A SUPPLEMENT TO

JOURNAL OF DRUGS IN DERMATOLOGY

JDD

DRUGS • DEVICES • METHODS

Demystifying Acne Algorithms

ISSN: 1545 9616

June 2011 • Volume 10 • Issue 6 (Supplement)

© 2011-Journal of Drugs in Dermatology. All Rights Reserved.
This document contains proprietary information, images and marks of Journal of Drugs in Dermatology (JDD).
No reproduction or use of any portion of the contents of these materials may be made without the express written consent of JDD.
If you feel you have obtained this copy illegally, please contact JDD immediately.

JO0611

Disclosure of Commercial Support

This supplement to the Journal of Drugs in Dermatology *is supported by an educational grant from Galderma Laboratories, L.P.*

© 2011-Journal of Drugs in Dermatology. All Rights Reserved.
This document contains proprietary information, images and marks of Journal of Drugs in Dermatology (JDD).
No reproduction or use of any portion of the contents of these materials may be made without the express written consent of JDD.
If you feel you have obtained this copy illegally, please contact JDD immediately.

JDD
DRUGS • DEVICES • METHODS

JOURNAL OF DRUGS IN DERMATOLOGY

JUNE 2011 VOLUME 10 ISSUE 6 (SUPPLEMENT)

ORIGINAL ARTICLES

© 2011-Journal of Drugs in Dermatology. All Rights Reserved.
This document contains proprietary information, images and marks of Journal of Drugs in Dermatology (JDD).
No reproduction or use of any portion of the contents of these materials may be made without the express written consent of JDD.
If you feel you have obtained this copy illegally, please contact JDD immediately.

© 2011-Journal of Drugs in Dermatology. All Rights Reserved.
This document contains proprietary information, images and marks of Journal of Drugs in Dermatology (JDD).
No reproduction or use of any portion of the contents of these materials may be made without the express written consent of JDD.
If you feel you have obtained this copy illegally, please contact JDD immediately.

Demystifying Acne Algorithms

Release Date: June 1, 2011
Termination Date: May 31, 2012
Estimated Time to Complete this CME Activity: 1 Hour

Statement of Need

Acne affects most of the population at some point in their lives and is not subject to a specific age group, sex or demographic. Adolescents continue to be the most widely affected by acne, however almost 30 percent of all patients treated for acne are over 24 years of age. Over fifty percent of adult women have experienced acne within their adult years. Providing optimal patient outcomes continues to be a challenge in the treatment and management of acne vulgaris. The availability of multiple treatment options for acne vulgaris increases the probability of effective therapy. It is important for clinicians to know what treatment options are effective in treating various levels of severity. The lack of extensive education on combination acne therapy in residency programs, coupled with the vast etiologic nature of acne and the changing role of antibiotics, creates a need to increase clinician knowledge in optimal acne management.

Educational Objectives

At the conclusion of this CME activity, attendees will be able to:

- Identify topical treatment options for various levels of acne severity, including "severe."
- Develop a treatment strategy for topical acne treatments including benzoyl peroxide, retinoids and fixed-dose combinations.
- Recall the potential effect of vehicle use in acne patient outcomes and treatment
- Recognize patient-centered approaches in acne therapy and their application in individual patient treatment outcomes

Target Audience

This activity is intended for dermatology practitioners who treat patients with acne vulgaris.

Accreditation Statement

This activity has been planned and implemented in accordance with the essential areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the National Association for Continuing Education and the *Journal of Drugs in Dermatology*. The National Association for Continuing Education is accredited by the ACCME to provide Continuing Medical Education for physicians.

Credit Designation

The National Association for Continuing Education designates this journal-based CME activity for a maximum of 1 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

How to Obtain CME Credit

You can earn one (1) *AMA PRA Category 1 Credit*™ by reading the articles contained and completing a web-based post-test and evaluation.

Test is valid through May 31, 2012 (no credit will be given after this date).

To receive credit for this activity, please go to www.JDDonline.com and click on the link "Medical Education Library." You will find instructions for taking the post-test and completing the program evaluation. Once you have completed the form online, you will be able to print your certificate directly. You can also receive credit for this activity by completing the post-test and evaluation at the end of this supplement and faxing or mailing it to *JDD*, 377 Park Avenue South, 6th Floor, NY, NY 10016, fax: 212-213-5435. There is no charge for this CME activity.

Faculty and Credentials

Diane Thiboutot, MD: The Pennsylvania State University College of Medicine, Hershey, PA; Andrew F. Alexis, MD, MPH: Skin of Color Center, St. Luke's Roosevelt Hospital, Columbia University College of Physicians and Surgeons, New York, NY; Leon H. Kircik, MD: Indiana University School of Medicine, Indianapolis, IN.

DISCLOSURES

Policy on Faculty and Provider Disclosure: It is the policy of the National Association for Continuing Education to ensure fair balance, independence, objectivity and scientific rigor in all activities. All faculty participating in CME activities sponsored by the National Association for Continuing Education are required to present evidence-based data, identify and reference off-label product use and disclose all relevant financial relationships with those supporting the activity or others whose products or services are discussed.

Any real or apparent conflicts of interest have been addressed through a peer-review process, as required by ACCME.

The peer reviewers have the following disclosed conflicts of interest:

© 2011-Journal of Drugs in Dermatology. All Rights Reserved.
This document contains proprietary information, images and marks of Journal of Drugs in Dermatology (JDD).
No reproduction or use of any portion of the contents of these materials may be made without the express written consent of JDD.
If you feel you have obtained this copy illegally, please contact JDD immediately.

Dr. James Q. Del Rosso has served as consultant for Allergan, Coria/Valeant, Galderma, Intendis/Bayer, Medicis, Onset Dermatologics, Ortho Dermatologics, Promius, Ranbaxy, Graceway, Leo Pharma, Unilever, TriaBeauty, Warner-Chilcott, Obagi Medical Products and Pharmaderm/Nycomed. He has performed clinical research for Galderma, Intendis/Bayer, Onset Dermatologics and Graceway.

Dr. Joseph B. Bikowski has served as consultant for Allergan, Coria, Galderma, Intendis and Stiefel. He has served as an advisor for and is a stockholder of Quinnova. He has served as advisor and speaker for Coria, Galderma, Intendis and Stiefel and as a consultant for Onset Pharmaceuticals and Promius (for which company he has also served as an advisor and speaker).

Dr. Martha P. Arroyo has no relevant conflicts of interest to disclose.

The faculty/authors have the following disclosed conflicts of interest:

Dr. Diane Thiboutot served as a consultant or investigator for Allergan, DOW Pharmaceutical Sciences, Galderma, Intendis, Johnson & Johnson, Medicis and Stiefel.

Dr. Andrew F. Alexis is on the Speakers Bureau of Galderma, Stiefel and Sanofi-Aventis; he is also on the Advisory Board of Galderma and Allergan.

Dr. Leon H. Kircik has served as an investigator and speaker, consultant or advisory board member for Allergan, Amgen, Astellas Pharma US, Colbar, CollaGenex, Connetics Corporation, Ferndale Laboratories, Galderma, Genentech, Intendis, Johnson & Johnson, Leo Pharma, 3M, Nano Bio, Vovartis AG, Onset Therapeutics, OrthoNeutrogena, Promius, PharmaDerm, SkinMedica, Stiefel, Valeant, Warner-Chilcott; a speaker for Abbott Laboratories, Dermik, Embil, Innovail, Merck Serono and Triax; an investigator for Acambis, Asubio, Bayer HealthCare, Biolife, Biopelle, Breckinridge Pharma, Centocor, Combinatrix, Coria, Dow Pharmaceutical Sciences, Dusa, GSK, Health Point, Medicis, Nucryst, Obagi, QLT, Pfizer, QuatrixTolerRx and UCB; and as a consultant for Laboratory Skin Care, Medical International Technologies and ZAGE.

The planning committee of this activity, James Gormley, Editor, *JDD*; Elza Tamazashvili, Editorial Assistant, *JDD*; Nick Gillespie, Publication Manager, *JDD* and Ruben Mercado, Design, *JDD*, have no relevant conflicts of interest to disclose.

Disclosure of Unlabeled Use: This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by FDA. National Association for Continuing Education, *Journal of Drugs in Dermatology* and the activity supporters do not recommend the use of any agent outside of the labeled indications. The opinions expressed in the educational activity are those of the faculty and do not necessarily represent the views of National Association for Continuing Education, *Journal of Drugs in Dermatology* and the activity supporters. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings.

Disclosure of Commercial Support: This supplement to the *Journal of Drugs in Dermatology* is supported by an educational grant from Galderma Laboratories, L.P.

© 2011-Journal of Drugs in Dermatology. All Rights Reserved.
This document contains proprietary information, images and marks of Journal of Drugs in Dermatology (JDD).
No reproduction or use of any portion of the contents of these materials may be made without the express written consent of JDD.
If you feel you have obtained this copy illegally, please contact JDD immediately.

Copyright © 2011

Introduction


Diane Thiboutot, MD

Despite the fact that acne is among the most common conditions treated by dermatologists, challenges in managing acne patients are encountered on a daily basis. The articles in this supplement help to address some of those challenges, namely, choice of appropriate topical formulations, management of acne in patients with skin of color and appropriate use of oral antibiotics in an age of emerging antibiotic-resistant bacteria.

As dermatologists, we are familiar with the importance of a topical formulation in terms of performance, patient preference and adherence to therapy. Dr. Leon H. Kircik discusses key formulation ingredients that impart desirable characteristics to a variety of topical medications, like humectants and solubilizers, such as those that permit topical dosing of dapsone. A review of the benefits of microsphere technology in dosing of retinoids and benzoyl peroxide is presented. Other unique polymers afford the opportunity to combine previously chemically incompatible agents such as adapalene and benzoyl peroxide in a fixed-dose combination. Dr. Kircik discusses the fixed-dose combination products available for acne that allow once daily dosing which can improve treatment adherence and therapeutic outcomes.

Acne vulgaris is a leading dermatologic concern in patients with skin of color. In his article, Dr. Andrew F. Alexis points out differences in clinical presentation, potential sequelae and contributing cultural factors in the treatment of patients with Fitzpatrick skin types IV–VI. Avoidance of postinflammatory hyperpigmentation is the most notable challenge in treating acne in patients with skin of color. Dr. Alexis discusses the factors involved in choosing appropriate treatment regimens that reduce the likelihood of exacerbating postinflammatory hyperpigmentation as well as strategies for managing this condition. In retinoid naïve patients, Dr. Alexis suggests starting topical retinoids at every-other-night dosing for the first one or two weeks and then increased to every night as tolerated. He points out that starting topical retinoids at lower concentrations and if needed, titrating upward over time as tolerated is a useful strategy for patients with sensitive skin. He addresses potential factors that may aggravate acne, such as the use of pomades or over-the-counter bleaching creams that contain steroids and offers helpful suggestions on recommending alternative hair care product ingredients.

One of the major public health concerns over the past few years has been the emergence of antibiotic resistance among bacteria, particularly with serious pathogens such as *Staph aureus*. Topical and oral antibiotics are widely used in the treatment of acne and resistance of *P. acnes* bacteria to antibiotics is increasing. Since acne can persist throughout the teenage years and sometimes beyond, one of the major questions in acne therapy concerns the length of time for which treatment with oral antibiotics is needed. The article on "Rethinking Treatment of Acne in the Severe Patient" reviews studies aimed at addressing the question as to whether maintenance treatment with a topical retinoid can sustain the improvement in acne seen with a previous 12 week regimen that contained an oral antibiotic. The study with doxycycline and adapalene and the study of minocycline and tazarotene indicate that improvement can be maintained with the retinoid in the majority of patients for months after the antibiotic is stopped. Data are available from the first part of a recent trial using oral doxycycline and the fixed combination of adapalene/benzoyl peroxide which demonstrate significant improvement in acne, and we are looking forward to learning how patients do in the maintenance phase of the study. Although patients may differ in their therapeutic response, these studies provide a rationale for a treatment approach using oral antibiotics plus a topical retinoid to achieve a remission, then discontinuing the antibiotic and maintaining the topical, similar to the approach advocated in the European guidelines for the treatment of acne.

Diane Thiboutot, MD
The Pennsylvania State University College of Medicine,
Hershey, PA

© 2011-Journal of Drugs in Dermatology. All Rights Reserved.
This document contains proprietary information, images and marks of Journal of Drugs in Dermatology (JDD).
No reproduction or use of any portion of the contents of these materials may be made without the express written consent of JDD.
If you feel you have obtained this copy illegally, please contact JDD immediately.

Copyright © 2011

Rethinking Treatment of Acne in the Severe Patient

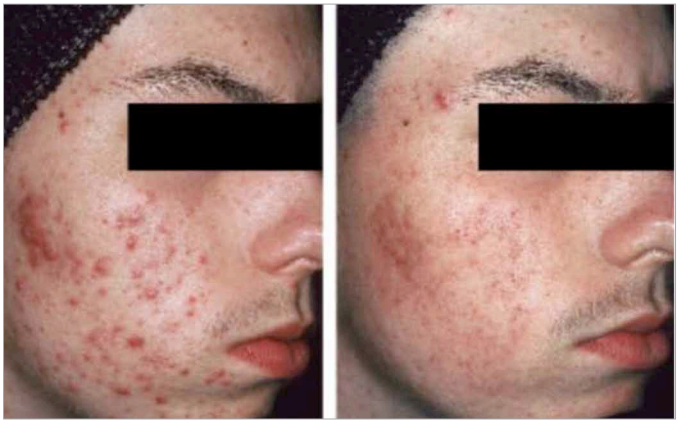
Diane Thiboutot, MD
The Pennsylvania State University College of Medicine, Hershey, PA

INTRODUCTION

Antibiotics are a standard of care in the treatment of acne. Acne treatment algorithms often recommend use of topical antibiotics in mild-to-moderate acne and oral antibiotics in the more moderate-to-severe acne patient.[1] With increasing concerns regarding the development of antibiotic-resistant strains of *P. acnes* and other bacteria, current recommendations advocate the inclusion of benzoyl peroxide in combination therapies that involve antibiotics in order to minimize the development of resistant bacteria.[1,2] One question often not addressed, however, is the length of time that patients should be treated with antibiotics for their acne. In many cases, acne can persist throughout adolescence and even into early adulthood or beyond. Some acne patients are treated consistently for years with antibiotics. Due to concerns regarding the development of antibiotic-resistant bacteria and based on review of studies where oral antibiotics were used in combination with a topical retinoid for six months, experts in Europe advocate the use of antibiotics for a three-month period in most acne patients.[3]

What are some of the reasons that acne is managed with long-term use of antibiotics? The major reason would be efficacy as oral antibiotics such as tetracycline, doxycycline and minocycline are effective in treating acne. The side effect profiles of oral antibiotics are known and physicians feel comfortable educating their patients with regard to potential adverse reactions. Oral antibiotics are easy to administer and many patients prefer their use over topical agents in terms of treatment adherence. Patients may be reluctant to stop use of antibiotics for fear that their acne will flare and this mindset makes it challenging for physicians to recommend alternative regimens that don't involve oral antibiotics. Until recently, little clinical data was available that support the use of combination regimens that limit the duration of treatment with oral antibiotics.

FIGURE 1. Acne severity before and after 12 or 15 weeks of treatment with a retinoid.



Efficacy of Topical Therapy in Inflammatory Acne

Other reasons for the potential long-term use of oral antibiotics in acne include the perception that patients with inflammatory acne cannot be adequately managed with topical therapies. Many physicians are reluctant to initiate use of topical retinoids in acne associated with moderate-to-severe inflammation for fear of exacerbation of the inflammation. There is a body of both in vitro and in vivo evidence that demonstrates the anti-inflammatory effects of topical retinoids. In vitro studies indicate that retinoids inhibit leukocyte migration, activity of transcription factors that induce cytokine release and inhibition of the toll-like receptor 2 that mediates the proinflammatory effects of *P. acnes*.[1,4] Numerous clinical trials of topical retinoids, benzoyl peroxide, the retinoid/BP combination and topical dapsone demonstrate statistically significant reductions in the numbers of inflammatory acne lesions in addition to reduction in noninflammatory lesions.[5-11] In addition to lesion count data, photographic analysis of the response of patients with moderate and even more severe acne treated with a topical retinoid alone supports the ability of these agents to improve inflammatory acne[7] (Figure 1).

Combination Regimens That Limit Antibiotic Use Are Effective in Moderate and Severe Acne

Since 2005, there have been three studies examining the efficacy of combination regimens for moderate or severe acne that limit the use of oral antibiotics.[12-15] In general, these studies examine the efficacy of an oral antibiotic (doxycycline or minocycline) combined with a topical retinoid (tazarotene, adapalene or the fixed combination of adapalene/BP) or vehicle for approximately three months and then examine the ability of the topical retinoid or adapalene/BP combination to maintain the improvement noted in the first phase of the study.

Leyden et al. studied 189 patients with moderate-to-severe acne that received minocycline 100 mg twice daily plus tazarotene gel 0.1% daily for 12 weeks.[12] Subjects that attained 75 percent

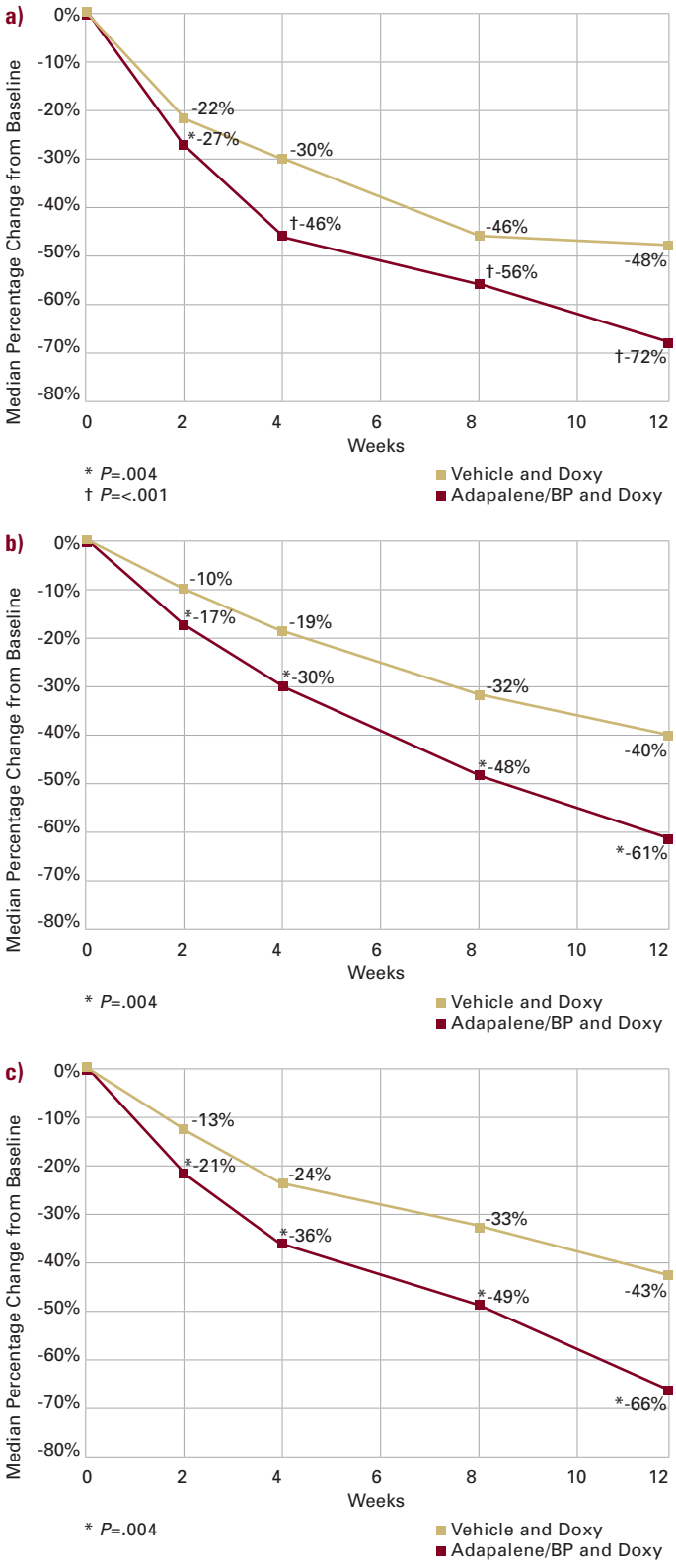
© 2011-Journal of Drugs in Dermatology. All Rights Reserved.
This document contains proprietary information, images and marks of Journal of Drugs in Dermatology (JDD).
No reproduction or use of any portion of the contents of these materials may be made without the express written consent of JDD.
If you feel you have obtained this copy illegally, please contact JDD immediately.

improvement in their acne after 12 weeks were then randomized to one of three arms: minocycline 100 mg twice daily + vehicle gel; minocycline 100 mg twice daily + tazarotene gel 0.1% or to tazarotene gel 0.1% + placebo capsules. After the first 12 weeks, 114 patients had greater than 75 percent improvement in their acne. In the second (maintenance) phase of the study, more than 80 percent of the patients in each group maintained 50 percent of the improvement achieved in the first phase of the study and more than 50 percent of subjects maintained 75 percent of the improvement achieved in the first phase. There were no statistically different results in lesion counts between the three arms in the maintenance phase of the study, although there was a trend for greater maintenance of the improvement in inflammatory lesions in the arms containing minocycline.

Thiboutot et al. studied 467 patients with severe acne that were randomized to receive doxycycline 100 mg daily plus adapalene 0.1% gel daily or doxycycline 100 mg daily plus vehicle for 12 weeks.[13,15] At week 12, the combination of doxycycline and adapalene was statistically significantly superior to the doxycycline alone for all lesion types. Reductions in inflammatory lesion count were on the order of 60 percent in the combination arm. Subjects that achieved 50 percent improvement in their acne after 12 weeks in the first phase were then eligible to enter the 16 week maintenance phase. Two hundred and fifty three subjects were randomized to receive either adapalene gel 0.1% or vehicle gel once daily for 16 weeks. Successful maintenance was defined as the ability to maintain 50 percent of the improvement in acne noted at the end of the first phase of the study. Subjects treated with adaplene in the maintenance phase had higher rates of success compared to those receiving vehicle (75% success vs. 54% success, $P<.001$), as well as significantly lower lesion counts.

More recently, a two-phase study was conducted in patients with severe acne with the goal of determining the ability of the fixed combination of adapalene 0.1%/BP 2.5% gel to maintain the improvement in severe acne following an initial regimen containing oral doxycycline with or without the topical adapalene/BP. The results of the maintenance phase of this study are pending. Stein Gold et al. reported on the first phase of the study, in which 459 patients with severe acne were randomized to receive either doxycycline hyclate 100 mg daily in combination with either the fixed combination of adapalene 0.1%/BP 2.5% gel or vehicle gel for 12 weeks.[14] Acne severity was evaluated on a 5-point scale and patients with a grade of 4: ("Severe") were enrolled. Lesion counts and global severity were assessed at weeks 2, 4, 8 and 12. Statistically significant reduction in all lesion counts was noted as early as week 2 in the group receiving the adapalene/BP with the doxycycline compared to the group receiving vehicle plus doxycycline (Figure 2). At the end of 12 weeks, 31.5 percent of patients in the doxycycline + adapalene/BP group were "Clear" or "Almost Clear"

FIGURE 2. a) Inflammatory Lesion Reduction. **b)** Non-inflammatory Lesion Reduction. **c)** Total Lesion Reduction.



© 2011-Journal of Drugs in Dermatology. All Rights Reserved.
This document contains proprietary information, images and marks of Journal of Drugs in Dermatology (JDD).
No reproduction or use of any portion of the contents of these materials may be made without the express written consent of JDD.
If you feel you have obtained this copy illegally, please contact JDD immediately.

FIGURE 3. Treatment Success (Clear/Almost Clear).

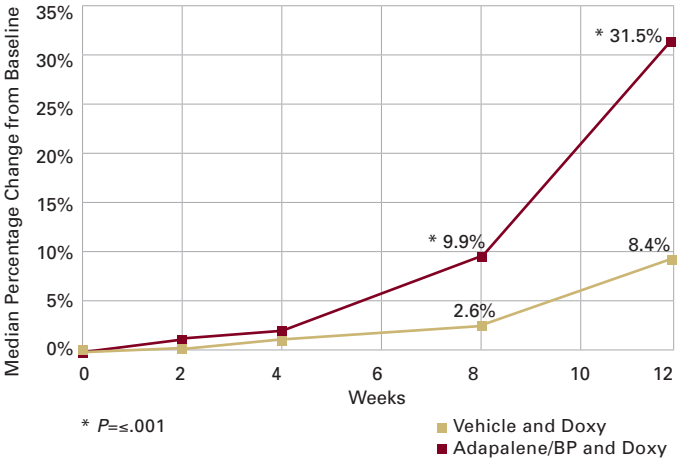
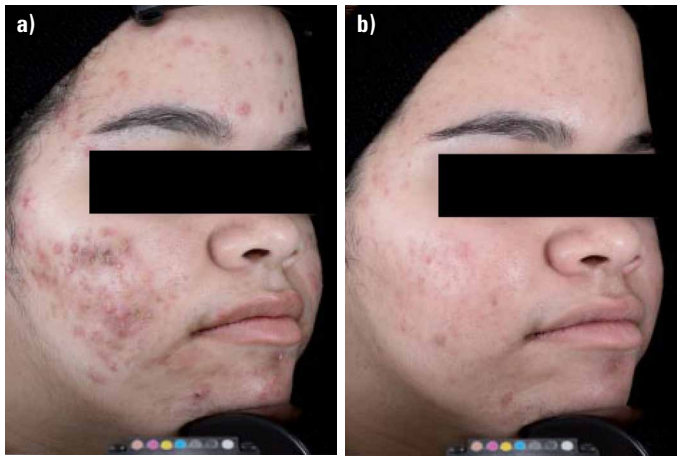


FIGURE 4. a) A participant with severe acne vulgaris at baseline. **b)** After 12 weeks of adapalene 0.1%–benzoyl peroxide 2.5% gel with doxycycline therapy.



compared to 8.4 percent in the doxycycline + vehicle group ($P< 0.001$) (Figure 3). Reductions in lesion counts in the combination group were 61 percent, 72 percent and 66 percent for noninflammatory, inflammatory and total lesions, respectively, compared to 40 percent, 48 percent and 43 percent in the doxycycline + vehicle group for noninflammatory, inflammatory and total lesions, respectively. An example of a successfully treated patient is seen in Figure 4.

Despite the fact that acne is one of the most common skin conditions affecting adolescents and young adults, management of acne can be challenging, particularly with regard to its chronic nature and sometimes sporadic treatment adherence by patients.[16,17] Over the past few decades, there have been increasing efforts to limit the use of oral antibiotics to situations in which they are needed due to concerns with the emergence of antibiotic-resistant strains of bacteria.[2,18] Numerous studies report the emergence of antibiotic-resistant strains of *P. acnes*.[19-21] Initially, resistance developed to erythromycin, which was once widely used in the systemic treatment of acne.[20] This was followed by increasing reports of resistance to tetracycline, doxycycline and then minocycline. Laboratory evaluation of *P. acnes* resistance is not part of routine clinical practice, but evidence of resistance exists in the clinical observation that patients respond initially to certain antibiotics but efficacy may wane over time. Strategies are needed to limit the use of oral antibiotics in acne to situations where they are clearly needed. Such strategies will help to preserve the efficacy of antibiotics in the acne therapeutic armamentarium.

In clinical practice, with a few exceptions (such as severe nodular acne with scarring treated with isotretinoin), it is rare to treat moderate-to-severe acne with a single agent. Combination therapy is the standard of care in most cases of acne of this severity. Until recently, there was little data regarding the efficacy of combination regimens containing oral antibiotics and topical retinoids in moderate-to-severe acne. The studies discussed in this paper begin to address the question of how long patients need to be on an oral antibiotic to achieve significant improvement and what happens to the course of acne in these patients once the antibiotic is stopped with continuation of a topical retinoid. These studies demonstrate that efficacy is increased when topical retinoids or adapalene/BP are added to a regimen containing minocycline or doxycycline. In these studies after 12 weeks, reductions in inflammatory lesions are on the order of 66 percent, 65 percent and 72 percent for tazarotene + minocycline, adapalene + doxycycline and adapalene/BP + doxycycline, respectively. Reductions in noninflammatory lesions were 64 percent, 60 percent and 61 percent for the oral antibiotic combined with tazarotene, adapalene and adapalene/BP, respectively.

Furthermore, these studies indicate that a significant majority of patients will maintain at least 50 percent of the improvement seen with the combination of oral antibiotic + retinoid for up to 12 or 16 weeks after the antibiotic is discontinued. It will be interesting to learn about the efficacy of the fixed combination of adapalene/BP in maintaining acne improvement following discontinuation of doxycycline once these data become available. Taken together, the studies discussed in this paper support the rationale for limiting the duration of oral antibiotic treatment in patients with moderate or severe acne by demonstrating the efficacy of topical retinoids in maintenance therapy of acne. It is important to keep in mind that clinical trial data is presented as mean or median values and individual patients may differ in their response in terms of the duration of antibiotic therapy needed to achieve meaningful improvement, so adjustments may be needed for individual patients.

© 2011-Journal of Drugs in Dermatology. All Rights Reserved.
This document contains proprietary information, images and marks of Journal of Drugs in Dermatology (JDD).
No reproduction or use of any portion of the contents of these materials may be made without the express written consent of JDD.
If you feel you have obtained this copy illegally, please contact JDD immediately.

In terms of relating these data to clinical practice, it would make sense to initiate treatment of patients with moderate-to-severe acne with an oral antibiotic, topical retinoid and benzoyl peroxide. Once-a-day use of the fixed-dose adapalene/BP with an oral antibiotic can simplify a patient's regimen and may lead to improved treatment adherence. If the patient's acne fails to respond to the oral antibiotic, topical retinoid and BP after a reasonable time period, or if the acne is very severe and associated with significant scarring, isotretinoin should be considered. In the majority of cases, once significant improvement in the acne is obtained with the combination regimen of oral antibiotic/retinoid/BP, the oral antibiotic can be stopped and the topical agent continued. Again, patients may differ in the degree of improvement maintained with a single topical agent or a single topical combination product, and repeat courses of oral antibiotics and/or additions to the topical regimen may be required. This may be influenced by patient age, as in the case of a young teenager whose likelihood of recurrence of acne may be higher compared to a patient in late adolescence or early adulthood. The overall effect would be to move away from consistent use of oral antibiotics in acne patients for years at a time whenever possible.

CONCLUSION

Managing acne continues to be a challenge. The data presented here provide a rationale for rethinking our approach to the use of oral antibiotics in moderate-to-severe acne and suggest strategies that favor combination regimens that limit the use of oral antibiotics.

DISCLOSURES

Dr. Diane Thiboutot has served as a consultant or investigator for Allergan, DOW Pharmaceutical Sciences, Galderma, Intendis, Johnson & Johnson, Medicis and Stiefel.

REFERENCES

1. Thiboutot D, Gollnick H, Bettoli V, et al. New insights into the management of acne: An update from the Global Alliance to Improve Outcomes in Acne group. *J Am Acad Dermatol*. 2009;60(suppl 5):1S-50S.
2. Del Rosso JQ, Leyden JJ, Thiboutot D, et al. Antibiotic use in acne vulgaris and rosacea: Clinical considerations and resistance issues of significance to dermatologists. *Cutis*. 2008;82(2 suppl 2):5-12.
3. Dreno B, Bettoli V, Ochsendorf F, et al. European recommendations on the use of oral antibiotics for acne. *Eur J Dermatol*. 2004;14(6):391-399.
4. Liu PT, Krutzik SR, Kim J, et al. Cutting edge: All-trans retinoic acid down-regulates TLR2 expression and function. *J Immunol*. 2005;174(5):2467-2470.
5. Gold LS, Tan J, Cruz-Santana A, et al. A North American study of adapalene-benzoyl peroxide combination gel in the treatment of acne. *Cutis*. 2009;84(2):110-116.
6. Shalita AR, Chalker DK, Griffith RF, et al. Tazarotene gel is safe and effective in the treatment of acne vulgaris: A multicenter, double-blind, vehicle-controlled study. *Cutis*. 1999;63(6):349-354.
7. Leyden JJ, Shalita A, Thiboutot D, et al. Topical retinoids in inflammatory acne: A retrospective, investigator-blinded, vehicle-controlled, photographic assessment. *Clin Ther*. 2005;27(2):216-224.
8. Thiboutot D, Pariser DM, Egan N, et al. Adapalene gel 0.3% for the treatment of acne vulgaris: A multicenter, randomized, double-blind, controlled, phase III trial. *J Am Acad Dermatol*. 2006;54(2):242-250.
9. Berger R, Barba A, Fleischer A, et al. A double-blinded, randomized, vehicle-controlled, multicenter, parallel-group study to assess the safety and efficacy of tretinoin gel microsphere 0.04% in the treatment of acne vulgaris in adults. *Cutis*. 2007;80(2):152-157.
10. Thiboutot D, Eichenfield L, Shalita A, et al. A 3-step acne system containing solubilized benzoyl peroxide versus clindamycin-benzoyl peroxide. *Cutis*. 2009;84(1):48-55.
11. Draelos ZD, Carter E, Maloney JM, et al. Two randomized studies demonstrate the efficacy and safety of dapsone gel, 5% for the treatment of acne vulgaris. *J Am Acad Dermatol*. 2007;56(3):439 e1-10. Epub January 17, 2007.
12. Leyden J, Thiboutot DM, Shalita AR, et al. Comparison of tazarotene and minocycline maintenance therapies in acne vulgaris: A multicenter, double-blind, randomized, parallel-group study. *Arch Dermatol*. 2006;142(5):605-612.
13. Thiboutot DM, Shalita AR, Yamauchi PS, et al. Combination therapy with adapalene gel 0.1% and doxycycline for severe acne vulgaris: A multicenter, investigator-blind, randomized, controlled study. *Skinmed*. 2005;4(3):138-146.
14. Gold LS, Cruz A, Eichenfield L, et al. Effective and safe combination therapy for severe acne vulgaris: A randomized, vehicle-controlled, double-blind study of adapalene 0.1%-benzoyl peroxide 2.5% fixed-dose combination gel with doxycycline hyclate 100 mg. *Cutis*. 2010;85(2):94-104.
15. Thiboutot DM, Shalita AR, Yamauchi PS, et al. Adapalene gel, 0.1%, as maintenance therapy for acne vulgaris: A randomized, controlled, investigator-blind follow-up of a recent combination study. *Arch Dermatol*. 2006;142(5):597-602.
16. Dreno B, Thiboutot D, Gollnick H, et al. Large-scale worldwide observational study of adherence with acne therapy. *Int J Dermatol*;49(4):448-456.
17. Strauss JS, Krowchuk DP, Leyden JJ, et al. Guidelines of care for acne vulgaris management. *J Am Acad Dermatol*. 2007;56(4):651-663.
18. Eady E, Jones C, Tipper J, et al. Antibiotic resistant propionibacteria in acne: Need for policies to modify antibiotic usage. *Br Med J*. 1993;306:555-556.
19. Bojar R, Eady E, Jones C, et al. Inibition of erythromycin-resistant propionibacteria on the skin of acne patients by topical erythromycin with and without zinc. *Br J Dermatol*. 1994;130(3):329-336.
20. Coates P, Vyakrnam S, Eady E, et al. Prevalence of antibiotic-resistant propionibacteria on the skin of acne patients: 10-year surveillance data and snapshot distribution study. *Br J Dermatol*. 2002;146:840-848.

© 2011-Journal of Drugs in Dermatology. All Rights Reserved.
This document contains proprietary information, images and marks of Journal of Drugs in Dermatology (JDD).
No reproduction or use of any portion of the contents of these materials may be made without the express written consent of JDD.
If you feel you have obtained this copy illegally, please contact JDD immediately.

21. Eady E, Jones C, Gardner K, et al. Tetracycline-resistant propionibacteria from acne patients are cross-resistant to doxycycline, but sensitive to minocycline. *Br J Dermatol*. 1993;128:556-560.

ADDRESS FOR CORRESPONDENCE

Diane Thiboutot, MD
The Pennsylvania State University College of Medicine
Department of Dermatology Research Laboratory
The Milton S. Hershey Medical Center
500 University Drive
Hershey, PA 17033
Phone: ..... (717) 531-7437
Fax: ..... (717) 531-4821

© 2011-Journal of Drugs in Dermatology. All Rights Reserved.
This document contains proprietary information, images and marks of Journal of Drugs in Dermatology (JDD).
No reproduction or use of any portion of the contents of these materials may be made without the express written consent of JDD.
If you feel you have obtained this copy illegally, please contact JDD immediately.

Acne in Patients With Skin of Color

Andrew F. Alexis MD MPH
Skin of Color Center, St. Luke's Roosevelt Hospital, Columbia University College of Physicians and Surgeons, New York, NY

INTRODUCTION

Acne vulgaris is among the most common diagnoses for which patients in industrialized nations visit a dermatologist. When acne presents in patients with darkly pigmented skin or "skin of color" (i.e., Fitzpatrick skin types IV–VI), differences in clinical presentation, potential sequelae and contributing cultural factors are observed. These differences contribute to nuances in patient education, selection of treatment regimens and therapeutic goals for the acne patient with skin of color.

Epidemiology of Acne Vulgaris in Skin of Color

Published practice and community-based survey studies have reported that acne is the most frequent skin condition in numerous populations with skin of color, including blacks (in New York, NY[1]; Washington, DC[2]; and London, UK[3]), Latinos (in New York, NY[4]) and Arab-Americans (in Southeast Michigan[5]). In a recent study by Perkins et al.[6] where unilateral facial photographs of 2,835 females (10 to 70 year of age) from four cities (Los Angeles, USA; London, UK; Akita, Japan; and Rome, Italy) were examined, the prevalence of acne was found to be 37 percent, 32 percent, 30 percent, 24 percent and 23 percent in African Americans, Hispanics, Asians, Caucasians and Continental Indians, respectively.

Potential Sequelae and Excacerbating Factors

The most notable clinical difference observed in acne vulgaris among patients with skin of color is the frequent development of postinflammatory hyperpigmentation (PIH). PIH is the most common sequela of acne in darker skin types and is characterized by small hyperpigmented macules at sites of previous acne lesions that typically persist for several weeks to several months.[7] In many instances, PIH is the presenting complaint among patients with skin of color and is therefore of equal or greater concern to the patient than the acne itself.[7,8] In extensive cases PIH can be considerably disfiguring and contribute to the psychological distress associated with acne. Patients often refer to the PIH as "scars" and may have a limited understanding of the cause or the expected prognosis. In the aforementioned community-based photographic assessment study by Perkins et al.,[6] hyperpigmentation was observed in 65 percent, 48 percent and 18 percent of African American, Hispanic and Asian women with acne, respectively. In a survey of 313 acne patients (239 Black, 55 Hispanic, 19 Asian and other) by Taylor et al.,[9] PIH was observed in 65 percent of blacks, 52 percent of Hispanics, and 47 percent of Asians. The average duration of PIH was reported to be four months or longer.[9]

Keloids (as well as hypertrophic scars) are another potential long-term sequela of acne that occurs more frequently in patients with skin of color.[1,7,8,10] Although they are far less common an association with acne than PIH, keloids result in greater morbidity given their more chronic course and symptomatology. The risk of acne-associated keloids is generally limited to patients with moderate or severe trunkal acne and a genetic predisposition toward keloid scarring (which may be identified by a personal or family history of keloids).

A number of culturally related skin and hair care practices can contribute to acne vulgaris in some populations with skin of color. Pomade acne, which is characterized by a predominance of comedones on the upper forehead and temples, is associated with the use of comedogenic hair care products,[11] which traditionally have been used by blacks to add manageability and sheen to the hair. Thicker, more greasy hair care products that contain petrolatum, lanolin and mineral oil are the common culprits (although the comedogenicity of petrolatum has recently been questioned[12]). However, this variant of acne has become considerably less prevalent in the U.S., where the use of thicker hair pomades has lessened in popularity compared to several decades ago and has been largely replaced by lighter, less comedogenic products. However, when pomade acne is observed, the patient should not only be advised to discontinue the offending hair product, but should also be given a recommendation for an effective alternative. In this author's experience, hair serums containing dimethicone or cyclomethicone are useful alternatives to thicker hair products and are unlikely to exacerbate acne.

The use of cocoa butter containing creams is commonly observed among African American patients with acne and PIH due to the widely held belief in their ability to "even the skin tone" and improve imperfections. This practice, in turn, may exacerbate acne due to the comedogenicity of cocoa butter. Similarly, patients with PIH frequently turn to make-ups to camouflage the dyschromia and in so doing may use increased amounts of potentially comedogenic cosmetics to ensure complete coverage of the hyperigmented macules.

© 2011-Journal of Drugs in Dermatology. All Rights Reserved.
This document contains proprietary information, images and marks of Journal of Drugs in Dermatology (JDD).
No reproduction or use of any portion of the contents of these materials may be made without the express written consent of JDD.
If you feel you have obtained this copy illegally, please contact JDD immediately.

Far less common but equally important to note is the presentation of steroid acne due to the use of bleaching creams that contain potent or superpotent topical corticosteroids. This may be seen in a specific subset of acne patients with skin of color—most commonly female patients from parts of Africa, Asia, or the Middle East—who use various topical bleaching creams that contain potent corticosteroids on the face and other anatomic areas in an effort to lighten their complexion.[13] Such patients present with characteristic clinical features of steroid acne (e.g., monomorphic papules and pustules on the face and/or trunk) along with other hallmarks of prolonged use of topical steroids and hydoquinone.[13] In the U.S. these bleaching products are often purchased illegally without a prescription in "ethnic" neighborhood beauty supply stores and via the internet. The patient is typically not aware of the ingredients of these products and as such, it is up to the physician to have an index of suspicion when features of steroid acne are identified. In such instances, the patient should be asked to bring in all skin products they have used in the past six months so that the ingredients can be reviewed in the office and the offending products are discontinued.

Histopathologic Features

A study by Halder et al.,[14] which examined biopsies from the face of 30 black female subjects with acne vulgaris, identified inflammation histopathologically around lesions that were not clinically inflamed (i.e., comedones). Papules and pustules demonstrated marked inflammation with many neutrophils and mononuclear cells that extended considerably beyond the borders of the individual lesions. It is proposed that this subclinical inflammation may contribute to the propensity toward postinflammatory hyperpigmentation in acne patients with skin of color. However, subclinical inflammation is likely a feature of acne vulgaris in general and not specific to skin of color, as studies in other populations have identified inflammatory responses in clinically non-inflamed skin using immunohistochemistry[15] and the development of clinically inflammatory lesions de novo (arising from normal appearing skin) using serial digital photography.[16]

Nuances to Treatment

The potential for PIH and keloid scarring in skin of color has important treatment implications for the acne patient. Early and efficacious treatment is paramount to help prevent or minimize the risk and severity of pigmentary abnormalities and scarring. Given that PIH can occur as a sequela of acne itself, or as a complication of treatment, treatment regimens must not only be aggressive enough to reduce inflammation and other pathogenic factors, but also well tolerated so that irritation is avoided.

Ensuring tolerability requires careful selection of topical treatment regimens, taking into consideration the active ingredients, concentration, vehicle and dosing regimen. In addition, discontinuation of any potentially irritating concomitant skin care products is paramount.[7] These may include toners, scrubs, or astringents that if used together with topical prescription products may contribute varying degrees of irritation and dryness. In retinoid naïve patients, topical retinoids are best started at every-other-night dosing for the first one or two weeks and then increased to every night as tolerated. Starting topical retinoids at lower concentrations and if needed, titrating upward over time as tolerated is a useful strategy for patients with sensitive skin.[9] Benzoyl peroxide formulations applied to the face in the 5% and lower range are generally well tolerated and preferred over higher concentrations for tolerability reasons (although microsphere formulations may allow for higher concentrations to be used without a significant increase in irritation[17]). To combat treatment associated dryness, stinging, or burning, a non-comedogenic moisturizer can be applied subsequent to the prescription topical medication. With respect to vehicle considerations, aqueous gels, lotions, or creams are preferred over ethanolic gels given their lower irritation potential.

CONCLUSION

While there are comparative differences and individual variations in tolerability, all of the topical acne medications currently available in the U.S. are safe and appropriate options for the patient with skin of color. In the current author's opinion, most topical formulations approved by the Food and Drug Administration (FDA) in the past five years have included satisfactory numbers of subjects with skin of color based on review of demographic information in Phase 3 clinical trials (where an adequate proportion of the study populations belongs to various nonwhite racial/ethnic groups).[18-21] In addition, a number of Phase 4 studies have helped to establish the safety of numerous agents in nonwhite patient populations.[22-25]

Retinoids are a particularly important component of the topical treatment regimen in patients with skin of color. First, topical retinoids have been shown to reduce acne-associated hyperpigmentation.[24,26,27] Proposed mechanisms for this effect include: Inhibition of tyrosinase induction; increased dequamation; inhibition of melanosome transfer from melanocytes to keratinocytes; and redistribution or dispersion of epidermal melanin.[26,28] Second, anti-inflammatory effects of retinoids have been demonstrated in vitro.[29,30] Theoretically, this may help to reduce inflammation that may lead to PIH. Third, given the topical retinoids' efficacy as a maintenance therapy,[31,32] it is plausible that fewer acne lesions over time would be associated with less PIH over time (when retinoid therapy is continued long-term). The latter two hypotheses warrant validation in a well-designed research study.

© 2011-Journal of Drugs in Dermatology. All Rights Reserved.
This document contains proprietary information, images and marks of Journal of Drugs in Dermatology (JDD).
No reproduction or use of any portion of the contents of these materials may be made without the express written consent of JDD.
If you feel you have obtained this copy illegally, please contact JDD immediately.

All currently available topical retinoids may be safely used on darker skin types, but variations in tolerability may be observed based on the specific retinoid, the concentration and the vehicle. Studies of topical retinoids specifically in acne subjects with skin of color include: Tretinoin 0.1% cream in African Americans[26]; tazorotene 0.1% cream in Fitzpatrick skin types III–VI (94% of active treatment arm was African American); and adapalene 0.1% gel in South African blacks[27] and Japanese subjects.[25] Meta-analyses of adapalene 0.1% gel[33] and the fixed combination adapalene 0.1% gel-benzoyl peroxide 2.5% gel[34] have demonstrated comparable tolerability between dark skinned subjects and white subjects. In both of the above meta-analyses, erythema was less frequent in dark skinned subjects than in white subjects, however, this may be confounded by the difficulty in visualizing erythema in very darkly pigmented skin (i.e., Fitzpatrick skin type VI).

Given the high frequency of acne-associated PIH, adjunctive therapies are recommended to prevent and treat this potential sequela of acne in skin of color. First, sun protection is advised to prevent exacerbation of PIH secondary to ultraviolet radiation induced melanogenesis. A non-comedogenic moisturizer containing a broad-spectrum sunscreen with an SPF of 30 or higher is therefore a useful adjunct to the topical acne regimen for patients with skin of color. Second, topical bleaching agents, including hydroquinone, kojic acid or azelaic acid, may be considered for application to persistent hyperpigmented macules.[7,9] When hydroquinone 4% cream formulations are used, patients should be warned about the potential for a temporary "halo" of hypopigmentation on perilesional skin. With this adverse event in mind, the current author reserves hydroquinone for larger, persistent acne-associated hyperpigmented macules that do not resolve after several months of topical retinoid therapy; patients are instructed to apply the hydroquinone with a cotton tip applicator to help target the lesions with precision and minimize application to surrounding normal skin. Third, superficial chemical peels can be considered to help improve PIH. While strong evidence to support the use of chemical peels in the treatment of PIH is lacking,[35] salicylic acid[36,37] and glycolic acid peels[38] were found to be useful in small open label studies and the adjunctive use of superficial chemical peels in the treatment of acne in skin of color has been advanced by several authors.[7,8,39-41]

The use of laser and light based therapies for acne in skin of color has not been well studied. However, several small studies (primarily in East Asian subjects) have demonstrated safety and efficacy in higher Fitzpatrick skin phototypes.[42-47]

DISCLOSURES

Dr. Andrew F. Alexis is on the Speakers' Bureau of Galderma, Stiefel and Sanofi-Aventis; he is also on the Advisory Board of Galderma and Allergan.

REFERENCES

1. Alexis AF, Sergay AB, Taylor SC. Common dermatologic disorders in skin of color: A comparative practice survey. *Cutis*. 2007;80(5):387-394.
2. Halder RM, Grimes PE, McLaurin CI, Kress MA, Kenney JA, Jr. Incidence of common dermatoses in a predominantly black dermatologic practice. *Cutis*. 1983;32(4):388, 390.
3. Child FJ, Fuller LC, Higgins EM, Du Vivier AW. A study of the spectrum of skin disease occurring in a black population in south-east London. *Br J Dermatol*. 1999;141(3):512-517.
4. Sanchez MR. Cutaneous diseases in Latinos. *Dermatol Clin*. 2003;21(4):689-697.
5. El-Essawi D, Musial JL, Hammad A, Lim HW. A survey of skin disease and skin-related issues in Arab Americans. *J Am Acad Dermatol*. 2007;56(6):933-938.
6. Perkins A, Cheng C, Hillebrand G, Miyamoto K, Kimball A. Comparison of the epidemiology of acne vulgaris among Caucasian, Asian, Continental Indian and African American women. *J Eur Acad Dermatol Venereol*. Epub November 25, 2010.
7. Shah SK, Alexis AF. Acne in skin of color: Practical approaches to treatment. *J Dermatolog Treat*. 2010;21(3):206-211.
8. Davis EC, Callender VD. A review of acne in ethnic skin: Pathogenesis, clinical manifestations, and management strategies. *J Clin Aesthet Dermatol*. 2010;3(4):24-38.
9. Taylor SC, Cook-Bolden F, Rahman Z, Strachan D. Acne vulgaris in skin of color. *J Am Acad Dermatol*. 2002;46(2 suppl Understanding):98S-106S.
10. Halder R, Brooks H, Callender V. Acne in Ethnic Skin. *Dermatol Clin*. 2003;21(4):609-615.
11. Plewig G, Fulton JE, Kligman AM. Pomade acne. *Arch Dermatol*. 1970;101(5):580-584.
12. Nguyen SH, Dang TP, Maibach HI. Comedogenicity in rabbit: Some cosmetic ingredients/vehicles. *Cutan Ocul Toxicol*. 2007;26(4):287-292.
13. Dadzie OE, Petit A. Skin bleaching: Highlighting the misuse of cutaneous depigmenting agents. *J Eur Acad Dermatol Venereol*. 2009;23(7):741-750.
14. Halder RM, Holmes YC, Bridgeman-Shah S, Kligman A. A clinical pathological study of acne vulgaris in black females. *J Invest Dermatol*. 1996;106:888.
15. Jeremy AH, Holland DB, Roberts SG, Thomson KF, Cunliffe WJ. Inflammatory events are involved in acne lesion initiation. *J Invest Dermatol*. 2003;121(1):20-27.
16. Do TT, Zarkhin S, Orringer JS, Nemeth S, Hamilton T, Sachs D, et al. Computer-assisted alignment and tracking of acne lesions indicate that most inflammatory lesions arise from comedones and de novo. *J Am Acad Dermatol*. 2008;58(4):603-608.
17. Kircik L, Friedman A. Optimizing acne therapy with unique vehicles. *J Drugs Dermatol*. 2010;9(5 suppl ODAC Conf Pt 1):53S-57S.
18. Schlessinger J, Menter A, Gold M, Leonardi C, Eichenfield L, Plott RT, et al. Clinical safety and efficacy studies of a novel formulation combining 1.2% clindamycin phosphate and 0.025% tretinoin for the treatment of acne vulgaris. *J Drugs Dermatol*. 2007;6(6):607-615.
19. Draelos ZD, Carter E, Maloney JM, Elewski B, Poulin Y, Lynde C, et al. Two randomized studies demonstrate the efficacy and safety of dapsone gel, 5% for the treatment of acne vulgaris. *J Am Acad Dermatol*. 2007;56(3):439 e1-10.

© 2011-Journal of Drugs in Dermatology. All Rights Reserved.
This document contains proprietary information, images and marks of Journal of Drugs in Dermatology (JDD).
No reproduction or use of any portion of the contents of these materials may be made without the express written consent of JDD.
If you feel you have obtained this copy illegally, please contact JDD immediately.

20. Thiboutot D, Pariser DM, Egan N, Flores J, Herndon JH, Jr., Kanof NB, et al. Adapalene gel 0.3% for the treatment of acne vulgaris: A multicenter, randomized, double-blind, controlled, phase III trial. *J Am Acad Dermatol.* 2006;54(2):242-250.
21. Thiboutot DM, Weiss J, Bucko A, Eichenfield L, Jones T, Clark S, et al. Adapalene-benzoyl peroxide, a fixed-dose combination for the treatment of acne vulgaris: Results of a multicenter, randomized double-blind, controlled study. *J Am Acad Dermatol.* 2007;57(5):791-799.
22. Fernandez-Obregon A, Davis MW. The BEST study: Evaluating efficacy by selected demographic subsets. *Cutis.* 2003;71(suppl 2):18-26.
23. Taylor SC. Utilizing combination therapy for ethnic skin. *Cutis.* cutaneous medicine for the practitioner. 2007;80(suppl 1):15-20.
24. Grimes P, Callender V. Tazarotene cream for postinflammatory hyperpigmentation and acne vulgaris in darker skin: A double-blind, randomized, vehicle-controlled study. *Cutis.* 2006;77(1):45-50.
25. Kawashima M, Harada S, Loesche C, Miyachi Y. Adapalene gel 0.1% is effective and safe for Japanese patients with acne vulgaris: A randomized, multicenter, investigator-blinded, controlled study. *J Dermatol Sci.* 2008;49(3):241-248.
26. Bulengo-Ransby SM, Griffiths CE, Kimbrough-Green CK, et al. Topical tretinoin (retinoic acid) therapy for hyperpigmented lesions caused by inflammation of the skin in black patients. *N Engl J Med.* 1993;328(20):1438-1443.
27. Jacyk WK. Adapalene in the treatment of African patients. *J Eur Acad Dermatol Venereol.* 2001;15(suppl 3):37-42.
28. Alexis AF, Taylor, S.C. Acne and Scarring. In: H. BELJM, ed. *Ethnic Skin and Hair.* New York: Informa HealthCare USA; 2007.
29. Tenaud I, Khammari A, Dreno B. In vitro modulation of TLR-2, CD1d and IL-10 by adapalene on normal human skin and acne inflammatory lesions. *Exp Dermatol.* 2007;16(6):500-506.
30. Liu PT, Krutzik SR, Kim J, Modlin RL. Cutting edge: All-trans retinoic acid down-regulates TLR2 expression and function. *J Immunol.* 2005;174(5):2467-2470.
31. Thiboutot DM, Shalita AR, Yamauchi PS, Dawson C, Kerrouche N, Arsonnaud S, et al. Adapalene gel, 0.1%, as maintenance therapy for acne vulgaris: A randomized, controlled, investigator-blind follow-up of a recent combination study. *Arch Dermatol.* 2006;142(5):597-602.
32. Leyden J, Thiboutot DM, Shalita AR, Webster G, Washenik K, Strober BE, et al. Comparison of tazarotene and minocycline maintenance therapies in acne vulgaris: A multicenter, double-blind, randomized, parallel-group study. *Arch Dermatol.* 2006;142(5):605-612.
33. Czernielewski J, Poncet M, Mizzi F. Efficacy and cutaneous safety of adapalene in black patients versus white patients with acne vulgaris. *Cutis.* 2002;70(4):243-248.
34. Callender VD, Preston N, Osborn C, Johnson L, Gottschalk RW. A Meta-analysis to Investigate the Relation Between Fitzpatrick Skin Types and Tolerability of Adapalene-Benzoyl Peroxide Topical Gel in Subjects with Mild or Moderate Acne. *J Clin Aesthet Dermatol.* 2010;3(8):15-19.
35. Joshi SS, Boone SL, Alam M, Yoo S, White L, Rademaker A, et al. Effectiveness, safety, and effect on quality of life of topical salicylic acid peels for treatment of postinflammatory hyperpigmentation in dark skin. *Dermatol Surg.* 2009;35(4):638-644; discussion 44.
36. Grimes PE. The safety and efficacy of salicylic acid chemical peels in darker racial-ethnic groups. *Dermatol Surg.* 1999;25(1):18-22.
37. Lee HS, Kim IH. Salicylic acid peels for the treatment of acne vulgaris in Asian patients. *Dermatol Surg.* 2003;29(12):1196-1199; discussion 9.
38. Burns RL, Prevost-Blank PL, Lawry MA, Lawry TB, Faria DT, Fivenson DP. Glycolic acid peels for postinflammatory hyperpigmentation in black patients. A comparative study. *Dermatol Surg.* 1997;23(3):171-174; discussion 5.
39. Garg VK, Sinha S, Sarkar R. Glycolic acid peels versus salicylic-mandelic acid peels in active acne vulgaris and post-acne scarring and hyperpigmentation: A comparative study. *Dermatol Surg.* 2009;35(1):59-65.
40. Wang CM, Huang CL, Hu CT, Chan HL. The effect of glycolic acid on the treatment of acne in Asian skin. *Dermatol Surg.* 1997;23(1):23-29.
41. Alexis AF, Lamb A. Concomitant therapy for acne in patients with skin of color: A case-based approach. *Dermatol Nurs.* 2009;21(1):33-36.
42. Terrell S, Aires D, Schweiger ES. Treatment of acne vulgaris using blue light photodynamic therapy in an African-American patient. *J Drugs Dermatol.* 2009;8(7):669-671.
43. Noborio R, Nishida E, Morita A. Clinical effect of low-energy double-pass 1450 nm laser treatment for acne in Asians. *Photodermatol Photoimmunol Photomed.* 2009;25(1):3-7.
44. Yeung CK, Shek SY, Bjerring P, Yu CS, Kono T, Chan HH. A comparative study of intense pulsed light alone and its combination with photodynamic therapy for the treatment of facial acne in Asian skin. *Lasers Surg Med.* 2007;39(1):1-6.
45. Yeung CK, Shek SY, Yu CS, Kono T, Chan HH. Treatment of inflammatory facial acne with 1,450-nm diode laser in type IV to V Asian skin using an optimal combination of laser parameters. *Dermatol Surg.* 2009;35(4):593-600.
46. Yin R, Hao F, Deng J, Yang XC, Yan H. Investigation of optimal aminolaevulinic acid concentration applied in topical aminolaevulinic acid-photodynamic therapy for treatment of moderate to severe acne: A pilot study in Chinese subjects. *Br J Dermatol.* 2010;163(5):1064-1071.
47. Kawana S, Tachihara R, Kato T, Omi T. Effect of smooth pulsed light at 400 to 700 and 870 to 1,200 nm for acne vulgaris in Asian skin. *Dermatol Surg.* 2010;36(1):52-57.

ADDRESS FOR CORRESPONDENCE

Andrew F. Alexis MD, MPH
St. Luke's-Roosevelt Hospital
Columbia University College of Physicians and Surgeons
Dermatology Associates of St. Luke's-Roosevelt
425 West 59th Street, Suite 5C
New York, NY 10019
Phone: ..... (212) 523-6003
Fax: ..... (212) 523-6293

© 2011-Journal of Drugs in Dermatology. All Rights Reserved.
This document contains proprietary information, images and marks of Journal of Drugs in Dermatology (JDD).
No reproduction or use of any portion of the contents of these materials may be made without the express written consent of JDD.
If you feel you have obtained this copy illegally, please contact JDD immediately.

Copyright © 2011

Importance of Vehicles in Acne Therapy

Leon H. Kircik MD
Indiana University School of Medicine, Indianapolis, IN

ABSTRACT

Topical drug therapy is an intuitively sound approach to the management of skin diseases. Depositing medication at the site of disease involvement is potentially efficient and reduces systemic exposure. Topical drugs are absorbed usually by passive diffusion. In clinical practice, the choice of an optimized formulation that will be effective and well tolerated is essential. Data confirm that patient adherence with therapy leads to better outcomes and lower long-term treatment costs, while poor adherence is directly linked to poor treatment outcomes and patient dissatisfaction. Local cutaneous irritation, which may be linked to components of the formulation and/or to the active drug itself, is a common cause of non-adherence. Well-designed drugs are important in the management of acne vulgaris and acne rosacea. Formulators have sought to improve treatment efficacy and tolerability by several different techniques, such as delayed release of the active drug, fixed combinations of two different molecules, or incorporating ingredients into the formulation vehicle that improve epidermal barrier function and offset the irritating effects of the active drugs.

INTRODUCTION

Topical application is probably the most commonly used method of drug delivery for cutaneous diseases. Intuitively, applying a drug at the site of the disease process would be expected to be efficient and associated with minimal systemic risk. These observations, though generally true, belie the complexities of topical drug formulation.

Topical drugs are absorbed mostly by passive diffusion. Transappendegeal and epidermal transport are the two major ways of getting molecules across the stratum corneum. Transappendegeal delivery may be preferred for diseases of the pilosebaceous unit, such as acne, folliculitis and some fungal diseases, because it can be used to create a reservoir effect.[1,2] However, this route accounts for less than one percent of all cutaneous transport. Epidermal pathways include both intracellular and transcellular routes, depending on the active molecule's characteristics. The transcellular route is the most common path, where drugs pass through corneocytes by partitioning in and out of the lipid bilayer. On the other hand, drugs can pass around the corneocytes via the lipid rich extracellular domains in the intercellular pathway.

There are several challenges to formulating topical drugs, including the fact that biotransformation of the active molecules takes place as they pass through the epidermis. This is in addition to the physical changes occurring to the vehicle itself as it is applied to the skin. For example, one way of increasing the concentration of the active drug on the skin surface is to use evaporating volatile components in the vehicle. Vehicles usually include ingredients that disrupt skin barrier, fluidize the lipid channels between corneocytes and alter partitioning of the drug into the cutaneous structures, thus enhancing penetration of the drug. Detergents, emulsifiers and solubilizing agents can be used as excipients. For example, detergents and emulsifiers disrupt the barrier. Another example of a powerful penetration enhancer used in sprays is ispopropyl myristate, which helps to reduce the evaporation of moisture from the stratum corneum and helps hydrate the skin to facilitate percutaneous absorption. It also helps by fluidizing and partially dissolving stratum corneum lipids. Propylene glycol is probably the most common excipient in topical vehicles. It is multifunctional and may play different roles at different concentrations. It has solvent, humectant and antimicrobial characteristics, as well as being a penetration enhancer. At high concentrations, it promotes desquamation and thus widening of the cellular pathways but also disrupts the epidermal barrier, so it ends up being an irritating agent. On the other hand, at low concentrations, it can act as a humectant and help hydrate the stratum corneum.

The topical dosage form or "delivery system" is an important consideration, as it must accommodate the drug being formulated and be suitable for application to the body site requiring treatment. FDA recognizes eight topical dosage forms: Solution, Suspension, Lotion, Paste, Gel, Ointment, Cream, or "Other," which includes aerosols, powders, patches, etc.[3] Ironically, the "other" category includes most of the novel formulations, such as spray, foam and hydrogel. All these new vehicles have become increasingly available in recent years and offer cosmetic acceptability, ease of use and therefore better adherence.

© 2011-Journal of Drugs in Dermatology. All Rights Reserved.
This document contains proprietary information, images and marks of Journal of Drugs in Dermatology (JDD).
No reproduction or use of any portion of the contents of these materials may be made without the express written consent of JDD.
If you feel you have obtained this copy illegally, please contact JDD immediately.

In clinical practice, the prescriber's selection of an optimized formulation that will be effective and well tolerated is essential.[4] Data confirm that patient adherence with therapy leads to better outcomes and lower long-term treatment costs,[5,6] while poor adherence is directly linked to poor treatment outcomes and patient dissatisfaction. Local cutaneous irritation, which may be linked to components of the formulation and/or to the active drug itself, is a common cause of non-adherence.[6]

Vehicles and Acne Treatment

Recognizing that vehicle formulation is a complex and multifaceted process with direct clinical consequences, we will now review the role of the vehicles developed for acne therapies. Well-designed drugs are important in the management of acne vulgaris, a common, multi-factorial disease prevalent among adolescents but common in many adults, as well.[7,8] Since acne is a multifactorial disease, it requires combination treatment in order to address different pathophysiologic etiologies. Novel fixed combination formulations have simplified acne treatment with once-a-day application and thus increased adherence. Novel formulations and delivery techniques also help decrease irritation, which also increases adherence.

Acne is chronic and has a negative impact on an individual's appearance as well as on psychosocial function, and can be associated with potential physical discomfort.[8] As in other skin conditions with significant impact and possible long-term consequences, initiation of effective therapy as early as possible within the disease course is advocated to provide better therapeutic outcomes.[9-13]

Common Therapies and Historical Challenges

Topical retinoids and benzoyl peroxide (BPO), which are inherently irritating and historically associated with poor tolerability and diminished patient adherence,[14,15] remain among the most prescribed treatment options for mild-to-moderate acne vulgaris.[16] Current guidelines for acne treatment emphasize the use of topical retinoids and benzoyl peroxide as maintenance treatment for acne vulgaris.[15] In light of increasing concern about the development of bacterial resistance, dependence on topical benzoyl peroxide (BPO) has increased. *P. acnes* has not developed resistance to BPO, a bactericidal agent.[17] Therefore, its use in conjunction with topical and/or systemic antibiotics is advocated to reduce the development of *P. acnes* resistance.[15] BPO is also shown to confer some degree of comedolytic and anti-inflammatory effects.[18] Topical retinoids, on the other hand, are anti-comedolytic; they regulate keratinization and target the microcomedone to reduce the formation of new acne lesions and can significantly interrupt disease progression.[19] Topical clindamycin has been used for more than 30 years in the management of acne vulgaris. The agent is bacteriostatic against *P. acnes* and confers anti-inflammatory effects.[20]

In recognition of the importance of combination treatment with topical antimicrobials, BPO and retinoids in the management of acne vulgaris, novel formulations of these agents have been developed in recent years. The aim of formulators has been reducing irritation, enhancing therapeutic outcomes and promoting patient adherence. This has been achieved by reducing the concentration of active drug, providing for delayed release of the active drug, or incorporating ingredients into the formulation vehicle that repair the impaired epidermal barrier and offset the irritating effects of drugs.[6]

Topical Retinoid and BPO Microspheres

Topical microspheres—biologically inert polymer particles that absorb, trap or bind drugs or other chemical compounds—are associated with improved therapeutic outcomes and minimal irritation.[21] The macroporous beads typically measure 10–25 nm in diameter and release active ingredient over time or in response to certain stimuli, such as change in pH, temperature, or physical manipulation when rubbed into the skin.[21] When drugs that are not soluble in water are entrapped in microsphere pores, the drug functions as microscopic particles, producing a greater surface area and increasing the rate of solubilization.[22] However, it is the delayed and controlled release that mostly contributes to the decrease in irritation.

An investigator-blind, evaluator-blind, split-face trial in subjects with healthy skin showed no significant difference in tolerability (measured by erythema, skin dryness, itching and stinging) between tretinoin microsphere gel 0.04% and tretinoin 0.025% cream, despite the fact that the microsphere formulation had the higher tretinoin concentration.[23]

Microsphere formulations improve drug stability.[24,25] Standard tretinoin has been shown to degrade significantly upon exposure to UV radiation as well as when combined with benzoyl peroxide, but microsphere-encapsulated tretinoin did not degrade upon exposure to UV and benzoyl peroxide.[24] After six hours of exposure to UV light, 84 percent of tretinoin in microsphere gel remained versus only 10 percent in standard tretinoin 0.025% gel. Furthermore, after six hours of exposure to UV light, a strong oxidizing agent such as benzoyl peroxide and an antibiotic such as erythromycin, 81 percent of tretinoin in microsphere gel 0.1% remained, compared to no tretinoin in the standard 0.025% gel. In a recent study, patients who cleansed the face with a benzoyl peroxide 5% wash each morning then applied topical tretinoin microsphere gel 0.04% had a therapeutic response similar to that seen in individuals who used the same wash each morning but tretinoin microsphere gel each evening.[26] The once-daily regimen, which was well tolerated, may be associated with better adherence than the two-times-a-day regimen.

© 2011-Journal of Drugs in Dermatology. All Rights Reserved.
This document contains proprietary information, images and marks of Journal of Drugs in Dermatology (JDD).
No reproduction or use of any portion of the contents of these materials may be made without the express written consent of JDD.
If you feel you have obtained this copy illegally, please contact JDD immediately.

It appears that microsphere vehicles confer additional clinically-appreciable benefits. Use of tretinoin microsphere formulations reduces facial shine, a common concern among acne patients. In a single-center, double-blind, split-face study, 35 subjects (ages 12 to 24 years) with moderate acne vulgaris and moderate facial oiliness applied tretinoin microsphere on one side and standard gel medications on the other for four consecutive days. At three hours after the final application, patients rated the reduction in facial "shine" as significantly greater on sides treated with tretinoin gel microsphere 0.1% versus tretinoin cream 0.05%. Similarly, investigators noted significantly reduced facial shine at three and six hours post-treatment associated with tretinoin gel microsphere use.[27]

The use of microsphere delivery of benzoyl peroxide has been associated with improved tolerability and good efficacy, even with lower BPO concentrations.[28] Compared to plain BPO, BPO microspheres provide a low and consistent drug delivery that may be associated with reduced irritation.[29]

In a series of cases recently published, benzoyl peroxide microsphere gel was associated with favorable efficacy and a very low potential for irritation.[30] An investigator-blinded, randomized, multicenter, 12-week study involving 48 subjects aged 12 and older with mild-to-moderate facial acne vulgaris compared BPO microsphere cream 5.5% twice daily to BPO gel 6% twice daily.[31] Investigators observed complete clearance or marked improvement of acne in a greater proportion (33 percent) of subjects treated with BPO microsphere cream 5.5% than in those subjects (16 percent) treated with BPO gel 6%. Tolerability scores were significantly better for BPO microsphere gel (37 percent incidence of tolerability reactions) than for standard BPO cream (79 percent incidence of tolerability reactions).

Microsphere delivery has also been incorporated into a 5.5% BPO wash formulation that, when compared to a gentle skin cleanser, was found by investigators and subjects to have good tolerability. BPO wash tended to be associated with lower but not statistically significant ratings for erythema, dryness and scaling as rated by investigators at day 14 and day 21, compared to the gentle cleanser.[32] Basically, 5.5% BPO was as tolerable as the over-the-counter gentle cleanser.

Like tretinoin microspheres, benzoyl peroxide microspheres appear to reduce surface sebum accumulation and associated facial shine. Treatment with benzoyl peroxide microsphere cream 5.5% following skin cleansing was associated with greater surface sebum reductions at 30 minutes, two, four and six hours, compared to skin cleansing alone in split-face trials.[33]

An alternative approach to optimizing benzoyl peroxide delivery while minimizing irritation is through solubilization. BPO is naturally hydrophobic with poor solubility in water and appears to have an affinity for the lipid-rich follicle. A relatively large particle, conventional BPO tends to reside on the surface of the skin or the follicular opening, where its benefit is limited. Even micronized BPO, as found in many topical formulations, is a relatively large particle, ranging in size from five to 100 µm. These physically manufactured particles are poorly soluble and may form clusters, producing an uneven distribution in the formulation and possibly leading to inconsistent clinical efficacy.[34] Electron microscopic analysis of skin following application of standard BPO formulations shows the molecules on the skin surface.

Chemically solubilized BPO in solution is a small molecule, measuring 10^{-4} µm. BPO is solubilized through a chemical process prior to being incorporated into the final manufactured product. The formulation is both lipophilic and hydrophilic, which allows penetration into the follicle and dissolution of sebaceous secretions.

The unique features of this formulation permit BPO alone to confer efficacy similar to combination BPO/clindamycin. At three hours after application, solubilized BPO reduced *P. acnes* counts by about 1.5 log units, compared to less than one log unit for BPO/clindamycin. At eight hours, *P. acnes* counts were reduced by about 2.5 log units by solubilized BPO, compared to about 1.5 log units by BPO/clindamycin. Results from one study (n=65) showed that solubilized BPO gel resulted in significantly greater reductions in non-inflammatory lesion counts than BPO/clindamycin at weeks 1, 2, 3, 4 and 12, with comparable reductions in inflammatory lesion counts at all time points.[35] In all published studies, treatment was well tolerated with scores for local irritation (erythema, dryness, etc.) rated less than mild.[35]

An Old Molecule in a New Formulation

Topical dapsone gel 5% is a recent addition to our armamentarium for treatment of acne vulgaris. Systemic dapsone has been used for inflammatory conditions of the skin for many years. However, stabilization of topical dapsone has been a challenge until recently. The dapsone gel vehicle contains diethylene glycol monoethyl esther (DGME), which facilitates permeation of the active drug into the skin and then enables the undissolved dapsone to remain in the pilosebacious unit. DGME is a hydroscopic liquid with excellent solubilizing properties and cutaneous biocompatibility. It facilitates cutaneous accumulation of the active molecule without increasing systemic absorption.[36]

Topical Antimicrobial Formulations

Fixed combination clindamycin/benzoyl peroxide formulations are well-established for the management of mild-to-moderate inflammatory acne vulgaris. The aqueous gel vehicle of clindamycin/BPO 5% contains two different and complementary moisturizers: glycerin 4% and dimethicone 1% intended to off-set the potential irritation associated with benzoyl peroxide.[37] Glycerin is a humectant; these are hydroscopic substanc-

© 2011-Journal of Drugs in Dermatology. All Rights Reserved.
This document contains proprietary information, images and marks of Journal of Drugs in Dermatology (JDD).
No reproduction or use of any portion of the contents of these materials may be made without the express written consent of JDD.
If you feel you have obtained this copy illegally, please contact JDD immediately.

es that draw water from the epidermis/dermis to the stratum corneum. However, humectants can increase transepidermal water loss (TEWL)—a sign of barrier dysfunction seen in most inflammatory skin conditions—if they are used without an occlusive. Dimethicone is an occlusive that conditions the skin and forms a barrier to prevent transepidermal water loss.[38]

Compared to non-treatment, the application of the combination of dimethicone and glycerin is shown to reduce transepidermal water loss.[39] In fact, TEWL, as measured by tewameter from a small forearm biopsy before and after two weeks of daily application of a gel containing 10% glycerin, 2.5% dimethicone and 35% silicone, was reduced by 13 percent compared to controls. The moisturizing, TEWL-reducing effects of the vehicle may be particularly important, given that acne itself is associated with impaired barrier function.[37]

The excellent tolerability of this clindamycin/BPO formulation was demonstrated in a trial in which its use in combination with tazarotene cream was compared to tazarotene monotherapy.[40] Combination treatment was more tolerable for the first four weeks compared to tazarotene monotherapy. Emollient features of the clindamycin/BPO formulation are credited with contributing to enhanced tolerability.

Fixed Combinations

Second-generation retinoids, such as the naphthoic-acid derivative adapalene, are now available.[41] Adapalene is photostable and not degraded in the presence of benzoyl peroxide.[41] The molecule has selective affinity for RAR-γ and RAR-β. Importantly, adapalene gel has demonstrated better tolerability than tretinoin and similar or greater reductions in inflammatory, non-inflammatory and total lesion counts.[41]

The fixed combination gel formulation of adapalene 0.1% and benzoyl peroxide 2.5% is relatively new to the market. The efficacy, safety and tolerability of the fixed combination formulation has been established in multiple controlled trials in which the combination provided more significant reductions in inflammatory, non-inflammatory and total lesion counts than its constituents alone or vehicle.[42-44] The tolerability profile for the fixed combination gel was similar to that for adapalene alone.[42] Of note, a pooled analysis of trial data for 3,855 patients from three double-blind, randomized, and controlled studies of similar design demonstrated synergy for adapalene/BPO gel.[45] For example, at week 1, reduction in total lesion counts relative to vehicle for adapalene/BPO was 7.4 percent, compared to 1.4 percent for adapalene alone and 2.4 percent for BPO alone. At week 1, synergy of adapalene/BPO contributed 48.7 percent of the efficacy in reducing total lesion counts. The contribution of synergy to total mean percent lesion count reductions was 44.4 percent, 20 percent and 9.5 percent, respectively, at weeks 2, 4 and 8. Investigator's Global Assessment (IGA) ratings also showed that adapalene/BPO has synergistic success. Contribution of synergy to efficacy of adapalene/BPO in IGA success was 128.6 percent, 13.2 percent, 41.7 percent and 22.2 percent, respectively, at weeks 1, 2, 4 and 8.[45] Synergy is defined as two agents in combination having more than cumulative effect; the efficacy of the combination is greater than the sum of the efficacy of each agent used alone.

The precise basis for synergy of adapalene/BPO combination gel is not clear. BPO reduces *P. acnes* counts and provides a keratolytic effect to enhance penetration of adapalene, which downregulates toll-like receptor 2, used by *P. acnes* to induce production of inflammatory cytokines.[45,44] Adapalene is also shown to alter the expression of CD1d and IL-10.[45] Furthermore, by altering the follicular microclimate, adapalene potentially enhances penetration of BPO.[44,45]

It seems likely that characteristics of the vehicle contribute to enhanced efficacy of adapalene 0.1%/benzoyl peroxide 2.5% gel. Of note, in Tan et al.'s analysis, vehicle treatment alone provided a median 33 percent reduction in total lesions and median 38 percent reduction in inflammatory lesions at 12 weeks (their data analysis on synergy accounted for vehicle effect).[45] The vehicle contains a proprietary gelling agent that does not to interfere with the pharmacokinetic properties of adapalene. This copolymer facilitates a homogenous dispersion of adapalene and benzoyl peroxide in the water-based gel. The vehicle also contains humectants glycerol and propylene glycol. Additional stabilizing excipients include disodium edetate, docusate sodium and poloxamer. It is suspected but not proven that the formulation's stability, that is, its non-susceptibility to fluctuations in pH, may protect the active constituents from degradation and preserve their efficacy.

Another fixed combination formulation—of topical tretinoin with clindamycin—is intended to provide both the anticomedonal effects of the retinoid and the bacteriostatic and anti-inflammatory effects of the topical antibiotic. A novel, alcohol-free, aqueous gel formulation of tretinoin 0.025% and clindamycin phosphate 1.2% has been shown to be effective in mild-to-moderate acne vulgaris.

While clindamycin and tretinoin provide complementary methods of action, they are not readily combined into a single formulation. One of the essential components of the gel vehicle is Laureth 4 (polyoxyether of lauryl alcohol), a clear, colorless liquid that functions as both a surfactant and an emulsifier to help solubilize and disperse otherwise non-mixable substances.[46,47]

In clinical trials, the combination formulation was associated with excellent tolerability. Observed local treatment-related adverse reactions (≥1%) were application site reactions, including dryness, irritation, exfoliation, erythema, pruritus and

© 2011-Journal of Drugs in Dermatology. All Rights Reserved.
This document contains proprietary information, images and marks of Journal of Drugs in Dermatology (JDD).
No reproduction or use of any portion of the contents of these materials may be made without the express written consent of JDD.
If you feel you have obtained this copy illegally, please contact JDD immediately.

dermatitis. Sunburn was also reported. The incidence of skin reactions peaked at week 2 and gradually decreased through the treatment period.

Tretinoin 0.025%/clindamycin phosphate 1.2% gel provided a statistically significantly better improvement in acne than did its components alone or vehicle. At 12 weeks, 36.3 percent of combination-treated patients had a 2-grade improvement in IGA, compared to 26.6 percent, 26.1 percent and 20.2 percent for clindamycin alone, tretinoin alone and vehicle, respectively. The mean percent reduction in total lesions was 55 percent for combination therapy, compared to 49 percent, 50.5 percent and 39.1 percent for clindamycin alone, tretinoin alone and vehicle, respectively. Reduction in inflammatory lesions was statistically significant for combination gel (60.4%) versus tretinoin gel (54.5%) and vehicle gel (43.3%), but not compared to clindamycin gel (56.5%). Reduction in non-inflammatory lesions was statistically significant for combination gel (51%) versus clindamycin gel (42.9%) and vehicle gel (36%), but not compared to tretinoin gel (47.3%).

Special Considerations for Acne Rosacea

Another example of the importance of vehicle is the newest topical formulation of metronidazole, a standard therapy for rosacea.[48] Metronidazole 1% topical gel is a potent once-daily formulation for treatment of rosacea. Well-controlled studies have shown that it is effective in the treatment of moderate-to-severe rosacea and well tolerated by all patient types.[49] The gel formulation was found not to be irritating under occlusive application with a low potential for causing sensitization reactions, and there was no evidence of phototoxic or photoallergic reactions.[50]

The formulation's tolerability may be due to the elegant gel vehicle, which consists primarily of purified water (92%). The novel, stable, aqueous gel vehicle is capable of solubilizing greater concentrations of metronidazole with a novel combination of hydrosolubilizing agents (HSA-3™).[51]

The primary components of HAS-3 are niacinamide, which has been shown to improve the appearance of facial skin texture by enhancing skin barrier function[52]; betadex (beta cyclodextrin), a humectant moisturizer[53]; and propylene glycol, a solvent and humectant.[51]

As a complexing agent, betadex increases the aqueous solubility of highly water-insoluble and lipophilic drugs, such as metronidazole, and increases their bioavailability and stability. Betadex creates a core that enables the solubilization of metronidazole gel 1%. The metronidazole 1% gel formulation, therefore, has an exterior hydrophillic surface that generates water-solubility and enhances moisturization, and an interior hydrophobic cavity than encapsulates the metronidazole molecules and increases drug solubility. Propylene glycol increases drug partitioning into the tissue and provides a lubricating effect.

CONCLUSION

Optimized vehicle formulations contribute to enhanced therapeutic efficacy and improved tolerability, which translates to more rapid clearance of disease and increased rates of patient satisfaction. Selection of the right drug in the proper vehicle to meet the patient's needs is especially important in common cutaneous diseases like acne vulgaris and acne rosacea. Despite decades of use and proven efficacy of topical antimicrobials and retinoids, their use by patients historically has been marred by local cutaneous irritation, inconvenient dosing and subsequently poor compliance.

Novel formulations often require less-frequent application (once-a-day versus twice-a-day) and enable co-application of drugs previously considered incompatible. By reducing irritation and increasing patient convenience, these new formulations can be expected to improve patient adherence, which will lead to better therapeutic outcomes.

DISCLOSURES

Dr. Leon H. Kircik has served as an investigator, speaker, consultant or advisory board member for Allergan, Amgen, Astellas Pharma US, Colbar, CollaGenex, Connetics Corporation, Ferndale Laboratories, Galderma, Genentech, Intendis, Johnson & Johnson, Leo Pharma, 3M, Nano Bio, Vovartis AG, Onset Therapeutics, OrthoNeutrogena, Promius, PharmaDerm, SkinMedica, Stiefel, Valeant, Warner-Chilcott; a speaker for Abbott Laboratories, Dermik, Embil, Innovail, Merck Serono and Triax; an investigator for Acambis, Asubio, Bayer HealthCare, Biolife, Biopelle, Breckinridge Pharma, Centocor, Combinatrix, Coria, Dow Pharmaceutical Sciences, Dusa, GSK, Health Point, Medicis, Nucryst, Obagi, QLT, Pfizer, QuatrixTolerRx and UCB; and as a consultant for Laboratory Skin Care, Medical International Technologies and ZAGE.

REFERENCES

1. Chourasia R, Jain SK. Drug targeting through pilosebaceous route. *Curr Drug Targets*. 2009;10(10):950-967.
2. Wosicka H, Cal K. Targeting to the hair follicles: Current status and potential. *J Dermatol Sci*. Epub January 6 2010.
3. Buhse L, Kolinski R, Westenberger B, et al. Topical drug classification. *Int J Pharm*. 2005;295:101-112.
4. Kircik L, et al. Vehicles Matter. *Supplement to Practical Dermatology*. 2010;7(suppl 3).
5. Balkrishnan R, Kulkarni AS, Cayce K, Feldman SR. Predictors of healthcare outcomes and costs related to medication use in patients with acne in the United States. *Cutis*. 2006;77(4):251-255.
6. Dréno B, Thiboutot D, Gollnick H, Finlay AY, Layton A, Leyden JJ, et al. Global Alliance to Improve Outcomes in Acne. Large-scale worldwide observational study of adherence with acne therapy.

© 2011-Journal of Drugs in Dermatology. All Rights Reserved.
This document contains proprietary information, images and marks of Journal of Drugs in Dermatology (JDD).
No reproduction or use of any portion of the contents of these materials may be made without the express written consent of JDD.
If you feel you have obtained this copy illegally, please contact JDD immediately.

Int J Dermatol. 2010;49(4):448-456.
7. Yentzer BA, Hick J, Reese EL, Uhas A, Feldman SR, Balkrishnan R. Acne vulgaris in the United States: A descriptive epidemiology. *Cutis*. 2010;86(2):94-99.
8. Demircay Z, Seckin D, Senol A, Demir F. Patient's perspective: An important issue not to be overlooked in assessing acne severity. *Eur J Dermatol*. 2008;18(2):181-184.
9. Zaenglein AL. Making the Case for Early Treatment of Acne. *Clin Pediatr (Phila)*. 2010;49(1):54-59. Epub September 8, 2009.
10. Tristani-Firouzi P, Krueger GG. Efficacy and safety of treatment modalities for psoriasis. *Cutis*. 1998;61(suppl 2):11-21.
11. Feldman SR. Approaching psoriasis differently: Patient-physician relationships, patient education and choosing the right topical vehicle. *J Drugs Dermatol*. 2010;9(8):908-911.
12. Richards HL, Fortune DG, Griffiths CE. Adherence to treatment in patients with psoriasis. *J Eur Acad Dermatol Venereol*. 2006;20(4):370-379.
13. Lee IA, Maibach HI. Pharmionics in dermatology: A review of topical medication adherence. *Am J Clin Dermatol*. 2006;7:231-236.
14. Gollnick H, Cunliffe W, Berson D, Dreno B, Finlay A, Leyden JJ, et al. Global Alliance to Improve Outcomes in Acne. Management of acne: A report from a Global Alliance to Improve Outcomes in Acne. *J Am Acad Dermatol*. 2003;49(suppl 1):1S-37S.
15. Thiboutot D, Gollnick H, Bettoli V, Dréno B, Kang S, Leyden JJ, et al. Global Alliance to Improve Outcomes in Acne. New insights into the management of acne: An update from the Global Alliance to Improve Outcomes in Acne group. *J Am Acad Dermatol*. 2009;60(suppl 5):1S-50S.
16. Ghali F, Kang S, et al. Changing the face of acne therapy. *Cutis*. 2009;(suppl 2):4-15.
17. Del Rosso JQ. Selection of therapy for acne vulgaris: Balancing concerns about antibiotic resistance. *Cutis*. 2008;82(suppl 5):12-16.
18. Dutil M. Benzoyl peroxide: Enhancing antibiotic efficacy in acne management. *Skin Therapy Lett*. 2010;15(10):5-7.
19. Shalita A. The integral role of topical and oral retinoids in the early treatment of acne. *J Eur Acad Dermatol Venereol*. 2001;15(suppl 3):43-49.
20. Del Rosso JQ, Schmidt NF. A review of the anti-inflammatory properties of clindamycin in the treatment of acne vulgaris. *Cutis*. 2010;85(1):15-24.
21. Embil K, Nacht S. The Microsponge Delivery System (MDS): A topical delivery system with reduced irritancy incorporating multiple triggering mechanisms for the release of actives. *J Microencapsul*. 1996;13(5):575-588.
22. Chadawar V, Shaji J. Microsponge delivery system. *Curr Drug Deliv*. 2007;4(2):123-129.
23. Leyden JJ, Grossman R, Nighland M. Cumulative irritation potential of topical retinoid formulations. *J Drugs Dermatol*. 2008;7(suppl 8):14S-18S.
24. Nighland M, Yusuf M, Wisniewski S, Huddleston K, Nyirady J. The effect of simulated solar UV irradiation on tretinoin in tretinoin gel microsphere 0.1% and tretinoin gel 0.025%. *Cutis*. 2006;77(5):313-316.
25. Nyirady J, Lucas C, Yusuf M, Mignone P, Wisniewski S. The stability of tretinoin in tretinoin gel microsphere 0.1%. *Cutis*. 2002;70(5):295-298.
26. Pariser D, Bucko A, Fried R, Jarratt MT, Kempers S, Kircik L, et al. Tretinoin gel microsphere pump 0.04% plus 5% benzoyl peroxide wash for treatment of acne vulgaris: Morning/morning regimen is as effective and safe as morning/evening regimen. *J Drugs Dermatol*. 2010;9(7):805-813.
27. Nyirady J, Nighland M, Payonk G, Pote J, Phillips S, Grossman R. A comparative evaluation of tretinoin gel microsphere, 0.1%, versus tretinoin cream, 0.025%, in reducing facial shine. *Cutis*. 2000;66(2):153-156.
28. Wester RC, Patel R, Nacht S, Leyden J, Melendres J, Maibach H. Controlled release of benzoyl peroxide from a porous microsphere polymeric system can reduce topical irritancy. *J Am Acad Dermatol*. 1991;24(5 Pt 1):720-726.
29. Nokhodchi A, Jelvehgari M, Siahi MR, Mozafari MR. Factors affecting the morphology of benzoyl peroxide microsponges. *Micron*. 2007;38(8):834-840.
30. Bikowski J, Del Rosso JQ. Benzoyl peroxide microsphere cream as monotherapy and combination treatment of acne. *J Drugs Dermatol*. 2008;7(6):590-595.
31. Smith SR, Kempers S. A study of 5.5% benzoyl peroxide microsphere cream versus 6% benzoyl peroxide gel in the treatment of acne vulgaris. *Cosmet Dermatol*. 2006;19:537-542.
32. Del Rosso JQ, Kircik L. Comparison of the tolerability of benzoyl peroxide microsphere cream wash versus gentle cleanser when used in combination with clindamycin and tretinoin gel: A multicenter, investigator-blind, randomized study. Poster presented at: American Academy of Dermatology 67th Annual Meeting, March 6-10, 2009; San Francisco, California.
33. Del Rosso JQ. Benzoyl Peroxide Formulations: What is the science supporting microsphere vehicle technology and clinical use. *J Clin Aesthet Dermatol*. 2009;2(9):46-54.
34. Leyden J. New developments in topical antimicrobial therapy for acne. *J Drugs Dermatol*. 2008;7(suppl 2):8S-11S.
35. Kircik L, Green L, Thiboutot D, Tanghetti E, Wilson D, et al. Comparing a novel solubilized benzoyl peroxide gel with benzoyl peroxide/clindamycin: Final data from a multicenter, investigator-blind, randomized study. *J Drugs Dermatol*. 2009;8(9):812-818.
36. Kircik LH. Harnessing the anti-inflammatory effects of topical dapsone for management of acne. *J Drugs Dermatol*. 2010;9(6):667-671.
37. Del Rosso JQ. The role of the vehicle in combination acne therapy. *Cutis*. 2005;76:15-8.
38. Draelos ZD. Therapeutic moisturizers. *Dermatol Clin*. 2000;18:597-607.
39. Short RW, Chan JL, Choi JM, Egbert BM, Rehmus WE, Kimball AB. Effects of moisturization on epidermal homeostasis and differentiation. *Clin Exp Dermatol*. 2007;32:88-90.
40. Tanghetti E, Abramovits W, Solomon B, Loven K, Shalita A. Tazarotene versus tazarotene plus clindamycin/benzoyl peroxide in the treatment of acne vulgaris: A multicenter, double-blind, randomized parallel-group trial. *J Drugs Dermatol*. 2006;5(3):256-261.
41. Czernielewski J, Michel S, Bouclier M, Baker M, Hensby JC. Adapalene biochemistry and the evolution of a new topical retinoid for treatment of acne. *J Eur Acad Dermatol Venereol*. 2001;15(suppl 3):5-12
42. Thiboutot DM, Weiss J, Bucko A, Eichenfield L, Jones T, Clark S, et al. Adapalene-BPO Study Group. Adapalene-benzoyl peroxide,

© 2011-Journal of Drugs in Dermatology. All Rights Reserved.
This document contains proprietary information, images and marks of Journal of Drugs in Dermatology (JDD).
No reproduction or use of any portion of the contents of these materials may be made without the express written consent of JDD.
If you feel you have obtained this copy illegally, please contact JDD immediately.

a fixed-dose combination for the treatment of acne vulgaris: Results of a multicenter, randomized, double-blind, controlled study. *J Am Acad Dermatol*. 2007;57(5):791-799.
43. Gold LS, Tan J, Cruz-Santana A, Papp K, Poulin Y, Schlessinger J, Gidner J, Liu Y, Graeber M; Adapalene-BPO Study Group. A North American study of adapalene-benzoyl peroxide combination gel in the treatment of acne. *Cutis*. 2009;84(2):110-116.
44. Gollnick HP, Draelos Z, Glenn MJ, Rosoph LA, Kaszuba A, et al. Adapalene-BPO Study Group. Adapalene-benzoyl peroxide, a unique fixed-dose combination topical gel for the treatment of acne vulgaris: A transatlantic, randomized, double-blind, controlled study in 1670 patients. *Br J Dermatol*. 2009;161(5):1180-1189.
45. Tan J, Gollnick HP, Loesche C, Ma YM, Gold LS. Synergistic efficacy of adapalene 0.1%-benzoyl peroxide 2.5% in the treatment of 3855 acne vulgaris patients. *J Dermatolog Treat*. Epub July 28, 2010.
46. European Commission Enterprise and Industry Web Site. Available at: http://ec.europa.eu/consumers/cosmetics/cosing/index.cfm?fuseaction=search.detailsa&id=34915. Accessed September 24, 2010.
47. Cosmetics Info Web site. Available at: http://www.cosmeticsinfo.org/ingredient_details.php?ingredient_id=387. Accessed September 24, 2010.
48. Del Rosso JQ, Baldwin H, Webster G; American Acne & Rosacea Society. American Acne & Rosacea Society rosacea medical management guidelines. *J Drugs Dermatol*. 2008;7(6):531-533.
49. Wolf JE Jr, Kerrouche N, Arsonnaud S. Efficacy and safety of once-daily metronidazole 1% gel compared with twice-daily azelaic acid 15% gel in the treatment of rosacea. *Cutis*. 2006;77(suppl 4):3-11.
50. Beutner KR, Lemke S, Calvarese B. A look at the safety of metronidazole 1% gel: Cumulative irritation, contact sensitization, phototoxicity, and photoallergy potential. *Cutis*. 2006;77(suppl 4):12-17.
51. Dow G. A Novel Aqueous Metronidazole 1% Gel with Hydrosolubilizing Agents (HAS-3™). *Cutis*. 2006;77(suppl 4):18-26.
52. Draelos, Z. Assessment of Skin Barrier Function in Rosacea Patients with a Novel 1% Metronidazole Gel. *J Drugs Dermatol*. 2005;4(5):557-562
53. Data on file.

ADDRESS FOR CORRESPONDENCE

Leon H. Kircik, MD
Physicians Skin Care, PLLC
1169 Eastern Parkway, Suite 2310
Louisville, KY 40217
Phone: ..... (502) 456-2783
Fax: ..... (502) 456-2728

© 2011-Journal of Drugs in Dermatology. All Rights Reserved.
This document contains proprietary information, images and marks of Journal of Drugs in Dermatology (JDD).
No reproduction or use of any portion of the contents of these materials may be made without the express written consent of JDD.
If you feel you have obtained this copy illegally, please contact JDD immediately.

CME Post-Test: Please select your best answer for each of the following questions and insert into the Answer Grid found on the Evaluation/Certificate Request Form on page s26. **Return your completed Evaluation/Certificate Request Form to *JDD*** by fax to (212) 213-5435, mail to 377 Park Avenue South, 6th Floor, New York, NY 10016, or to complete this activity online, please visit www.JDDonline.com in the Medical Education Library. Successful completion of the Post-Test is required to earn *AMA PRA Category 1 Credit*™.

1. *Which of the following statements is false?*

   a. P. acnes *has become increasingly resistant to antibiotics since the late 1970s*
   b. *Resistance of* P. acnes *has not been reported to minocycline*
   c. *Antibiotic resistance genes can be transferred between bacteria*
   d. *Benzoyl peroxide can help reduce antibiotic-resistant strains of* P. acnes

2. *Preferred regimens aimed at reducing the emergence of antibiotic-resistant strains of bacteria include:*

   a. *Use of oral antibiotics as single agents in the induction phase followed by initiation of topical retinoids in the maintenance phase*
   b. *Use of antibiotics in combination with retinoids or benzoyl peroxide in the induction phase followed by maintenance with topical retinoids (+BP)*
   c. *Use of oral antibiotics in the induction phase followed by use of topical antibiotics in the maintenance phase*
   d. *Use of topical and oral antibiotics in the induction phase followed by topical antibiotics in the maintenance phase*

3. *Which of the following statements is true?*

   a. *Photographic review of patients in clinical trials using topical retinoids alone indicates that significant improvement can be achieved in some patients with moderate-to-severe acne in 12 weeks*
   b. *Addition of fixed-combination of adapalene/BP to a regimen of oral antibiotics does not significantly improve acne compared to use of the oral antibiotic alone.*
   c. *Experts in Europe recommend that patients with acne should be treated with oral antibiotics for a minimum of six months*

4. *Which of the following has NOT been reported as an anti-inflammatory mechanism of action of retinoids?*

   a. *Inhibition of neutrophil migration*
   b. *Decreased expression of transcription factors involved in cytokine production*
   c. *Inhibition of the toll-like receptor 2 on inflammatory cells*
   d. *Increased proliferation of lymphocytes*

5. *At the end of a 12 week study of doxycycline plus fixed-combination adapalene/BP vs. doxycycline plus vehicle, what percentage of patients in the doxycycline + adapalene/BP arm were "clear or almost clear"?*

   a. *8.4%*
   b. *16%*
   c. *31.5%*
   d. *72%*

6. *Recent clinical trials suggest that in patients with moderate-to-severe acne, the majority of subjects will achieve 50-75 percent improvement in acne with the use of oral antibiotics for how many weeks?*

   a. *6 weeks*
   b. *10 weeks*
   c. *12 weeks*
   d. *16 weeks*

7. *Factors that lead to the long term use of oral antibiotics in acne include all EXCEPT*

   a. *Patients' perception that acne cannot be controlled without oral antibiotics*
   b. *Physicians' perception that severe acne must be managed with ongoing use of oral antibiotics*
   c. *Preference some patients have for oral vs. topical therapy*
   d. *Concerns regarding the emergence of antibiotic resistant bacteria.*
   e. *Is there a difference between encapsulated tretinoin versus not encapsulated tretinoin?*

8. *Is there a difference in efficacy between the fixed combination of adapalene 1% and BPO 2.5% versus applying each medication separately?*

   a. *Yes*
   b. *No*

9. *What are the different characteristics of propylene glycol?*

   a. *Humectant*
   b. *Occlusive moisturizer*
   c. *Penetration enhancer*
   d. *A and C*

© 2011-Journal of Drugs in Dermatology. All Rights Reserved.
This document contains proprietary information, images and marks of Journal of Drugs in Dermatology (JDD).
No reproduction or use of any portion of the contents of these materials may be made without the express written consent of JDD.
If you feel you have obtained this copy illegally, please contact JDD immediately.

CME Post-Test: Please select your best answer for each of the following questions and insert into the Answer Grid found on the Evaluation/Certificate Request Form on page s26. **Return your completed Evaluation/Certificate Request Form to *JDD*** by fax to (212) 213-5435, mail to 377 Park Avenue South, 6th Floor, New York, NY 10016, or to complete this activity online, please visit www.JDDonline.com in the Medical Education Library. Successful completion of the Post-Test is required to earn *AMA PRA Category 1 Credit*™.

10. Metronidazole is.....?

a. Hydrophobic molecule
b. Hydrophilic molecule
c. None of the above

11. Topical retinoids have.....?

a. Anti-inflammatory effects
b. Effect on toll like receptor – 2
c. A and B
d. None of the above

12. BPO helps to prevent antibiotic resistance when used with?

a. Topical antibiotic
b. Oral antibiotic
c. A and B
d. None of the above

13. Vehicles matter in topical treatment?

a. Yes
b. No

© 2011-Journal of Drugs in Dermatology. All Rights Reserved.
This document contains proprietary information, images and marks of Journal of Drugs in Dermatology (JDD).
No reproduction or use of any portion of the contents of these materials may be made without the express written consent of JDD.
If you feel you have obtained this copy illegally, please contact JDD immediately.

Evaluation/Certificate Request Form

Demystifying Acne Algorithms

To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this Evaluation/Certificate Form and return to *JDD* by fax to (212) 213-5435, mail to 377 Park Avenue South, 6th Floor, NY, NY 10016, or complete online at JDDonline.com in the Medical Education Library. ***You must complete and submit this form or complete the CME activity online to receive credit for completing this activity. There is no fee for this CME activity.***

Please answer the following questions by circling the appropriate rating:

1 = Strongly Disagree	2 = Disagree	3 = Neutral	4 = Agree	5 = Strongly Agree

Overall Effectiveness of the Activity

The content presented:

Was timely and will influence how I practice
1 2 3 4 5

Enhanced my current knowledge base
1 2 3 4 5

Addressed my most pressing questions
1 2 3 4 5

Provided new ideas or information I expect to use
1 2 3 4 5

Addressed competencies identified by my specialty
1 2 3 4 5

Avoided commercial bias or influence
1 2 3 4 5

Impact of the Activity

Name one new strategy you learned as a result of completing this activity:

_____

_____

Please list any topics you would like to see addressed in future educational activities:

_____

_____

Additional comments about this activity:

_____

_____

Name one thing you intend to change in your practice as a result of completing this activity:

_____

_____

Follow-up

As part of our continuous quality improvement effort, we conduct postactivity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate if you would be willing to participate in such a survey:

I would be interested in participating in a follow-up survey.
☐ *Yes* ☐ *No*

I would be interested in receiving similar educational programs.
☐ *Yes* ☐ *No*

The National Association for Continuing Education designates this journal-based CME activity for a maximum of 1 AMA PRA Category 1 Credit™. *Physicians should claim only credit commensurate with the extent of their participation in the activity.*

I certify my actual time spent to complete this educational activity to be:

☐ *I participated in the entire activity and claim _____ credits.*

☐ *I participated in only part of the activity and claim _____ credits.*

Name		*Degree*	
Organization		*Specialty*	
Address			
City, State, Zip			
Telephone		*Fax*	
Email			

Signature		*Date*	

Post-Test Answer Key

1	2	3	4	5	6	7	8	9	10	11	12	13

© 2011-Journal of Drugs in Dermatology. All Rights Reserved.
This document contains proprietary information, images and marks of Journal of Drugs in Dermatology (JDD).
No reproduction or use of any portion of the contents of these materials may be made without the express written consent of JDD.
If you feel you have obtained this copy illegally, please contact JDD immediately.

© 2011-Journal of Drugs in Dermatology. All Rights Reserved.
This document contains proprietary information, images and marks of Journal of Drugs in Dermatology (JDD).
No reproduction or use of any portion of the contents of these materials may be made without the express written consent of JDD.
If you feel you have obtained this copy illegally, please contact JDD immediately.

JOURNAL OF DRUGS IN DERMATOLOGY

JDD

DRUGS • DEVICES • METHODS

© 2011-Journal of Drugs in Dermatology. All Rights Reserved.
This document contains proprietary information, images and marks of Journal of Drugs in Dermatology (JDD).
No reproduction or use of any portion of the contents of these materials may be made without the express written consent of JDD.
If you feel you have obtained this copy illegally, please contact JDD immediately.

JO0611