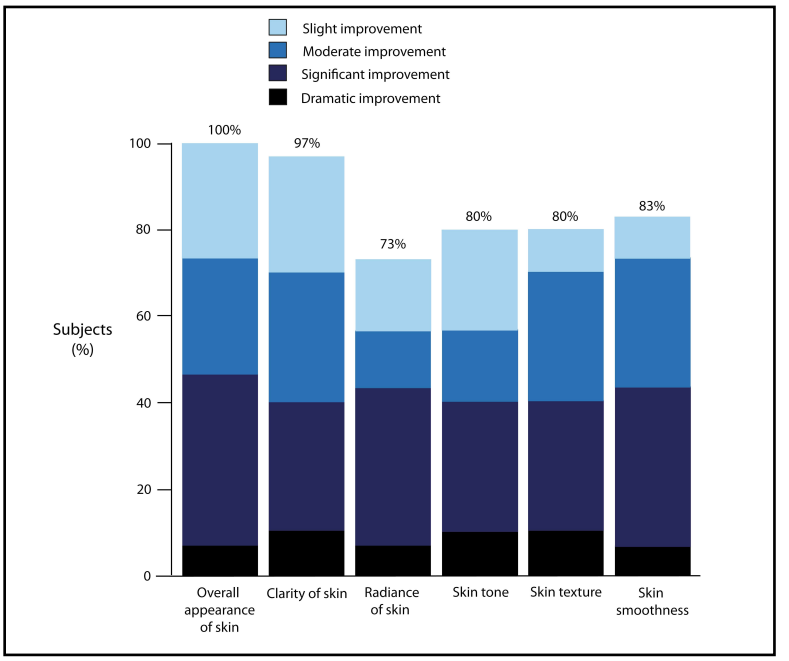

Figure 5. Proportion of subjects reporting improvements in their skin at Week 8

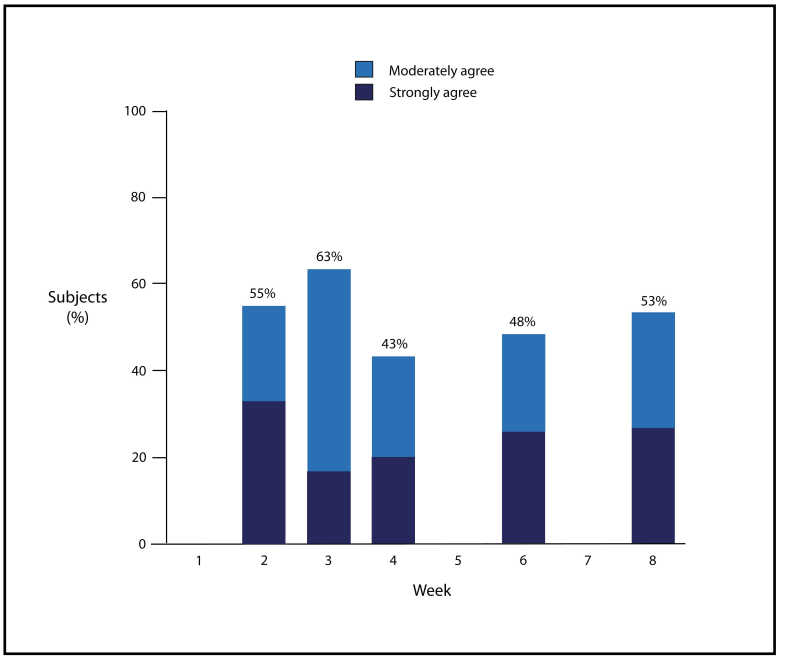

Figure 6. Proportion of subjects considering the blue light treatment was much gentler than traditional acne treatments

CONCLUSION

The blue light device treatment is effective and well tolerated, offering rapid, gentle, and convenient treatment of inflammatory acne, with the majority of subjects reporting that they were satisfied, very satisfied, or extremely satisfied with treatment. The blue light treatment is associated with significant reductions in the number, severity, and redness of flares and improvements in the skin's overall appearance as well as in clarity, radiance, tone, texture, and smoothness.

Because of its effectiveness against *P. acnes*, and its gentleness on the skin, the blue light device offers a

TABLE 2. Comparison of results at Week 8 from this study with those from another study[4] using a similar protocol except that the blue light device was used as part of a treatment system (i.e., in conjunction with a proprietary foaming cleanser and skin rebuilding serum, both of which contain salicylic acid)

	BLUE LIGHT TREATMENT ALONE (STUDY PRESENTED IN THIS MANUSCRIPT)	BLUE LIGHT TREATMENT + PROPRIETARY CLEANSER + PROPRIETARY SKIN REBUILDING SERUM[4]
Median reduction in inflammatory lesion count (%)	60% in Area A 46% in Area B	80% in Area A 67% in Area B
Subjects reporting reduced frequency of flares (%)	100%	100%
Subjects reporting reduced severity of flares (%)	100%	96%
Subjects reporting treatment cleared flares better than other skin care products they had used (%)	53%	71%
Subjects reporting treatment prevented flares better than other skin care products they had used (%)	53%	79%
Subjects reporting improvement in overall appearance (%)	100%	96%
Subjects reporting improvement in skin clarity (%)	97%	96%
Subjects reporting improvement in skin radiance (%)	73%	100%
Subjects reporting improvement in skin tone (%)	80%	96%
Subjects reporting improvement in skin texture (%)	80%	93%
Subjects reporting improvement in skin smoothness (%)	83%	93%
Subjects reporting better improvement than with prior skin care regimen (%)	77%	82%
Subjects reporting significantly faster improvement than with their prior regimen (%)	56%	56%
Subjects reporting skin looked and felt healthier than with any other product they had used before (%)	57%	71%
Subjects reporting skin looked better than ever (%)	37%	68%
Subjects reported skin looked so much better they had reduced the amount of make-up they wore (%)	48%	64%
Subjects who were satisfied, very satisfied, or extremely satisfied with their treatment (%)	61%	82%
Subjects considering study treatment was much gentler than traditional acne treatments (%)	53%	86%
Adverse events probably related to study treatment	3 (from group of 32 subjects)	11 related to topical products and 8 related to blue light device (from group of 33 subjects)

valuable alternative to antibiotics and potentially irritating topical treatments and can also be used adjunctively to complement other therapies.

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Over-the-counter Acne Treatments
A Review

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ABSTRACT

Acne is a common dermatological disorder that most frequently affects adolescents; however, individuals may be affected at all ages. Many people who suffer from acne seek treatment from both prescription and over-the-counter acne medications. Due to convenience, lower cost, and difficulty getting an appointment with a dermatologist, the use of over-the-counter acne treatments is on the rise. As the plethora of over-the-counter acne treatment options can be overwhelming, it is important that dermatologists are well-versed on this subject to provide appropriate information about treatment regimens and potential drug interactions and that their patients see them as well-informed. This article reviews the efficacy of various over-the-counter acne treatments based on the current literature. A thorough literature review revealed there are many types of over-the-counter acne treatments and each are designed to target at least one of the pathogenic pathways that are reported to be involved in the development of acne lesions. Many of the key over-the-counter ingredients are incorporated in different formulations to broaden the spectrum and consumer appeal of available products. Unfortunately, many over-the-counter products are not well-supported by clinical studies, with a conspicuous absence of double-blind or investigator-blind, randomized, vehicle-controlled studies. Most studies that do exist on over-the-counter acne products are often funded by the manufacturer. Use of over-the-counter acne treatments is a mainstay in our society and it is important that dermatologists are knowledgeable about the different options, including potential benefits and limitations. Overall, over-the-counter acne therapies can be classified into the following five major groups: cleansers, leave-on products, mechanical treatments, essential oils, and vitamins. (*J Clin Aesthet Dermatol.* 2012;5(5):32–40.)

Acne vulgaris (AV) affects nearly everyone at some point in life. Each year, AV continues to be one of the top three dermatological disorders encountered in outpatient dermatological practice, historically affecting mainly teenagers and late preteens. However, the prevalence of adult AV is increasing, especially in women 25 years of age or older. Approximately 81 to 95 percent of adolescent boys and 79 to 82 percent of girls are affected, compared to 3 and 12 percent of adult men and women, respectively.[1] Despite prevalence of AV being highest among adolescents, the mean age of presentation to a physician for treatment is 24 years of age, with the average age of the patient enrolled in clinical trials.[2] There are approximately 45 million people affected by AV in the United States. In 2001, the healthcare expenditure of AV was estimated to exceed one billion dollars.[3]

While overall sales of prescription acne medications have decreased over recent years, there has been an increase in sales of over-the-counter (OTC) acne treatments. Different products line the shelves of pharmacies and department stores around the country, with many advertising that they are "dermatologist recommended." One popular OTC acne kit (Proactiv®), marketed as a treatment system, was projected to generate over 800 billion dollars in revenue in 2010.[4] An impressive marketing strategy and celebrity endorsements have made Proactiv® one of the most popular skincare lines of all time. Most OTC acne treatments are not supported by the same level of global media exposure, marketing dollars, or "pop culture power." Nevertheless, sales of OTC treatments for AV continue to grow because of lower immediate "out-of-pocket" cost compared to prescriptions, outcome promises made within certain marketing or promotional efforts, convenience, the desire to find that one special acne product or treatment program that clears acne quickly, and/or difficulties with access to dermatology practices. Sometimes these access difficulties

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are related to "gatekeeper" roadblocks associated with certain insurance plans. Other times, they are related to long appointment "wait times," especially in some geographic communities.

Commonly referred to as "cosmeceuticals," OTC acne treatments come in lotions, creams, washes, kits, scrubs, brushes, and devices. Due to the sheer number of different OTC brands, plus newer products constantly being developed, it is hard for both physicians and patients to keep abreast of the numerous products. However, all treatments for AV are theoretically designed to target one or more of the pathogenic pathways involved in the development of AV lesions. The conventional breakdown of these pathways includes 1) increased sebum production, 2) abnormal follicular keratinization (microcomedo formation), 3) proliferation of *Propionibacterium acnes*, and 4) inflammation.[5] Hyperkeratinization and increased sebum production creates the perfect environment for proliferation of *P. acnes* early in the pathogenesis of AV. *P. acnes* is a commensal facultative anaerobic bacterium that stimulates an innate immunological cascade and also exhibits several pro-inflammatory properties, with reduction in *P. acnes* colony counts correlating with clinical improvement. Both subclinical and visible inflammation in AV develops with or without follicular rupture, with superficial inflammatory acne lesions developing often without preceding follicular wall rupture. However, in the presence of follicular wall rupture of an obstructed pilosebaceous follicle, which has already been "jump started" to form an AV lesion , the spilling of follicular contents (i.e., sebum, keratin, hair, bacteria) into the dermis leads to deeper inflammation that is essentially akin to a "foreign body reaction" (inflammatory response) to those follicular contents invading the dermis. In this scenario, the visible counterparts of this "dermal intrusion" are more deeply seated inflammatory papules, pustules, and nodules.[6]

OTC acne therapies can be classified into the following five major categories: 1) cleansers, 2) leave-on products, 3) mechanical treatments, 4) essential oils, and 5) vitamins. In this article, cleansers and leave-on products are discussed together as they often contain similar active ingredients, such as benzoyl peroxide, salicylic acid, and others. Physicians, particularly dermatologists, are encouraged to be well-versed in OTC acne treatments to provide appropriate information about their treatment regimen and potential interactions with prescription treatments. The dermatologist who is knowledgeable in all treatments for AV, including OTC products, and who does not present a judgmental attitude regarding their previous use, is more likely to be perceived by patients as more interested in assisting them, thus augmenting their professional validity in the eyes of their patients.

CLEANSERS AND LEAVE-ON PRODUCTS

True soaps and synthetic detergents. Cleansing is a large part of personal health and hygiene, resulting in removal of unwanted dirt, bacteria, and dead skin cells, which theoretically should allow for better percutaneous penetration of topical drugs/medications.[7] When soap was first developed many years ago, it was used mainly for cleansing purposes, but over the decades, the function of skin cleaners, which has progressed beyond true soaps, has morphed to encompass both health and cosmetic benefits. Over time, true soap has evolved into much more than a cleansing agent, with synthetic detergents (syndets) used in both bar and liquid cleansers demonstrating lessened skin irritation. As a result, non-soap-based skin cleansers are now marketed to decrease aged appearance of skin, soften skin, and improve overall skin health.

By definition, a true soap is a salt made of an alkali and a fatty acid; the alkali either consists of sodium or potassium hydroxide with pH ranging from 9 to 10, which is markedly more alkaline than the natural "acid mantle" of the epidermis.[8] Daily use of a true soap compromises the permeability barrier of the stratum corneum (SC), resulting in damage to the intercellular lipid bilayer and SC proteins, both of which contribute to regulation of transepidermal water loss (TEWL) and SC hydration necessary for normal desquamation and prevention of xerosis.

Synthetic surfactants are the major ingredient in syndets; other ingredients include high-melting-point fatty acids, waxes, and esters. Due to the unique molecular properties of the surfactants, syndets are incorporated in the mildest bar and liquid cleaners available in the marketplace. Some incorporate lipid-based technologies, such as incorporation of free fatty acids for replenishment and optimal surfactant selection to reduce damage to integral SC proteins.

In a randomized, double-blind study by Subramanyan et al,[7] patients undergoing topical acne treatment were randomly assigned to use either a soap or syndet bar (N=25). The syndet bar group demonstrated a greater reduction in signs and symptoms of cutaneous irritation and some decrease in AV lesions compared to the group using soap.[7] In another study by Korting et al,[9] adolescents and young adults were randomized to wash with either conventional true soap or a syndet bar for three months duration (N=120). Results of this study showed an increase in inflammatory AV lesions in the group using conventional soap and a decrease in inflammatory AV lesions in the group using the syndet bar ($p<0.0001$). The authors of this paper hypothesized that use of the true soap increased the pH of the skin leading to a more favorable environment for proliferation of *P. acnes*.[9]

Since the skin has an acidic pH of 5.3 to 5.9, washing the skin with true soap can increase the pH by 1.5 to 2.0 units for 4 to 8 hours. The increase in pH contributes to amplifying TEWL, thus leading to production of visible changes of dryness. In addition, the increase in pH may facilitate microbial growth potentially leading to increase in *P. acnes* and development of AV lesions.[10,11] The pH of syndet cleansers hover around 5.5 and do not modify the pH of the skin.[12]

As an alkaline pH can also impair enzymes involved in normal SC functional integrity, true soaps contribute to xerotic changes within skin leading to fine fissuring, scaling, and sometimes low-grade inflammation, which produces

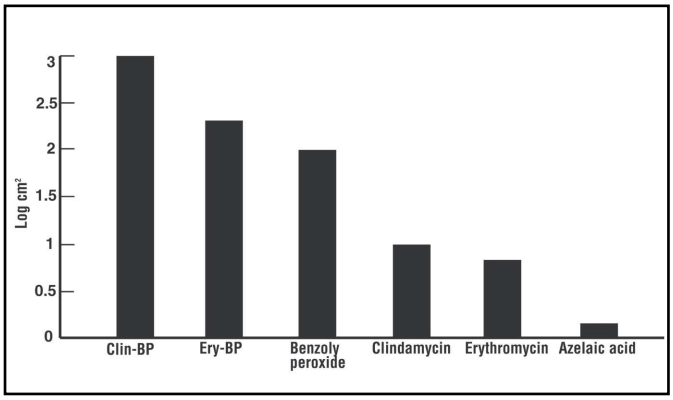

Figure 1. Reduction of *Propionibacterium acnes* with topical therapies. Reprinted with permission from: Leyden JJ. Current issues in antimicrobial therapy for the treatment of acne. *J Eur Acad Dermatol Venereol.* 2001;15(Suppl 3):51–55.

erythema. With regard to AV, these adverse xerotic changes may potentiate cutaneous irritation associated with some topical acne medications, such as retinoids and/or benzoyl peroxide. On the other hand, use of a syndet-based skin cleanser can reduce the potential for cutaneous irritation that is sometimes associated with topical therapies for AV.

Benzoyl peroxide. Benzoyl peroxide (BP) is an organic acid in the peroxide family that has been a fundamental component of therapy for AV for more than six decades. In addition, BP is used for a variety of other purposes (i.e., hair/teeth bleaching, preparation of flour, polymerization reactions). Since the 1930s, BP has been a popular choice for the treatment of AV due to its keratolytic, moderate comedolytic, and antibacterial properties, which include the reduction of *P. acnes* and *Staphylococcus aureus* on skin.[13,14] Cutaneous side effects of BP are most often irritant in nature, may be concentration and/or vehicle dependent, and are usually mild, including signs such as dryness, erythema, and fine scaling. A minority of the population treated with BP for AV will experience true allergic contact dermatitis (1:500). Although available OTC, BP is a pregnancy category C agent, suggesting that its use in pregnancy may not be prudent.

Common use worldwide of topical and oral antibiotics for treatment of AV over the past 3 to 4 decades has led to an increase in *P. acnes* strains that are less sensitive to antibiotics that are commonly used for treatment of AV, especially erythromycin and tetracycline. When the *in-vitro* mean inhibitory concentration of a specified antibiotic increases to predetermined breakpoints, the tested *P. acnes* strain is determined to be "resistant" to that antibiotic, with relative rates of high-level and low-level *P. acnes* resistance reported in some studies. Global rates for the presence of antibiotic-resistant *P. acnes* strains, most often highest to erythromycin followed by tetracycline, rose from 20 percent in 1978 to 62 percent in 1996. Resistance is most common with erythromycin, clindamycin, and tetracycline; however, reported rates with doxycycline, trimethoprim, and minocycline have increased in direct correlation with geographic usage patterns.[15]

When BP is combined with a topical antibiotic (i.e., erythromycin, clindamycin), there is an augment antibacterial effect based on log reductions of *P. acnes* in addition to a decrease in the emergence of both new and pre-existing antibiotic-resistant *P. acnes* strains.[16] Combination gel formulations of BP with erythromycin or clindamycin are only available by prescription in the United States. BP is equally effective against erythromycin-sensitive and erythromycin-resistant *P. acnes* and coagulase-negative *S. aureus in vitro*.[16] Clinical studies have shown that the combination gel formulations of BP and erythromycin or BP and clindamycin are more effective than either active agent used as monotherapy in decreasing acne lesions, especially inflammatory lesions (Figure 1).[13,15,17] The effectiveness of the topical antibiotic and BP may be explained by their independent antibacterial effects, the moderate comedolytic effect of BP, and potentially anti-inflammatory properties associated with erythromycin or clindamycin, although the latter are not as well defined.[13]

Available OTC, BP-based products for AV range in concentration from 2.5 to 10% and encompass a wide variety of vehicle formulations. In three double-blind studies of patients with mild-to-moderately severe acne vulgaris, 2.5% BP gel was compared to its vehicle and also to 5 and 10% BP gel preparations (N=153).[18] The results showed the 2.5% BP was more effective than its vehicle and equivalent to the 5 and 10% BP preparations. Cutaneous side effects, such as desquamation, erythema, and burning, were increased with the higher concentration formulas.[18] Therefore, BP concentrations greater than 2.5% do not necessarily increase the efficacy of treatment in patients with facial AV. However, higher concentrations may be associated with increased risk and severity of signs and symptoms of application-site irritation. In addition, efficacy, tolerability, safety, and microbiological data on OTC formulations of BP have not always been completed and/or are not often published. As a result, it is difficult for the practicing clinician to make specific BP product recommendations to patients based on clinical and scientific evidence. This latter issue is confounded by the recent mandate from the United States Food and Drug Administration (FDA) directing that all BP formulations be available OTC, including those currently available by prescription only. All such formulations are given a basic designated BP monograph that is ascribed to the product ("class labeling"), although each specific product has not been studied individually in support of all of the information included in the designated monograph.

BP is also available by prescription. To the authors' knowledge, there are no published direct-comparison ("head-to-head") trials comparing OTC BP formulations to prescription BP formulations. However, some prescription formulations contain additional ingredients, which may decrease irritation and enhance delivery, and many are supported by published clinical trials evaluating clinical efficacy, primarily for facial AV, and/or microbiological data

evaluating *P. acnes* reduction.

A six-week clinical study by Sawleshwarkar et al[19] examined the efficacy and tolerability associated with a 4% BP cream in a hydrophase base (Brevoxyl®, Steifel Labs, Research Triangle Park, North Carolina) that was until recently available only by prescription.[19] Results showed that the BP 4% cream was efficacious and well tolerated.[19] The hydrophase vehicle, which contains dimethyl isosorbide (DMI), produces dissolution of BP which is believed to reduce irritation that can occur with BP. Many formulations incorporate BP crystals that vary in size and do not necessarily fully dissolve completely or at the same rate. Larger crystals that are not capable of settling into the follicular ostia due to their size may randomly rest on the skin surface for more prolonged periods of time, thus producing scattered foci of "hot spots" that may present as patches of cutaneous irritation.

TABLE 1. Characteristics of alpha-hydroxy acids and beta-hydroxy acids

HYDROXY ACID	SOLUBILITY	SOURCE	PENETRATION	ACTION
Alpha-hydroxy acid	Water soluble	—	Dermis (at high concentrations)	Exfoliative
Glycolic acid	—	Sugar cane	—	—
Lactic acid	—	Sour milk	—	—
Beta-hydroxy acid	Lipid soluble		Epidermis and pilosebaceous unit	Exfoliative, comedolytic, anti-inflammatory
Salicylic	—	Willow bark, wintergreen, sweet birch	—	—

Hydroxy acids. Hydroxy acids can be divided into two major categories: α-hydroxy acids (AHA) and β-hydroxy acids (Table 1). Both AHA and β-hydroxy acids are used for cosmetic applications in dermatology but differ in their structures and chemical properties. AHAs are a group of chemical compounds that have a carboxylic acid moiety that is substituted with a hydroxyl group at the α position of the acid, which confers water solubility to the compound. Whereas, lipid-soluble β-hydroxyl acids are a group of chemicals containing a carboxyl and hydroxyl group separated by two carbons atoms, making the compound lipid soluble.

α-hydroxy acids (AHA). AHA's are a group of hydroxy acids including glycolic, lactic, and citric acid. The exact mechanism of action of AHAs is not completely understood. They exert some effect by thinning the stratum corneum, promoting epidermolysis, dispersing basal layer melanin, and increasing collagen synthesis within the dermis.[20] A study conducted by Ditre et al[21] showed patients that applied 25% glycolic, lactic, or citric acid for six months had an approximately 25-percent increase in both epidermal and dermal thickness. Histological staining demonstrated increased mucopoly-saccharides, improved quality of elastic fibers, and increased density of collagen.[21]

Hyperkeratinization (hyperkeratosis), subclinical, clinical, or both, often results secondary to abnormal SC desquamation and epidermal thicken-ing, both often responses to impairment of the SC permeability barrier. With loss of cutaneous hydration, the decrease in mechanical resiliency of the epidermis leads to microfissuring and often to visible skin splits (macrofissures), the latter being fine and superficial (eczema craquele) or discrete and deep (canyon-like fissures of hyperkeratotic hand-foot eczema or keratoderma). Hyper-keratinization may be acquired or may be inherent to the progression of a variety of underlying skin disorders that are focally or diffusely involved in the progression of many common skin diseases including AV, eczematous dermatoses, severe xerosis, plaque psoriasis, and verrucae. Histologically, hyperkeratinization presents as a thickened SC and is sometimes associated with epidermal thickening. At lower concentrations, AHA functions as an exfoliant, interrupting corneocyte adhesion in the upper SC by interfering with formation of ionic bonds. As a result, AHAs promote individual corneocyte desquamation and decrease corneocyte clumping, both of which lead to smoother skin texture and decreased visible scaling and flaking; a decrease in follicular hyperkeratois promotes resolution and prevents formation of AV lesions, especially comedones.[22,23] Higher concentrations of AHAs (8–10%) can lead to both epidermolysis and thickening of the dermis.

Brief exposure to glycolic acid at concentrations of 30 to 70 percent is frequently used in superficial peeling, which may serve as an effective adjunct in patients with multiple and/or persistent closed comedones.[23]

β-hydroxy acids. Salicylic acid, the only β-hydroxy acid that is used in dermatological practice, is lipophilic, and is a very common active ingredient in a plethora of OTC acne cleansers, astringents, and lotions. Due to its desmolytic properties, salicylic acid promotes individual corneocyte desquamation, thus simulating natural exfoliation, and exerts moderate comedolytic activity. The desmolytic and comedolytic properties of salicylic acid are concentration-dependent. In fact, salicylic acid is not keratolytic. Rather, it exerts its effect on SC desquamation by breaking the bonds created by corneodesmosomes, also called the "rivets" or "staples" of the SC, which sustain the adherence between contiguous corneocytes.[23] As a result, mild visible peeling may be noted, and some salicylic acid-containing vehicles may promote cutaneous irritation, while others (i.e., multivesicular emulsion, emollient foam) are associated with little-to-no skin tolerability reactions.

OTC salicylic acid acne treatments include con-

centrations of 0.05% to 5%. Higher concentrations are reserved for salicylic acid prescription medications and chemical peels. The "physiological" desquamation provided by salicylic acid provides smoother texture and appearance to the skin and can give the illusion of decreased pore sizes. Unfortunately, lower concentrations of salicylic acid may provide only a modest desmolytic activity, thus producing minimal therapeutic effects.

A 12-week, double-blind, randomized study by Shalita et al[24] evaluated the response of mild-to-moderate AV with use of Stridex® pads (0.5% salicylic acid, Blistex, Oak Brook, Illinois) twice daily as compared to patients using vehicle pads twice daily, both applied twice a day for 12 weeks. The actively treated group demonstrated greater reduction of both inflammatory lesions and open comedones.[24]

Kessler et al[25] compared the efficacy of α- and β-hydroxy peels in the treatment of mild-to-moderately severe facial AV in a split-face, double-blind, randomized, controlled study. Twenty patients were recruited to the study; a α-hydroxy (30% glycolic acid) was applied to one half of the face and a β-hydroxy (30% salicylic acid) to the contralateral side every two weeks for a total of six treatments. There was no significant difference in efficacy between the two peels; however, salicylic acid had fewer initial side effects and sustained effectiveness at two months after treatment.[25]

Hydroxy acids are categorized as pregnancy category C; animal studies demonstrate birth defects when given orally in doses six times the maximum topical dose. Salicylism, although rare, can occur, especially in patients with impaired stratum corneum permeability barrier function receiving treatment over a large body surface area.[26]

Polyhydroxy acids (lactobionic acid and gluconolactone). Polyhydroxy acids (PHA), the new generation of AHAs, provide similar effects of traditional AHAs without the associated sensory side effects of irritation and stinging.[27] PHAs are formulated as multiple strand molecules allowing for slower and gentler absorption rate, reducing aforementioned side effects, making them compatible for use on clinically sensitive skin.[28]

One PHA, lactobionic acid, has been suggested to be an inhibitor of the breakdown of matrix metalloproteinase enzymes (MMPs), possibly due to metal chelation. Breakdown of these MMPs due to sun exposure contribute to the appearance of photoaging. Lactobionic acid is a strong metal chelator conferring antioxidant properties; it is currently used as an antioxidant in organ transplantation. Additionally, PHAs have strong moisturizing and humectant properties.[28] The combination of PHAs and tretinoin has been shown to decrease the total number of acne lesions and both subjective and objective measures of irritation.[28]

Triclosan/triclocarban. Triclosan/triclocarban are bacteriostatic agents that can be found in a variety of household items and are often the key ingredient in OTC acne cleansers and washes. Triclosan is a bisphenol disinfectant, with action against gram-positive and most gram-negative organisms and is used in surgical scrubs/soaps and deodorants.[29] However, topical antibiotics should never be used as monotherapy and are preferably combined with other topical nonantibiotic antimicrobials such as benzoyl peroxide.[30]

MECHANICAL TREATMENTS

Scrubs. Abrasive scrubs came to fruition after the anecdotal observation that desquamation of the SC can lead to younger, smoother-appearing skin. Scrubs may contain different types of abrasives, such as polyethylene beads, aluminum oxide and ground fruit pits, or sodium tetraborate decahydrate granules.[31] The theoretical rationale behind the use of scrubs for acne treatment is that the abrasion may unroof closed comedones and prevent their progression.[32] However, the irritant effects and/or damage to SC functional integrity caused by physical abrading caused by scrubbing must be considered, as this is likely to augment the potential for cutaneous irritation that may be associated with topical acne therapies.

Because of their irregular shape, the most abrasive scrubs are those containing ground fruit pits and aluminum oxide. These are not recommended for patients with sensitive skin. Scrubs containing sodium tetraborate dechydrate granules dissolve during washing, making them the least abrasive.[31]

Cleansing cloth (nonwovens, towelettes). Cleansing cloths offer a less abrasive cleansing alternative in addition to providing conditioning and exfoliation in a simple application process. The cloths come in the following two forms: 1) cloths that lather, requiring wetting before and rinsing afterwards and 2) moist cloths that do not requiring rinsing after use. Most wipes tend to be mild because of the low surfactant content and also have the additional benefit of increased deposition of active ingredients onto the skin.[8]

Cloths are made of polyester, rayon, cotton, and cellulose fibers, which are joined together by a heating process known as thermobonding. The cloths are then saturated with cleanser that foams modestly when moistened. Humectants and emollients can also be added to the cloths, providing properties designed to counter damage to the SC in addition to cleansing.

The type of cleanser added to the cloth plays an important role in the effect it has on sebum removal and ultimately its role in the treatment of acne vulgaris. The type of weave (open vs. closed) also plays a role in the cutaneous effects of the cloth. Open weave fibers are more conducive to dry, sensitive skin. These open cloths have 2 to 3mm windows between the adjacent fiber bundles, thus decreasing surface contact with the skin while increasing the softness of the cloth providing a more gentle exfoliative effect. In contrast, the closed fiber cloths have a tighter weave and subsequently exhibit a greater exfoliative effect.[31]

The newest generation of cloths now incorporates formulations of BP, salicylic acid, and hydroxy acids in addition to cleansers. A BP containing cleansing cloth has several desirable characteristics compared to conventional 4 or 6% BP wash, including convenience, portability and cosmetic elegance.[33]

Cosmetic adhesive pads. Developed to remove adherent corneocytes, dirt, oil, or loose open comedones from the skin surface, adhesive pads can be used to remove

keratotic plugs (comedones) from the follicular orifices. Biore® (Kao Brands Company, Cincinnati, Ohio) pore strip is a commercially available adhesive pad, onto which a cationic adhesive polymer is deposited. Comedones (follicular plugs) contain anionic amino acids that are attracted to the cationic adhesive polymer; the active agent polyquaternium 37 purportedly binds to comedonal plugs facilitating their extraction on removal of the adhesive pad.[34]

Biore® Pore Strips are applied weekly to wet skin and allowed to harden before being peeled off. For optimal results, it is recommended not to use them more often than once every three days. No studies have been conducted looking at the efficacy of Biore® Pore Strips in the treatment of AV, but they have been reported in the treatment of trichostasis spinulosa.[34]

Brushes. Developed by the makers of the Sonicare® toothbrush, Clarisonic® (Pacific Life Bioscience, Bellevue, Washington) skin care brush is one of the most commonly found OTC skin brushes. Although not marketed for treating AV, many acne sufferers will inquire about this product due to the popular myth that unclean skin may cause AV. The Clarisonic® skin care brush has an oscillating motion that deeply cleanses the skin while removing makeup. Industry studies have shown Clarisonic® sonic cleansing is twice as effective in cleansing the skin compared to washing with soap and water. In addition, Clarisonic® sonic cleansing is reportedly six times better at removing mineral makeup than manual cleansing.[35] However, the impact of this approach in skin cleansing has not been adequately evaluated

Heating devices. Zeno® (Zeno Corporation, Houston, Texas) is an electronic heating device marketed to treat AV by directly contacting the lesion. The device heats to 121°F. The company claims that the heat "activates heat shock proteins of *P. acnes* causing the bacteria to be killed." Treatment protocol is two to three treatments for 2.5 minutes each over a 24-hour time period.[36] The No!No! Skin® (Radiance, Inc., Orangeburg, New York) is an electronic device postulated to treat acne through heat and phototherapy.

ESSENTIAL OILS

Tea tree oil. Australian tea-tree oil comes from trees of the *Melaleuca* genus; the most common species used is *Melaleuca alternifolia*.[37] Tea tree oil has been used medicinally for approximately 70 years, including for furunculosis and vaginal infections, due to its broad antimicrobial and antifungal properties.[38–40] *Staphylococcus aureus* and most gram-negative bacteria are reported to be sensitive to tea tree oil. Terpinen-4-ol is considered the active ingredient of tea tree oil, but studies have shown alpha-terpineol and alpha-pinene also have intrinsic antibacterial properties.[37] One comparison of tea tree oil and BP for treatment of mild-to-moderate acne revealed both compounds have similar efficacy, although the onset of action is slower for tea tree oil.[41] A randomized clinical trial compared tea tree oil to a placebo over six weeks in the treatment of AV measuring total lesion count (TLC) and acne severity index (ASI). Tea tree oil was 3.5 times more effective than the placebo in reducing TLC and 5.75 more effective than the placebo in reducing ASI.[42]

Some studies support that tea tree oil has anti-inflammatory activity as well. Terepin-4-ol has been shown in an *in-vitro* study to suppress production of pro-inflammatory mediators by activated human monocytes.[43] Another study demonstrated the water-soluble components, terpinen-4-ol, alpha-terpineol and 1,8-cineole, suppress the production of superoxide by monocytes, but not neutrophils.[44] *In-vivo* studies have demonstrated the ability of terepin-4-ol to modify vasodilation and plasma extravasation associated with histamine-induced inflammation.[45] These anti-inflammatory properties have been suggested to account for its potential usefulness in treating AV; however, the role of this pathway of inflammation in the pathogenesis of AV has not been defined.

Although tea tree oil may be beneficial, it can also induce allergic contact dermatitis. It has been proposed that photo-oxidized products from poor storage conditions are the cause of allergic reactions.[46,47] One study found the risk of developing allergic contact dermatitis induced by tea tree oil was less than one percent.[48]

VITAMINS AND THEIR ANALOGUES

Retinol. Retinoids are a biologically active group of compounds derived from vitamin A existing as both natural and synthetic derivatives.[49] These compounds play important roles in biological/physiological functions including vision, tissue maintenance/differentiation, glycoprotein synthesis, growth, and hematopoesis. Retinoids increase cell proliferation; however, paradoxically they have a normalizing effect in hyperproliferative epithelium as they stimulate epithelial differentiation.[49]

All-trans-retinol (ROL) is the predominant retinoid in circulation. It binds to either of two nuclear receptors in the keratinocyte, the retinoic acid receptor (RAR) and the retinoid X receptors (RXR), thus activating retinoid hormone response elements (HREs) where transcription is regulated. Retinoid HREs activate genes responsible for the normalization of keratinization and decreasing the cohesiveness of keratinocytes reducing development of microcomedones.[50] Other dermatological effects of vitamin A derivatives act through changes in cellular proliferation and differentiation, inflammation, and sebum production, the latter dependent on the specific compound and route of administration. Topical retinoids available in the United States have not been shown to inhibit or increase sebum production.

Retinol appears to exhibit greater cutaneous penetration than tretinoin. Retinol 0.25% may induce cellular and molecular changes observed with tretinoin 0.025%. Although retinol is less potent pharmacologically than tretinoin, it produces less skin irritation and erythema overall, and unlike tretinoin, has not been adequately evaluated for treatment of AV.[51–53] Consumers must be aware that not all products containing retinol have the same

concentration and/or formulation characteristics.

Zinc. Zinc is an essential trace element necessary for the survival of animals, plants, and micro-organisms. This metallic chemical element is found in more than 100 enzymes and serves as structural ions in transcription factors. The 2 to 4 grams of zinc distributed throughout the human body plays a role in the metabolism of ribonucleic acid (RNA)/deoxyribonucleic acid (DNA) signal transduction and gene expression.

The role of zinc salts in treatment of AV has not been fully explicated; however, the use of these salts has been routine since the 1970's in topical acne therapies. It is known that zinc salts have an anti-inflammatory effect mediated by the inhibition of chemotaxis in acne patients. In addition, zinc salts have the potential to decrease the release of inflammatory cytokines, increase superoxide dismutase activity, modulate the expression of integrins and inhibit Toll-like receptor-2 surface expression on keratinocytes, and have a sebosuppressive effect.[54,55]

A large, multicenter, randomized, double-blind, controlled, clinical trial compared oral zinc gluconate versus oral minocycline in the treatment of inflammatory acne. It was found that although both were effective treatments in inflammatory acne, minocycline had a superior effect after one month.[56] However, zinc can be an alternative treatment for pregnant women because of its safety profile, and it is not associated with side effects, such as vertigo or hyperpigmentation. Also, zinc does not cause bacterial resistance and when used in combination with erythromycin it has been shown to preclude the development of erythromycin-resistant strains of P. acnes.[55]

Nicotinamide. Nicotinamide, the water-soluble amide derivative of vitamin B_3 (niacin) is used both orally and topically in the treatment of AV and other inflammatory skin conditions.[57] It has been reported to inhibit cytokine release by keratinocytes and downregulate expression of the interleukin (IL)-8 gene and production of IL-8 protein, which is a focal point in promotion of inflammation. Topical nicotinamide gel 4% has been shown in one study to be as effective as clindamycin gel 1% in the treatment of AV without the development of antibiotic resistance, a factor that is important for patients undergoing treatment for a sustained period of time; however, a more thorough evaluation is needed including assessment based on severity of AV.[58,59]

The Nicomide Improvement in Clinical Outcomes Study (NICOS) evaluated the efficacy of oral pharmacological doses of zinc and nicotinamde in AV and rosacea over eight weeks. The formulation used in the study consisted of nicotinamide 50mg, zinc 25mg, copper 1.5mg, and folic acid 500µg. Improvement in appearance was reported in 79 and >50 percent of patients within the first four weeks of the study. Comparison with concomitant oral antibiotic treatment showed no difference in improvement rendering addition of an oral antibiotic regimen unnecessary. However, this suggestion is not applicable, as use of oral antibiotic therapy for AV without concomitant rational topical therapy is not recommended.[60]

Sulfur. Sulfur is a nonmetallic natural element found abundantly in the earth's crust. It has been shown to exhibit antimicrobial properties and has been used medicinally for hundreds of years, including the treatment of AV. The clinical effects of sulfur in the treatment of AV and seborrheic dermatitis is believed to be due at least partially to its keratolytic effects, thought to be due to the interaction between the keratinocyte and the cysteine component of sulfur.

Sulfur is usually combined with other topical agents, such as BP, salicylic acid, and resorcinol. In OTC acne products, sulfur is usually combined with resorcinol, whereas in prescription formulations it is found in a concentration of 10% in combination with sodium sulfacetamide.[50] Resorcinol is thought to have intrinsic antibacterial, antifungal, and keratolytic activity; however, it is not believed to be effective as monotherapy.[61] Use of sulfur and resorcinol causes mild irritation and sensitization.[30] In addition, the malodor associated with sulfur products has limited its popularity as an OTC acne product.

DISCUSSION

Many people use OTC acne treatments as their first attempt to treat AV or at different times over their lifetime due to the chronicity of the disorder. In addition to being available at local pharmacies or via the Internet, some ingredients commonly used in OTC acne treatments, such as BP and sulfur, are also available in prescription formulations. Major categories include 1) cleansers/leave-on products, 2) mechanical treatments, 3) essential oils, and 4) vitamins. To further establish the efficacy of OTC acne treatments, well-designed, adequately powered, blinded, randomized, clinical trials are needed to better establish the efficacy and tolerability of OTC products for AV. This is especially important as the FDA mandates that some active agents, such as BP, be designated for OTC use. Unless OTC acne products are supported by appropriate clinical trials, dermatologists and their staff will be without the necessary information essential to appropriately differentiate and recommend OTC products. OTC products may certainly be of benefit for patients; however, lack of good studies to support some OTC products for AV and other disorders creates a challenge for clinicians. Hopefully, manufacturers will step up to the challenge by designing and completing studies that provide clinically relevant that supports the recommendation of their products.

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Presentation of Reticulate Acropigmentation of Kitamura and Dowling-Degos Disease Overlap

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ABSTRACT

The authors report a case of overlapping reticulate acropigmentation of Kitamura and Dowling-Degos disease seen in a 57-year-old woman. This is a unique presentation of two rare entities that some believe to be the same disease with variable phenotypic expression. This is an interesting case of reticulated pigmentation that unfortunately has limited treatment options. (*J Clin Aesthet Dermatol.* 2012;5(5):41–43.)

Reticulated hyperpigmentation is an uncommon entity and initial evaluation should exclude some common disorders before diagnosis. Independently, both reticulate acropigmentation of Kitamura and Dowling-Degos disease are rare genodermatoses. The authors describe an interesting patient with an overlap presentation of both disorders.

A 57-year-old Hispanic woman presented with a nearly 40-year history of multiple hyperpigmented macules on her hands, feet, trunk, axilla, and groin. The lesions initially appeared at age 20, first presenting over the dorsal aspect of her hands and feet. Over the years, the macules had progressed proximally. Her first truncal lesions appeared approximately seven years ago. Addition evolutional features included an increase in size and in pigmentation. Of note, the lesions were pruritic when they initially erupted.

Her past medical history was significant for hypertension, benign liver cysts, and hidradenitis suppurativa. The patient was from Nicaragua and denied known Japanese or Asian ancestry. Her family history included similar hyperpigmented lesions in her paternal grandmother, father, and son. Her only reported medications were atenolol and petrolatum. Despite her aesthetic concerns, she had never received treatment for her hyperpigmented lesions. The patient was given a trial of azelaic acid with unknown response as she was subsequently lost to follow up.

On physical examination, the patient was a well-developed Hispanic woman with reticulate brown patches on the dorsal aspect of her hands and feet, back, chest, bilateral axilla, and groin (Figures 1 and 2). There were also multiple, diffuse brown stuck-on papules on her face, chest, neck, arms, and legs. In addition, there were palmar and plantar pits on her bilateral extremities (Figure 3). Biopsies were obtained from inframammary lesions and stained with hematoxylin and eosin (H&E). The histo-pathological features include a reticulated, lentiginous epidermis as well as basal hypermelanosis with papillo-matosis and pseudohorn cysts (Figures 4 and 5). A clinicopathological diagnosis of reticulate acropigmentation of Kitamura and Dowling Degos disease overlap was made.

DISCUSSION

Both reticulate acropigmentation of Kitamura and Dowling Degos disease fall under the category of reticulated pigmentary disorders. As with other disorders of this class, a review of family history should be performed as these two conditions follow an autosomal dominant pattern of inheritance. There have been several published reports of patients exhibiting features consistent with both diseases, prompting the belief that this may be the same disease with variable phenotypic expression.

Reticulate acropigmentation of Kitamura is a rare genodermatosis first described by Kitamura and Akamatsu in Japan in 1943.[1] The majority of reported cases occur in

DISCLOSURE: The authors report no relevant conflicts of interest.
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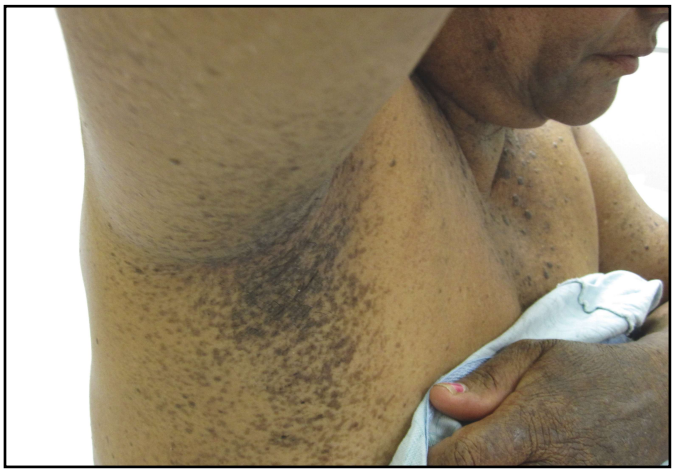

Figure 1. Lesions on right axilla

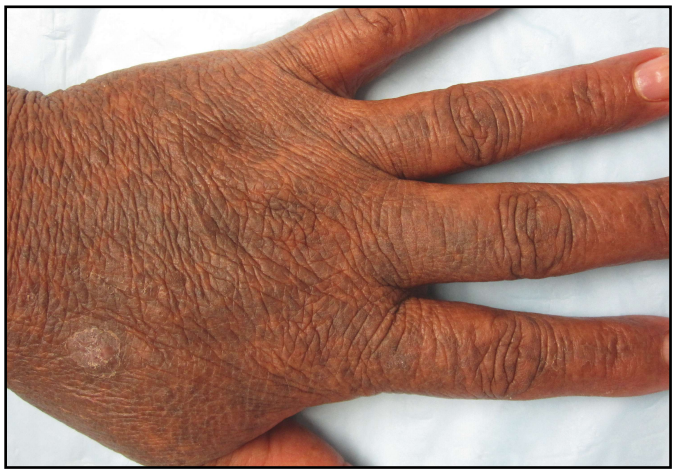

Figure 2. Lesions on dorsum of left hand

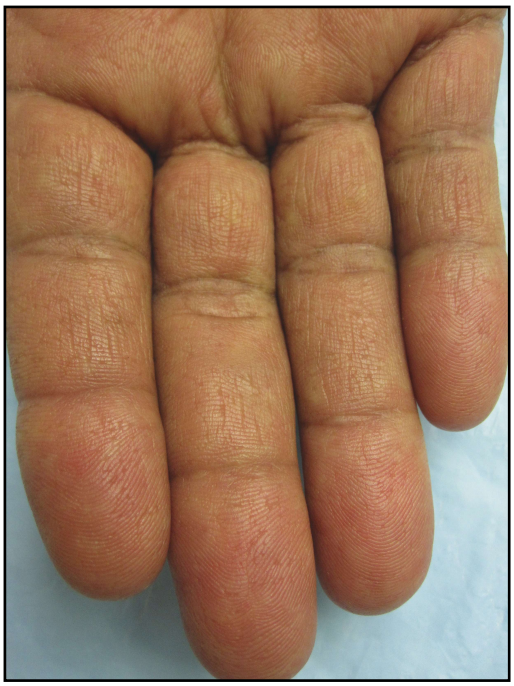

Figure 3. Palmar pits on right hand

Japanese patients, but the condition has also been recognized worldwide. The usual age of onset is during childhood or in the first and second decades of life. The lesions initially arise as lentiginous, hyperpigmented macules in a reticular pattern on the dorsal aspect of the hands and feet. A characteristic feature of the early lesions is atrophy. Over time, lesions may spread proximally and may darken. Palmoplantar pitting and dermatoglyphic disruption may also be present.

Dowling Degos disease is another rare genodermatosis otherwise known as reticular pigmented anomaly of the flexures. Dowling in 1938[2] and Degos in 1954[3] were the first to report this disorder. The onset of lesions is during adulthood in the third or fourth decades of life. The disease presents as reticular brown, black-pigmented hyperpigmentation in the flexural areas of the axillae, neck, inframammary, inguinal, and sternal areas. Pruritus is occasionally seen in these flexural regions. Facial pits and perioral scars may also be present. Associated conditions include hidradenitis suppurativa, squamous cell carcinoma, keratoacanthoma, and seborrheic keratosis.

The overlap between reticulate acropigmentation of Kitamura and Dowling Degos disease has been reported in the literature. The patient presented is unique such that she had hidradenitis suppurativa, a condition not previously encountered in reported cases of overlap. Controversy exists over whether reticulate acropigmentation of Kitamura, Dowling Degos disease, acropigmentation of Dohi, and Galli-Galli disease are variants of a single disease entity.[4,5] It is often difficult to discriminate the distinct disorders. However, important negative features that exclude the diagnosis of acropigmentation of Dohi and Galli-Galli disease in the patient described in this case are absence of concomitant hypopigmented lesions and absence of suprabasal acantholysis on histology, respectively.[6] Based on the locations of the hyperpigmented lesions, palmoplantar pitting, hidradenitis suppurativa, and histopathological findings, the diagnosis is more likely to be reticulate acropigmentation of Kitamura-Dowling Degos disease overlap.

Unfortunately, there are no effective treatment options for these conditions. Treatment with topical retinoids has been unsuccessful, and adapalene provides only temporary improvement.[7,8] Azelaic acid, a tyrosinase inhibitor commonly used for acne, rosacea, and postinflammatory hyperpigmentation, has been shown to be a potential treatment option.[9] Erbium-doped yttrium aluminium garnet (Er:YAG), an ablative laser that emits light at 2,940 nanometers for skin resurfacing and pigmentary disorders, is another therapeutic option.[10]

The authors present this interesting, overlapping case of two rare genodermatoses. When encountering reticulated hyperpigmentation disorders, it is important to recognize the distress they may impart on the patient. Unfortunately, these disorders are difficult to manage due to limited therapeutic options.

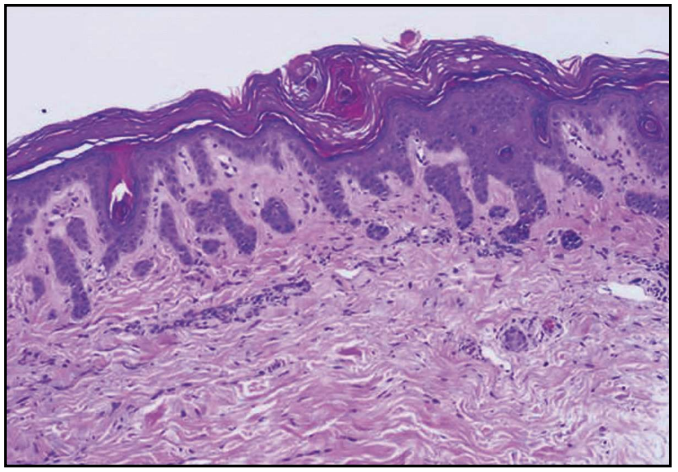

Figure 4. H&E of dorsal hand lesion at 2x

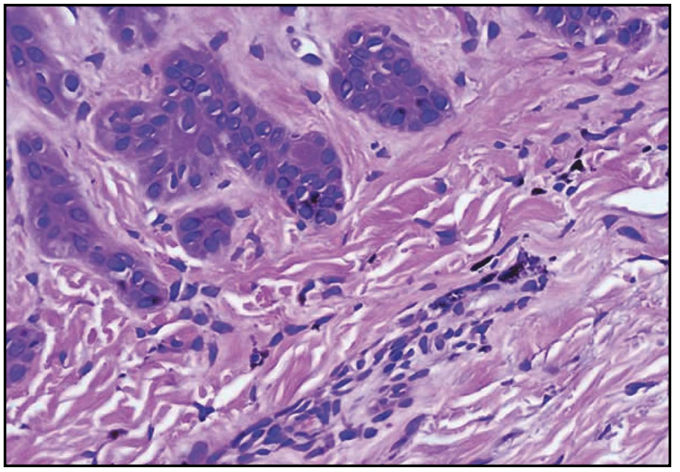

Figure 5. H&E of dorsal hand lesion at 10x

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A Treatment Protocol for Vascular Occlusion from Particulate Soft Tissue Augmentation

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ABSTRACT

Treatment protocols exist for vascular obstruction due to injections with hyaluronic acids. Options for vascular insult due to non-hyaluronic acid products are less defined. The authors report two cases of vascular insult due to calcium hydroxylapatite and discuss treatment options. Patients who have vascular occlusion due to calcium hydroxylapatite require immediate intervention. The authors' suggested protocol is elucidated and presented as a basis for future discussions and clinical trials. (*J Clin Aesthet Dermatol.* 2012;5(5):44–47.)

One of the most significant adverse events associated with injections of soft tissue augmentation products is vascular occlusion. Adverse events associated with vascular occlusion include pain, long-term erythema, neovascularization, epidermal and dermal necrosis, scarring, and pigment changes. While rare, these events are significant for both patient and physician.

Vascular compromise is a function of compression and/or embolization of material into the vasculature. When the material injected is a hyaluronic acid, the compromise may be partially mitigated by use of hyaluronidase. However, when the material is calcium hydroxylapatite, poly L lactic acid, silicone, fat, or methylmethacrylate, there is little mitigation that can be performed. Among injectors of soft tissue augmentation products, this lack of mitigation potential is one of the main reasons that semipermanent products are not used more frequently. Our goal is not to promulgate these as definitive measures, but rather to establish some treatment protocol that may be helpful as well as to provide the basis for future protocols.

The protocol outlined by Glaich et al[1] calls for a coherent, sequential treatment for vascular compromise resulting from injections of hyaluronic acids. This protocol elaborates a sequence of events that utilize topical nitroglycerin, hyaluronidase, and other modalities to minimize the damage from impending necrosis. Other authors have also published guidelines for the treatment of impending necrosis following soft tissue augmentation following injections of hyaluronic acid.[2,3] Typically, these events most frequently occur in the nasolabial crease where the angular artery is impacted. The glabella is another area that is impacted by vascular events. Early experience with cross-linked bovine collagen (Zyplast) prepared many injectors for this eventuality and many believe that necrosis in this site is linked not only to the nature of Zyplast but also to the proximity of the underlying vessels to the area that the injection needle is placed. The small injection area and bony foundation are likely to be contributing factors for vascular adverse events in this area. Necrosis of the marionette lines with soft tissue augmentation products is also a potential risk with injections into this area.

Illegal injections of hyaluronic acid into the vaginal area has been associated with pulmonary embolism.[4] Embolization of material is reported with several soft tissue augmentation products including fat and hyaluronic acid.[5] When the embolization involves the retinal artery, loss of vision may result.[6,7] Necrosis of the nasal ala has also been reported with injections of soft tissue augmentation products.[8] Particulate fillers, such as methylmethacrylate, may also cause embolization, but the rate of this occurrence with these molecules is unknown. Poly L lactic acid is now increasing in popularity. Depending on its reconstitution and time for hydration, it may be more or less of a particulate solute.

A controlled trial of various rescue treatments for vascular injury and compromise is not ethically possible. However, based upon experience with hyaluronic acid fillers and knowledge of rheologic and chemical properties of

DISCLOSURE: Dr. Beer is an investigator for Merz Aesthetics, Medicis, and Allergan and a consultant for Medicis and Allergan. Dr. Beer is a shareholder of Allergan Corporation. Dr. Downie is a consultant and investigator for Merz, Allergan, and Medicis.
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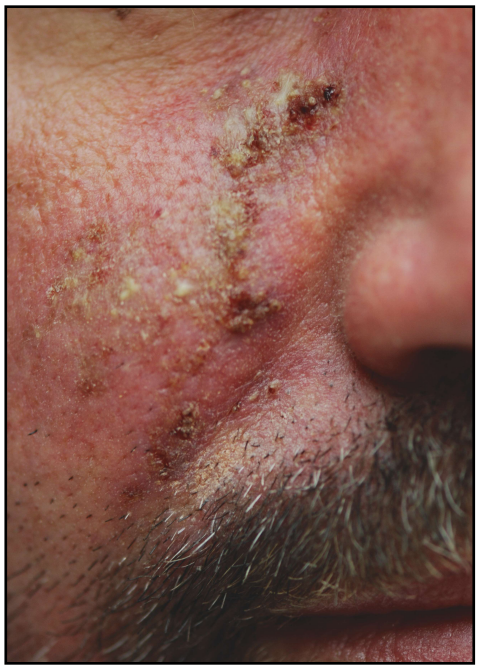

Figure 1. Case 1, three days after the injection. Crusted papules are visible in the distribution of the angular artery.

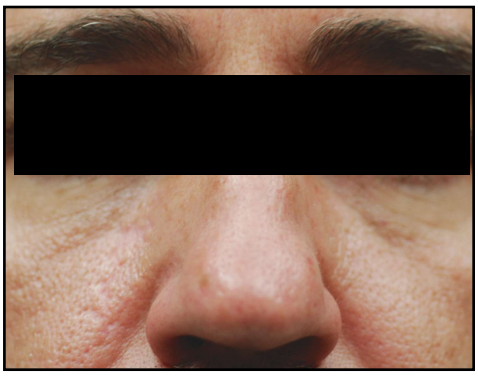

Figure 2. Case 1, four months after the occlusive incident. Treatments included fractionated erbium laser as well as pulsed dye laser.

particulate fillers, it is possible to develop a suggested treatment protocol for vascular compromise with these agents.

CASE SERIES

Case 1. A 40-year-old man presented for a cosmetic evaluation. Examination showed that he had moderate mid-face tissue loss with moderately deep nasolabial creases. He had Fitzpatrick type II skin and had no prior history of filler use. After reviewing the various options including particulate hyaluronic acid fillers and calcium hydroxylapatite (CAHA, Radiesse, Merz Aesthetics, Inc.) it was decided to proceed with injections of CAHA. Each syringe of CAHA was mixed with 0.1cc of 1% lidocaine with 1:100,000 epinephrine. A total of 1.5mL was injected on each side using a serial puncture technique and a 28-guage needle measuring $^3/_4$ of an inch in length. Upon injecting the superior aspect of his right nasolabial crease, a blanching was noted. The blanching extended along the lateral aspect of his nose and up to his inferior eyelid in a distribution that suggested vascular distribution. However, there was no sign of impending necrosis, such as development of a dusky hue, and it was thought that vascular spasm due to the epinephrine was the cause of the blanching.

However, the next morning, the patient called the office and complained of pain in the distribution of the angular artery. He was not able to come to the office for evaluation because of travel and a photo sent showed that there was faint erythema, but not any blue discoloration or dusky appearance. Treatment with oral corticosteroids (methylprednisolone) was initiated as well as aspirin. The next day, there was some vesiculation noted on another photograph he had sent. On the third post-procedure day, the patient was seen and there was a superficial erosion noted. Small yellowish papules were also noted at that time (Figure 1). The patient was started on both oral cephalexin and valcyclovir. Cultures taken at that visit were negative for bacterial and viral growth. Over the span of the next few days, the patient was seen at frequent intervals with a superficial slough noted in the medial cheek. No necrosis was noted on any of the distal aspects of the vascular distribution. One month after his injection, the scar was treated with low energy pulsed dye laser and thereafter with a fractionated 1550 erbium laser. Following several visits, the residual scar was minimal (Figure 2).

Case 2. A 49-year-old man presented for a lower face augmentation with CAHA. He was treated with this product in the past and wanted to enhance his chin and oral commissures. A small amount (0.1cc) was placed in his nasolabial crease in the midpoint of the fold. Unlike the prior case report, the CAHA in this instance was not mixed with lidocaine. Upon injection into the nasolabial crease, there was an immediate blanching in the distribution of the angular artery. The area covered by this blanch was approximately 4.5 x 7.5cm and was triangular in shape.

Nitroglycerin paste was immediately applied and the area was massaged. Following these procedures, the size of the blanching was reduced by about 50 percent. Over the span of a few minutes, the blanched areas turned a gray-purple (Figure 3). Approximately 30 minutes after the injection, the patient left the office.

Three hours after the injection, the patient returned for evaluation and nitroglycerin paste was again applied. In addition, 600 units of hyaluronidase was injected as well as 5mL of normal saline. The hyaluronidase was injected with the hope that it would dissolve some native hyaluronic acid, thereby decreasing the pressure on the blood supply. Incision and drainage were performed to attempt to extrude

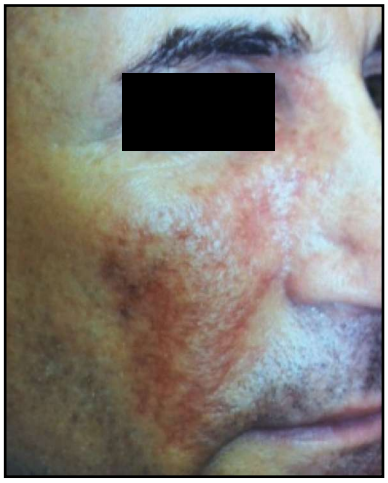

Figure 3. Case 2 two weeks after the injection. Bruising in the distribution of the angular artery is still prominent. This patient underwent a similar impetigo stage not shown here.

the product, and the upper portion of the occlusion cleared immediately with visible evidence of vascular flow. After consultation with several colleagues, the patient was placed on oral prednisone at a dose of 40mg/day with a gradual taper. In addition, aspirin 81mg/day was added. In an effort to dilate the arterial blood supply, sildenafil (Viagra, Pfizer Inc.) was also added at a dose of 50mg/day. Hyperbaric oxygen therapy was initiated the day after the occlusion.

The patient developed an impetigo and was placed on cephalexin 500mg twice daily as well as mupirocin ointment twice daily. On the 11th day, the patient discontinued all oral medications, but continued the topical mupirocin and sunblock. He continued hyperbaric oxygen for a total of 10 sessions.

DISCUSSION

Based upon the experience with hyaluronic acid occlusion, treatment for particulate fillers that occlude vascular structures should seek to increase blood flow to the affected areas. This may be accomplished by decreasing pressure in the anatomic compartment (using corticosteroids and hyaluronidase), increasing blood flow (with sildenafil or similar drugs, aspirin, and nitroglycerin paste), and increasing the oxygen content to the affected tissues (hyperbaric oxygen). However, unlike hyaluronic acid fillers, there is no simple reversal for CAHA, and injections with hyaluronidase are unlikely to digest the blockage. At the present time, protocols for the treatment of CAHA occlusion are based on relatively small amounts of clinical experience and empiric data rather than by evidence-based clinical trials. Thus, they are presented as suggestions rather than dogma.

One technique that may help to decrease the chance of vascular occlusion when injecting particulate fillers is the use of a cannula instead of a needle. Cannulae are available in two sizes for injection of CAHA. Each has a blunt tip and a port on the side of the cannula. This is in contrast with the needle, which has an opening at the leading edge of the cutting aspect. The design of the latter instrument will tend to introduce material into a vessel should one be encountered during injection while the design of the former will not only tend to push vessels to the side of the leading edge, but also not be as likely to introduce material into the vessel, instead injecting it to the side of it.

As with occlusion from gel-based fillers, it is imperative to minimize the degree of damage caused by vascular occlusion. One way to do this is to dilate the vasculature using 2% nitroglycerin paste applied liberally to the affected area. The authors recommend application of nitroglycerin paste 2 to 3 times daily provided that the patient does not develop symptoms such as headaches or light headedness.

Corticosteroids are indicated to diminish the inflammatory component of the injury, which can further inflame the compartment and lead to more vascular compromise. Oral corticosteroids in doses ranging from 40 to 60mg of prednisone are recommended for the first 2 to 3 days after occlusion. A taper over the first week is then initiated. Alternatively, use of a methylprednisolone dose pack is also reasonable.

Dilation of the blood vessels should be maximized with the use of drugs designed for the treatment of erectile dysfunction.[9] These drugs, including sildenafil (Viagra), tadalafil (Cialis, Lilly USA, LLC), and vardenafil (Levitra, Bayer Pharmaceuticals Corporation) are selective inhibitors of cyclic guanosine monophosphate (GMP) specific phosphodiesterase type 5.9 nitric oxide, which is released during normal activities, activates guanylate cyclase, which, in turn, increases cyclic GMP. Increases in GMP cause smooth muscle relaxation, dilation of the vascular wall, and increased blood flow. As with the use of these drugs in any patient, caveats regarding heart disease and other contraindications are still pertinent.

Aspirin is used to block platelet aggregation and has moderate anti-inflammatory properties. If the vascular injury from the particulate filler has not entirely occluded the vessel, aspirin may be able to help blood flow by inhibiting platelet aggregation and blood clotting. Keeping any aspect of the vessel patent will help to increase the viability of any tissue that relies on it for circulatory support. Doses of 81mg/day should be effective in decreasing platelet aggregation, and in the acute setting, aspirin may be placed sublingually.

Hyperbaric oxygen has the potential to deliver oxygen deep into the skin and may help to keep oxygen-dependent tissues viable. Its use in flaps, grafts, and other skin that has potential vascular compromise is controversial. However, if a facility exists that can provide hyperbaric oxygen to a patient with impending necrosis, it may be reasonable to attempt a course of this treatment.

In each of these cases, clinical signs of impetigo appeared after a few days. In both patients, cultures for bacteria as well as for virus were negative. Despite the negative cultures, the patients were placed on cephalosporin antibiotics as soon as the honey-colored crust appeared. It is possible that this crust represented an exudate from a com-promised epidermal barrier. However, in the event that a crust forms following vascular occlusion, it is prudent to use oral antibiotics while the cultures are pending.

CONCLUSION

Particulate-based fillers are becoming more popular for soft tissue augmentation and facial remodeling. As the numbers of patients treated increase, the likely occurrence of adverse events, including vascular obstruction, will also increase. Since there are rational protocols extant for hyaluronic acid based vascular obstruction, it seems reasonable to create a protocol for vascular occlusion with particulate fillers. The authors' suggested protocol is included in Table 1. The suggestions listed in this article form the basis for a discussion of what optimal treatments should be for vascular occlusion with particulate fillers. The authors look forward to more data as well as discussion on this subject.

TABLE 1. Suggested treatment for particulate filler vascular compromise

Nitroglycerin paste 2%	Apply immediately upon suspected necrosis and then for 5 minutes every 1–2 hours
Prednisone	20–40mg each day for 3–5 days
Aspirin 325mg	1 under the tongue immediately and then daily
Sildenafil 50mg	1 per day for 3–5 days
Warm compresses	Apply 5–10 minutes every 1–2 hours (avoid burning the skin)
Hyperbaric oxygen	Begin treatment daily as soon as possible with continued treatments until the area has improved

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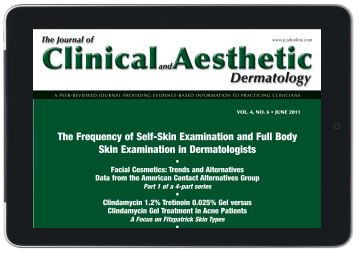

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Promiseb® Topical Cream is an off-white, steroid-free, fragrance-free, water-based emulsion.

Indications for Use:
Under the supervision of a healthcare professional, Promiseb Topical Cream is indicated to manage and relieve the signs and symptoms of seborrhea and seborrheic dermatitis such as itching, erythema, scaling and pain. Promiseb Topical Cream helps to relieve dry waxy skin by maintaining a moist wound & skin environment, which is beneficial to the healing process.

Directions for Use:
Apply Promiseb Topical Cream to the affected skin areas 2 to 3 times per day (or as needed), and massage gently into the skin. If the skin is broken, cover Promiseb Topical Cream with a dressing of choice.

Ingredients:
Promiseb Topical Cream is comprised of Purified Water, Isohexadecane, Butyrospermum parkii, Pentylene glycol, Ethylhexyl palmitate, Cera alba, PEG-30 Dipolyhydroxystearate, Bisabolol, Polyglyceryl-6 polyricinoleate, Tocopheryl acetate, Hydrogenated castor oil, Acifructol complex, Butylene glycol, Magnesium sulfate, Piroctone olamine, Allantoin, Magnesium stearate, Disodium EDTA, Vitis vinifera, Ascorbyl tetraisopalmitate, Glycyrrhetinic acid, Propyl gallate, and Telmesteine.

Caution:
The use of Promiseb Topical Cream is contraindicated in any patient with a known history of hypersensitivity to any of the ingredients. Promiseb Topical Cream does not contain milk, wheat, peanut or animal derivatives. Promiseb Topical Cream does contain shea butter (Butyrospermum parkii), a derivative of shea nut oil (not peanut oil). Patients with a known allergy to nuts or nut oils should consult their physician before using this topical preparation.

How Supplied:
30 g tube, 67857-803-30

To Open: Puncture seal with pointed end of cap.
Important: The opening of this product is covered by a metal seal. Do not use if seal has been punctured or is not visible.

Store at controlled room temperature 68° to 77°F (20° to 25°C), excursions permitted between 59° and 86°F (15° and 30°C).

Distributed by Promius Pharma, LLC, Bridgewater, NJ 08807

PROMIUS® PHARMA

Made in Italy

Federal law restricts this device to sale by or on the order of a physician or properly licensed practitioner.

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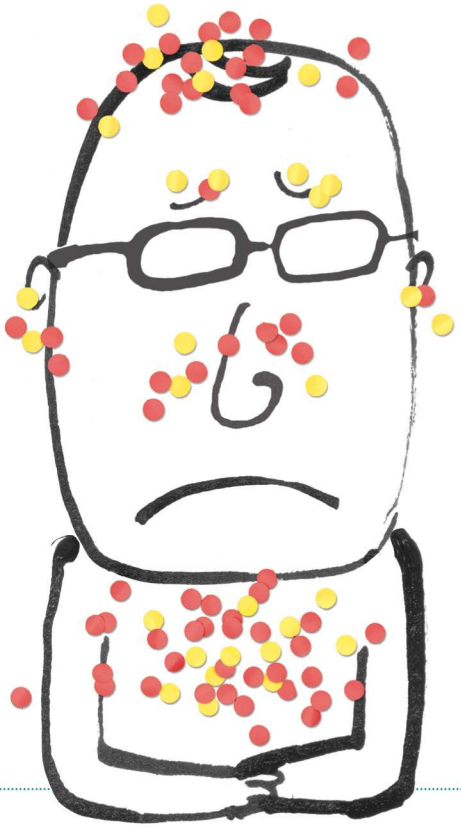
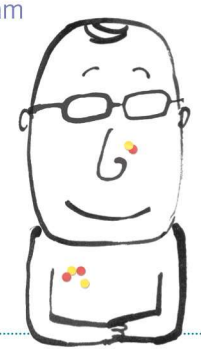
New Promiseb Complete™



Introducing a complete regimen for seborrheic dermatitis

- Includes new Promiseb Plus™ Scalp Wash
  - Can be used on the scalp or body
  - Fragrance free and cosmetically elegant
  - Massage gently upon application to loosen and wash away flakes
- Promiseb Complete Trial and Savings Program
  - Initial prescription of Promiseb Complete filled at no cost for eligible patients*
  - Eligible patients will receive up to 5 refills for no more than $20 each



*For a summary of all eligibility requirements please see back of rebate card available at www.promiseb.com

Promiseb® Topical Cream is a nonsteroidal prescription cream indicated to manage and relieve the signs and symptoms of seborrheic dermatitis such as scaling, erythema, pruritus, and pain. Promiseb Topical Cream is contraindicated in persons with a known hypersensitivity to any component of the formulation. Promiseb Topical Cream does not contain milk, wheat, peanut, or animal derivatives. Promiseb Topical Cream does contain shea butter (Butyrospermum parkii), a derivative of shea nut oil (not peanut oil). Patients with a known allergy to nuts or nut oil should consult their physician before using this topical preparation. Please see accompanying important safety information and full prescribing information. The use of Promiseb Plus Scalp Wash is contraindicated for patients with a history of hypersensitivity to any of the ingredients.
For more information, please visit www.Promiseb.com.