A SUPPLEMENT TO

JOURNAL OF DRUGS IN DERMATOLOGY

JDD

DRUGS • DEVICES • METHODS

Inflammatory Acne Vulgaris: Current Concepts in Pathogenesis and Management

CME Supplement

Take the Online CME Test Now for Instant Results!

ISSN: 1545 9616

January 2016 • Volume 15 • Issue 1 (Supplement 1)

JO0116

Disclosure of Commercial Support

This supplement to the *Journal of Drugs in Dermatology* is supported by an independent educational grant from Valeant Pharmaceuticals North America LLC, Copyright © 2016, and published by the *Journal of Drugs in Dermatology*. All rights reserved. No part of this publication may be reproduced or transmitted in any form, by any means, without prior written permission of the publisher. The opinions or views expressed in this professional educational supplement are those of the authors and do not reflect the opinions or recommendations of Valeant Pharmaceuticals North America LLC or the *Journal of Drugs in Dermatology*.

Inflammatory Acne Vulgaris
Current Concepts in Pathogenesis and Management

INTRODUCTION

ORIGINAL ARTICLES

CME

INFLAMMATORY ACNE VULGARIS: CURRENT CONCEPTS IN PATHOGENESIS AND MANAGEMENT

Release Date: January 1, 2016
Termination Date: December 30, 2016
Estimated Time to Complete This CME Activity: 1 hour
Medium or Combination of Media Used: Written supplement
Method of Physical Participation: Journal article, web-based post-test, and evaluation
Hardware/Software Requirements: High speed internet connection, any web browser

Statement of Need

Acne vulgaris is a chronic inflammatory cutaneous disease and is the most common skin disease in the United States, affecting 80% of the population at some point in their lifespan. Because the pathogenesis of acne is not fully understood, it is imperative that the dermatology healthcare practitioner expand their medical knowledge on the current understanding of the development of this condition so that effective treatment strategies may be explored and initiated with confidence. There is need for dermatologists to expand their knowledge of the rationale for combination therapy for the treatment of inflammatory acne, and to understand the efficacy of fixed dose combinations in the reduction of inflammatory and non-inflammatory acne lesions and acne severity and the reduction in skin irritation and dryness.

Educational Objectives

This activity is a multi-specialty, evidence-based initiative designed to increase the knowledge and competence of dermatological practitioners by providing them with the simultaneous integration of knowledge, skills, and judgment from thought-leader testimonials, science-based research, and evidence-based data to address the difference between present patient outcomes and those considered achievable in the field of dermatology.

Upon completion of this activity, participants should be able to:

- Cite the various factors influencing the pathogenesis of acne vulgaris
- Recognize the prevalence and impact of acne on the US population
- Summarize the efficacy of current acne treatment strategies
- State the rationale for the combination therapy approach to acne treatment in various patient types
- Identify the mechanism of action of the fixed dose clindamycin 1.2%/benzoyl peroxide 3.5% gel medication
- Cite the rationale for the using lower concentrations of potentially irritating active ingredients in combination acne

Target Audience

This activity is intended for dermatologists, residents in dermatology, and physician assistants who need expanded awareness of the current understanding of the pathogenesis of acne and the evidence of inflammation occurring at all stages of acne lesion development, as well as a review of current treatment strategies for inflammatory acne, with an emphasis on fixed dose combination modalities.

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 providership of the National Association for Continuing Education (NACE) and Physicians Continuing Education Corporation (PCE). The National Association for Continuing Education is accredited by the ACCME to provide Continuing Medical Education (CME) for physicians.

Credit Designation

The National Association for Continuing Education designates this journal-based CME activity for a maximum of 1.0 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

How to Obtain CME Credit

You can earn 1.0 *AMA PRA Category 1 Credits™* by reading the 2 articles contained in this supplement and completing a web-based post-test and evaluation.

Test is valid through December 30, 2016 (no credit will be given after this date).

To receive credit for this activity, please go to www.JDDonline.com and click on CME Activities under "Library." You will find instructions for taking the post-test and completing the program evaluation. You must earn a passing score of at least 70% and complete and submit the activity evaluation form in order to receive a certificate for 1.0 *AMA PRA Category 1 Credits™*. There is no fee for this CME activity. 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: (718) 407-0898.

Faculty Credentials

Joshua A. Zeichner MD (Department of Dermatology, Mount Sinai Hospital, New York, NY), Leon H. Kircik MD (Mount Sinai Medical Center, New York, NY; Indiana University School of Medicine, Indianapolis, IN; Physicians Skin Care, PLLC, Louisville, KY).

Peer Reviewer Credentials

Perry Robins MD (Professor Emeritus of Dermatology at New York University Medical Center, New York, NY

Disclosures

Policy on Faculty and Provider Disclosure: It is the policy of the National Association for Continuing Education (NACE) 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 faculty/authors have disclosed the following relationships with commercial interests: Dr. Kircik has served as an advisor, investigator, consultant, and speaker for Allergan, Bayer, Galderma, Promius Pharma, Quinnova, Stiefel/GSK, LeoPharma, Taro, Valeant, and Warner-Chilcott. Dr. Zeichner has worked as an advisory board member, consultant, and speaker for Allergan, Galderma, and Valeant and an advisory board member for Foamix.

The peer reviewers have disclosed no relationships with commercial interests.

The planning committee of this activity have disclosed the following relationships with commercial interests: Dr. Kircik has served as an advisor, investigator, consultant, and speaker for Allergan, Bayer, Galderma, Promius Pharma, Quinnova, Stiefel/GSK, LeoPharma, Taro, Valeant, and Warner-Chilcott. Dr. Zeichner has worked as an advisory board member, consultant, and speaker for Allergan, Galderma, and Valeant and an advisory board member for Foamix. Michelle Frisch (National Association for Continuing Education), Karin Beehler (Executive Editor JDD), Kathleen Leary RN (Assistant Editor JDD), Lucy James (Editorial Project Manager JDD), and Donald Morcone (Continuing Education Grants Manager 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 the US FDA. The National Association for Continuing Education, the *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 the National Association for Continuing Education, the *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 independent educational grant from Valeant Pharmaceuticals.

Special Services

If you need special accommodations due to a disability or require an alternative form of course materials, e-mail Nick Gillespie at Nick.Gillespie@jddonline.com. The *Journal of Drugs in Dermatology* is committed to providing whatever special assistance its users require to complete this educational activity.

Contact Information

If you need technical support or have questions about the course, please e-mail Nick.Gillespie@jddonline.com.

For questions about the CME activity content, please contact the National Association for Continuing Education at info@naceonline.com.

National Association for Continuing Education CME Privacy Policy

All information provided by course participants is confidential and will not be shared with any other parties for any reason without permission.

Copyright

All of the content in this educational activity is copyrighted by the *Journal of Drugs in Dermatology*. The National Association for Continuing Education has obtained permission from the *Journal of Drugs in Dermatology* to use the content in this educational activity.

Understanding and Addressing the Acne Vulgaris Paradigm Shift

Leon H. Kircik MD

A paradigm shift has occurred in our understanding of the pathogenesis and pathophysiology of acne vulgaris (AV). The outdated paradigm posited that AV lesions initially developed after abnormal desquamation of the keratinocytes that line the sebaceous follicle, which induced hyperkeratinization and comedogenesis.[1,2] The pathological process in AV was then facilitated by an increase in circulating androgens at the onset of puberty, which stimulated the production of sebum in the pilosebaceous unit, creating a milieu that was conducive for the colonization with *Propionibacterium acnes*[1,2]

In 2003, however, Jeremy et al published a landmark study which revealed that the involvement of inflammatory responses is fundamental to the earliest stages of AV lesion development and occurs during hyperkeratinization.[3] Subsequent studies have further demonstrated that cellular inflammatory events are present at every stage of AV, from subclinical manifestations to the clinical presentation of active lesions.[4]

In this supplement I will review the various inflammatory biomarkers and mechanisms that have been implicated in AV, as well as how the inflammatory processes continue even after the resolution of papules and pustules, which leads to hyperpigmentary changes and scarring. Finally, I will address our new understanding of the role *P. acnes* plays in the pathogenesis of AV.

My colleague Joshua Zeichner MD will go over the novel treatment modalities for AV that address the new paradigm of AV pathogenesis. Additionally, bacterial resistance to antibiotics has become a clinically relevant concern not only globally but also in day to day acne treatment since this practice of overuse or inappropriate use of antibiotics in dermatology has resulted in extensive treatment failure. In the wake of antibiotic resistance and failure to treat AV, benzoyl peroxide has emerged as an efficacious treatment for AV, especially in fixed combination formulations with other topical antibiotics or retinoids. Therefore, as our understanding of the pathogenesis of AV is evolving, the new treatment paradigm is also shifting now to more anti-inflammatory agents.

Finally, the constant presence of inflammation in AV, from the genesis to the end of lesion progression, may even force us to drop the existing nomenclature of "non- inflammatory lesions" for "open and closed comedones", given that these are actually inflammatory in nature!

"As our understanding of the pathogenesis of acne vulgaris is evolving, the new treatment paradigm is also shifting now to more anti-inflammatory agents."

DISCLOSURES

Dr. Kircik has received compensation from the *Journal of Drugs in Dermatology* for his editorial support.

Leon H. Kircik MD
Mount Sinai Medical Center, New York, NY
Indiana University School of Medicine, Indianapolis, IN
Physicians Skin Care, PLLC, Louisville, KY

References

1. Papakonstantinou E, Aletras AJ, Glass E, et al. Matrix metalloproteinases of epithelial origin in facial sebum of patients with acne and their regulation by isotretinoin. *J Invest Dermatol.* 2005;125(4):673-684.
2. Gollnick H, Cunliffe W, Berson D, et al. Management of acne: a report from a Global Alliance to Improve Outcomes in Acne. *J Am Acad Dermatol.* 2003;49(suppl 1):s1-s37.
3. 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.
4. Do TT, Zarkhin S, Orringer JS, 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.
5. Kircik LH. The role of benzoyl peroxide in the new treatment paradigm for acne. *J Drugs Dermatol.* 2013;12(6):s73-s76.

Advances in the Understanding of the Pathogenesis of Inflammatory Acne

Leon H. Kircik MD
Mount Sinai Medical Center, New York, NY
Indiana University School of Medicine, Indianapolis, IN
Physicians Skin Care, PLLC, Louisville, KY

ABSTRACT

Acne vulgaris (AV) is the most common skin disorder. It was traditionally thought that AV lesions developed after abnormal desquamation of the keratinocytes that line the sebaceous follicle, leading to hyperkeratinization and microcomedone formation. However, in recent years there has been a paradigm shift with regard to understanding the pathogenesis of AV, and it is now viewed as a primary inflammatory skin disorder. Research has implicated the presence of subclinical inflammation in the normal skin of acne patients, even before microcomedone formation. This article will review the novel concepts that play a role in the new pathogenesis of acne vulgaris.

J Drugs Dermatol. 2016;15(1 Suppl 1):s7-s10.

INTRODUCTION

Acne vulgaris (AV) is a chronic inflammatory disease of the pilosebaceous unit, and it is the most pervasive skin disorder regardless of gender, skin color, or ethnicity.[1-3] For decades it was thought that AV lesions initially developed after abnormal desquamation of the keratinocytes that line the sebaceous follicle, creating hyperkeratinization and microcomedone formation.[4-6] The pathological process in AV was then facilitated by an increase in circulating androgens at the onset of puberty, which stimulated the production of sebum in the pilosebaceous unit.[4-6] The combination of hyperkeratinization and the increase in circulating androgens then created a milieu that was conducive for the colonization of *Propionibacterium acnes,* resulting in various inflammatory molecules and chemotactic factors that initiate and perpetuate inflammatory cascades.[4-6]

However, a paradigm shift has occurred with regard to understanding the pathogenesis of AV. A seminal study demonstrating subclinical inflammatory cascades in AV was conducted by Norris and Cunliffe in 1988, and they observed lymphocytes and polymorphonuclear leukocytes prior to and concurrently with hyperkeratinization and microcomedone formation.[7] Moreover, in 1998, Layton et al found that CD4+ lymphocytes and macrophages (CD68+) were the earliest immune cells to infiltrate sites of nascent, subclinical inflammatory AV lesions.[8]

A New Acne Vulgaris Paradigm Emerges

In 2003, Jeremy et al published a landmark study regarding the pathogenesis of AV that produced a paradigm shift.[9] The investigators biopsied clinically normal follicles from the uninvolved skin of AV patients, the nascent lesions from AV patients, and the skin of healthy controls. After the biopsies were performed, cellular, vascular, and proliferative markers for inflammation were evaluated from the 3 groups.

Jeremy et al found that although CD3+ and CD4+ T cells were elevated in the uninvolved skin of AV patients, the elevation of these cells was not equivalent to the elevation in the papules of AV patients. The number of macrophages in the uninvolved skin of AV patients was also significantly increased and comparable to those in the papules of AV patients. E-selectin, vascular adhesion molecule 1, and interleukin-1 (IL-1) levels were also upregulated in the uninvolved skin of AV patients. The investigators concluded that vascular endothelial cell activation and the involvement of inflammatory responses are integral to the earliest stages of AV lesion development, and occur during hyperkeratinization.

The study conducted by Jeremy et al played a crucial role in deconstructing the dogma that the pathogenesis of AV commences with hyperkeratinization and comedogenesis. A subsequent study conducted by Do et al provided additional evidence that AV is an inflammatory skin disorder instead of an hyperproliferative disorder of the sebaceous follicle.[10] Using digital photographs and spatial alignment software, Do et al photographed 25 subjects with untreated facial AV every 2 weeks for 12 weeks. The investigators discovered that although 54% of inflammatory lesions were preceded by comedones, 28% of inflammatory lesions were preceded by normal-appearing skin. Consequently, Do et al further demonstrated that cellular inflammatory events occur at every stage of AV, from subclinical manifestations to the clinical presentation of active lesions.

The Role of *Propionibacterium acnes* in the Pathogenesis of Acne Vulgaris

Toll-Like Receptors

The paradigm shift regarding comedogenesis has initiated a reexamination of the involvement of *P. acnes* in the pathogenesis of AV. Although considerable evidence delineates the role of *P. acnes* in AV, the exact mechanisms by which it contributes to AV are currently in the process of being reevaluated. Studies have shown that *P. acnes* activates cytokine responses via toll-like receptors (TLRs), which recognize pathogen-associated molecular patterns on microorganisms and elicit immune responses.

In 2002, Kim et al established an association between *P. acnes* and TLR-2.[11] In that study, the investigators found that macrophages presenting TLR-2 were present in the acne lesions, around pilosebaceous follicles, and they increased during the evolution of the disease. In fact, *P. acnes* was able to induce nuclear factor-κB (NF-κB) activation from transfecting of TLR-2 into a non-responsive cell line. Moreover, in monocytes, *P. acnes* induced IL-12 and IL-8 protein production that was inhibited by anti-TLR-2 blocking antibodies. In a murine model, *P. acnes* initiated IL-12 p40 promoter activity via TLR-2, and IL-6 was elicited too. Kim et al felt that their data suggested that *P. acnes* triggers inflammatory cytokine responses in AV by activation of TLR-2.

A 2005 study conducted by Jugeau et al built on the study of Kim et al and further demonstrated the role that TLRs play in response to *P. acnes.*[12] The investigators found that the in vivo expression of TLR-2 and TLR-4 is increased in the acne lesions. In vitro tests also demonstrated that an increase in TLR-2 and TLR-4 expression occurred in human keratinocytes during the first hours of incubation with *P. acnes.* Additionally, Jugeau et al found that keratinocytes had an increased in vitro expression and secretion of metalloproteinase-9 (MMP-9) when incubated with *P. acnes.*

A 1992 study found that high levels of the pro-inflammatory cytokine IL-1α were expressed in acne lesions, and those findings were corroborated by Selway et al in 2013 and framed within the paradigm of TLRs playing a role in the inflammatory process that engenders AV.[13] Selway et al found TLR-2 to be expressed in basal and infundibular keratinocytes, and its activation elicited the release of IL-1α from primary human keratinocytes in vitro.[14] The in vitro exposure of micro-dissected human sebaceous glands to pathogen associated molecular patterns specific for TLR-2 also resulted in the increased expression of IL-1α.

Nucleotide-Binding Oligomerization Domain-Like Receptors

In addition to activating TLRs, *P. acnes* has been shown to activate nucleotide-binding oligomerization domain-like receptors, or NLRs, which are an important class of inflammasome genes that trigger inflammation and anti-microbial responses. Qin et al stimulated human monocytes with *P. acnes,* and found that *P. acnes*-induced NLRP3 activation that resulted in enhanced IL-1β secretion.[15] The investigators also determined that monocytes stimulated with *P. acnes* upregulated caspase-1 expression that resulted in further IL-1β secretion.

Additionally, the investigators noted a higher cellular expression of NLRP-3 and active caspase-1 in the dermis surrounding the pilosebaceous follicles in acne lesions compared with normal skin controls, and also a higher prevalence of CD68+ monocytes/macrophages in acne lesions compared with normal skin controls. Qin et al determined that *P. acnes* triggers a key inflammatory mediator, IL-1β, via NLRP-3 and caspase-1 activation, indicating a role for inflammasome-mediated inflammation in acne pathogenesis. A second study, conducted by Kistowska et al, has also demonstrated that NLRP-3 and IL-1β are integral to the inflammatory process induced by *P. acnes.*[16]

> "In recent years there has been a paradigm shift with regard to understanding the pathogenesis of acne vulgaris, and it is now viewed as a primary inflammatory skin disorder."

Proteinase-Activated Receptors

P. acnes has been shown to produce exogenous proteases, and Lee et al investigated the function of these proteases in the induction of inflammatory cascades. The Lee et al study found that *P. acnes* protease and proteinase-activated receptor-2 (PAR-2) activity were increased on keratinocytes in AV.[17] Furthermore, keratinocytes that had increased PAR-2 activity stimulated the mRNA expression of IL-1α, IL-8, tumor necrosis factor- α (TNF-α), human beta defensin-2, LL-37, MMP-1, MMP-2, MMP-3, MMP-9, and MMP-13. The results of this study indicate that PAR-2 plays an important role in the pathogenesis of AV by inducing inflammatory mediators in response to *P. acnes* proteases. The study also indicates that some of the inflammatory mediators that are augmented by PAR-2 activity are integral to AV prior to the presence of *P. acnes*, so *P. acnes* is merely enhancing their response.

Nuclear Factor-κB

An article by Kim et al, published in *Dermatology,* was referenced earlier regarding *P. acnes* inducing NF-κB activation via TLR-2. A subsequent study by Kang et al also demonstrated that NF-κB and activator protein-1 are activated in acne lesions.[18] Kang et al found that TNF-α and IL-1β secretion, which are the resultant effect of NF-κB activation, will further amplify the NF-κB signaling pathways that originally led to their production and stimulate nearby cells for additional pro-inflammatory responses.

For example, TNF-α and IL-1β have been shown to up-regulate adhesion molecules ICAM-1 and VCAM-1 on endothelial cells.[19,20] Consequently, Kang et al hypothesized that ICAM-1, VCAM-1, and E-selectin expression levels on the luminal surface of endothelial cells are increased in inflammatory acne papules due to TNF-α and IL-1β induction.

Gene Array Profiling

In the wake of mounting evidence that AV is initially driven by abnormal, subclinical inflammatory responses and also after various biomarkers in the disease progression of AV have been identified, Trivedi et al performed gene expression profiling of acne patients.[21] Skin biopsies were obtained from an inflammatory papule and from the normal skin of 6 patients with AV, as well as from the normal skin of 6 subjects without AV. The biopsies demonstrated that 211 genes were upregulated in the lesional skin of AV subjects compared with the non-lesional skin of AV subjects and healthy controls.

Trivedi et al found that a significant proportion of upregulated genes are involved in pathways that regulate inflammation and initiate inflammatory cascades. The upregulated genes included MMP-1, MMP-3, IL-8, human beta-defensin 4, and granzyme B. The investigators concluded that matrix metalloproteinases, inflammatory cytokines, and antimicrobial peptides play a salient role in AV lesions.

Although the Trivedi et al gene expression profiling of acne patients established that multiple inflammatory cascades were involved in the pathogenesis of AV, the investigators observed that the normal skin of AV patients did not elicit the plethora of up-regulated genes as biopsied lesional skin. In fact, there were no gene expression differences between the normal skin of subjects with AV patients and without AV in the array analysis. These results were most likely due to the nominal inflammation involved in the small, 5 mm biopsies that were taken from the AV patients.

Acne Vulgaris and Scarring

In addition to cellular inflammatory mechanisms playing a role from subclinical comedogenesis to the clinical presentation of active lesions, research has shown that cellular inflammatory mechanisms are involved in AV resolution and scarring. Lee et al conducted a histopathological analysis of atrophic acne scars from AV patients, and found cellular infiltrates from transforming growth factor-β, (MMP-1), MMP-2, MMP-9, and MMP-13 in 77% of the scars.[22]

In an effort to differentiate the cell-mediated immune responses in patients who were prone to AV scarring vs AV patients who were not prone to AV scarring, Holland et al investigated various cellular and vascular biomarkers from the biopsies of inflamed lesions on the backs of AV patients.[23] The lesions were 6 hours to 7 days in duration.

Holland et al observed that patients who did not have AV scarring had an effuse influx of CD4+ T cells, macrophages, and Langerhans cells early in the lesions' development, and a significant number of these cells expressed HLA-DR. In the patients without AV scarring, the investigators also noted significant angiogenesis and vascular adhesion molecule expression in the early phase of their lesion development.

Conversely, the patients with scarring had significantly less CD4+ T cells, Langerhans cells, and a lower cellular HLA-DR expression in the early development of their lesions. Moreover, patients with scarring had higher angiogenesis molecule expression after 48 hours, and they experienced a later influx of macrophages, and increased cellular HLA-DR expression. Holland et al concluded that patients with scarring had an initial cellular response to AV that was weaker and less effective, but that it was more protracted throughout the resolution of AV lesions.

Types of Propionibacterium acnes

As the understanding of the pathogenesis of AV has expanded, so has the understanding of multiple facets of *P. acnes,* including its various genotypes. *P. acnes* has been subdivided into type I, type II, and type III. Within type I, there are 2 subtypes, IA and IB, whose distinction was initially based on serologic differentiation of cell wall carbohydrates and phage typing and later confirmed by analysis of recA, tly, and CAMP gene sequences.[24,25] *P. acnes* type III was identified in a 2008 article in which the investigators found isolates belonging to a novel recA cluster of *P. acnes* that was distinct from types I and II.[26]

P. acnes type IA has an extremely high association with acne, and it has been shown to be phenotypically resistant to multiple antibiotics, including tetracycline, clindamycin, and erythromycin, because of resistance conferring mutations in the 16S ribosomal RNA gene and the 23S rRNA gene.[27] In contrast, *P. acnes* type 1B is not specifically associated with AV, which challenges the traditional concept that all *P. acnes* contributes to AV pathogenesis. When comparing the different *P. acnes* types for pro-inflammatory expression, Jasson et al found that *P. acnes* type III had the highest pro-inflammatory potential due to its up-regulation of PAR-2, TNF-α, MMP-13, and tissue inhibitor of metalloproteinases-2.[28]

P. acnes resistance to antibiotics is a major concern for clinicians. A growing body of evidence indicates that antibiotic resistance and AV pathogenesis are associated with particular types or subtypes of *P. acnes.* For example, resistance to erythromycin was described as early as 1972 and, since then, widespread resistance among *P. acnes* to macrolides, lincosamines, and tetracyclines has been reported in several countries.[29,30] Acne vulgaris patients who do not respond to antibiotics may carry a strain of *P. acnes* with diverse virulence potential and antibiotic resistance patterns. These findings provide an explanation for the difficulties in predicting the clinical effects of antibiotic treatment for AV.

CONCLUSION

A paradigm shift has occurred in our understanding of the pathogenesis of AV since it has moved from being viewed as primarily a hyperproliferative disorder of the sebaceous follicle to that of an inflammatory skin disorder. We also have a new perspective for the role of *P. acnes* in AV as well as the sequence of events in evolution of acne lesions. The fact that not every *P. acnes* type causes clinical acne is a revolutionary idea that shows how far we have come from the original idea of the infectious origin of the disease caused by *P. acnes.* Moreover, we have now accepted the presence of subclinical inflammation and therefore consider AV as a primary inflammatory process rather than a secondary inflammation to *P. acnes.* Additionally, inflammatory processes continue even after the resolution of papules and pustules, leading to persistent hyperpigmentary changes and finally scarring. All these changes in our understanding of acne pathogenesis may eventually lead to disappearance of nomenclature such as "non-inflammatory lesions" for comedones, and replacement of post-inflammatory hyperpigmentation with persistent inflammatory hyper-pigmentation.

DISCLOSURES

Dr. Kircik has served as an advisor, investigator, consultant, and speaker for Allergan, Bayer, Galderma, Promius Pharma, Quinnova, Stiefel/GSK, LeoPharma, Taro, Valeant, and Warner-Chilcott.

REFERENCES

1. Davis SA, Narahari S, Feldman SR, et al. Top dermatologic conditions in patients of color: an analysis of nationally representative data. *J Drugs Dermatol.* 2012;11(4):466-473.
2. Alexis AF. Acne vulgaris in skin of color: understanding nuances and optimizing treatment outcomes. *J Drugs Dermatol.* 2014;13(6):s61-s65.
3. Perkins AC, Cheng CE, Hillebrand GC, et al. Comparison of the epidemiology of acne vulgaris among Caucasian, Asian, Continental Indian and African American women. *J Eur Acad Dermatol Venereol.* 2011;25(9):1054-1060.
4. Papakonstantinou E, Aletras AJ, Glass E, et al. Matrix metalloproteinases of epithelial origin in facial sebum of patients with acne and their regulation by isotretinoin. *J Invest Dermatol.* 2005;125(4):673-684.
5. Gollnick H, Cunliffe W, Berson D, et al. Management of acne: a report from a Global Alliance to Improve Outcomes in Acne. *J Am Acad Dermatol.* 2003;49(suppl 1):s1-s37.
6. Harper JC, Thiboutot DM. Pathogenesis of acne: recent research advances. *Adv Dermatol.* 2003;19:1-10.
7. Norris JF, Cunliffe WJ. A histological and immunocytochemical study of early acne lesions. *Br J Dermatol.* 1988;118(5):651-659.
8. Layton AM, Morris C, Cunliffe WJ, Ingham E. Immunohistochemical investigation of evolving inflammation in lesions of acne vulgaris. *Exp Dermatol.* 1998;7(4):191-197.
9. Jeremy AH1, Holland DB, Roberts SG, Thomson KF, Cunliffe WJ. Inflammatory events are involved in acne lesion initiation. *J Invest Dermatol.* 2003;121(1):20-27.
10. Do TT, Zarkhin S, Orringer JS, 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.
11. Kim J, Ochoa MT, Krutzik SR, et al. Activation of toll-like receptor 2 in acne triggers inflammatory cytokine responses. *J Immunol.* 2002;169(3):1535-1541.
12. Jugeau S, Tenaud I, Knol AC, et al. Induction of toll-like receptors by Propionibacterium acnes. *Br J Dermatol.* 2005;153(6):1105-1113.
13. Ingham E, Eady EA, Goodwin CE, Cove JH, Cunliffe WJ. Pro-inflammatory levels of interleukin-1 alpha-like bioactivity are present in the majority of open comedones in acne vulgaris. *J Invest Dermatol.* 1992;98(6):895-901.
14. Selway JL, Kurczab T, Kealey T, Langlands K. Toll-like receptor 2 activation and comedogenesis: implications for the pathogenesis of acne. *BMC Dermatol.* 2013;13:10.
15. Qin M, Pirouz A, Kim MH, Krutzik SR, Garbán HJ, Kim J. Propionibacterium acnes induces IL-1β secretion via the NLRP-3 inflammasome in human monocytes. *J Invest Dermatol.* 2014;134(2):381-388.
16. Kistowska M, Gehrke S, Jankovic D, et al. IL-1β drives inflammatory responses to propionibacterium acnes in vitro and in vivo. *J Invest Dermatol.* 2014;134(3):677-685.
17. Lee SE, Kim JM, Jeong SK, et al. Protease-activated receptor-2 mediates the expression of inflammatory cytokines, antimicrobial peptides, and matrix metalloproteinases in keratinocytes in response to Propionibacterium acnes. *Arch Dermatol Res.* 2010;302(10):745-756.
18. Kang S1, Cho S, Chung JH, Hammerberg C, Fisher GJ, Voorhees JJ. Inflammation and extracellular matrix degradation mediated by activated transcription factors nuclear factor-kappaB and activator protein-1 in inflammatory acne lesions in vivo. *Am J Pathol.* 2005;166(6):1691-1699.
19. Hirose T, Patterson C, Pourmotabbed T, et al. Structure-function relationship of human neutrophil collagenase: identification of regions responsible for substrate specificity and general proteinase activity. *Proc Natl Acad Sci.* 1993;90(7):2569-2573.
20. Collins T, Read MA, Neish AS, Whitley MZ, Thanos D, Maniatis T. Transcriptional regulation of endothelial cell adhesion molecules: NF-kappa B and cytokine-inducible enhancers. *FASEB J.* 1995;9(10):899-909.
21. Trivedi NR, Gilliland KL, Zhao W, Liu W, Thiboutot DM. Gene array expression profiling in acne lesions reveals marked upregulation of genes involved in inflammation and matrix remodeling. *J Invest Dermatol.* 2006;126(5):1071-1079.
22. Lee WJ, Jung HJ, Lim HJ, Jang YH, Lee SJ, Kim DW. Serial sections of atrophic acne scars help in the interpretation of microscopic findings and the selection of good therapeutic modalities. *J Eur Acad Dermatol Venereol.* 2013;27(5):643-646.
23. Holland DB, Jeremy AH, Roberts SG, Seukeran DC, Layton AM, Cunliffe WJ. Inflammation in acne scarring: a comparison of the responses in lesions from patients prone and not prone to scar. *Br J Dermatol.* 2004;150(1):72-81.
24. Valanne S, McDowell A, Ramage G, et al. CAMP factor homologues in Propionibacterium acnes: a new protein family differentially expressed by types I and II. *Microbiology.* 2005;151(pt 5):1369-1379.
25. McDowell, Valanne S, Ramage G, et al. Propionibacterium acnes types I and II represent phylogenetically distinct groups. *J Clin Microbiol.* 2005;43(1):326-334.
26. McDowell A, Perry AL, Lambert PA, Patrick S. A new phylogenetic group of Propionibacterium acnes. *J Med Microbiol.* 2008;57(pt 2):218-224.
27. Fitz-Gibbon S, Tomida S, Chiu BH, et al. Propionibacterium acnes strain populations in the human skin microbiome associated with acne. *J Invest Dermatol.* 2013;133(9):2152-2160.
28. Jasson F, Nagy I, Knol AC, Zuliani T, Khammari A, Dréno B. Different strains of Propionibacterium acnes modulate differently the cutaneous innate immunity. *Exp Dermatol.* 2013;22(9):587-592.
29. Martin WJ, Gardner M, Washington JA 2nd. In vitro antimicrobial susceptibility of anaerobic bacteria isolated from clinical specimens. *Antimicrob Agents Chemother.* 1972;1(2):148-158.
30. Lomholt HB, Kilian M. Clonality and anatomic distribution on the skin of antibiotic resistant and sensitive Propionibacterium acnes. *Acta Derm Venereol.* 2014;94(5):534-538.

AUTHOR CORRESPONDENCE

Leon H. Kircik MD
E-mail:..... wedoderm@yahoo.com

Inflammatory Acne Treatment: Review of Current and New Topical Therapeutic Options

Joshua A. Zeichner MD
Department of Dermatology, Mount Sinai Hospital, New York, NY

ABSTRACT

Acne vulgaris (AV) is an inflammatory skin disease characterized by the presence of comedones, papules, pustules, and nodules. Consensus guidelines recommend the use of combination therapy using different drugs with complementary mechanisms of action to best address as many acne pathogenic factors as possible at the same time. Topical acne medications exist as individual agents that may be combined in physician-recommended regimens or as pre-formulated fixed-dose combination products. In addition, there are several new and promising topical therapies currently being developed that work by different mechanisms of action from traditionally used acne therapies. The following review will cover commonly used drugs, newcomers to the market, and what the future holds for the topical treatment of AV.

J Drugs Dermatol. 2016;15(1 Suppl 1):s11-s16.

INTRODUCTION

Acne vulgaris (AV) is the single most common reason that patients visit dermatologists.[1] An estimated 40 to 50 million Americans suffer from it, including 95% of teenage boys and 85% of teenage girls.[2,3,4] Acne imparts a significant psychosocial burden, and the effect has been likened to that of systemic diseases such as diabetes, asthma, and epilepsy.[5] Body image issues, anxiety, depression, poor self-esteem, and social disturbances affect up to half of adolescents with acne.[6,7] For all of these reasons, effective treatments are a necessity.

Acne is an inflammatory disease. Follicular hyperkeratinization,[8] sebum production,[9] *Propionibacterium acnes* bacteria colonization,[10] and resulting inflammation[11,12] all contribute to its pathogenesis. Hyperkeratinization leads to narrowing of the follicular ostium, which in turn allows for sebum accumulation beneath.[13,14] It is also thought that *P. acnes* forms a biofilm in the sebaceous gland further obstructing the follicle.[15] *P. acnes* is a commensal skin organism rather than an infection, and its lipases break down sebum triglycerides into pro-inflammatory free fatty acids[16] and activates an innate immune response through toll-like receptor 2 (TLR-2) binding with subsequent production of the pro-inflammatory cytokines TNF-α and IL-1α.[17] Collectively this inflammation promotes comedogenesis.[18]

Traditionally, acne has been categorized as having either "inflammatory" or "non-inflammatory" lesions. Inflammatory lesions include acne papules, pustules, cysts, and nodules. Non-inflammatory lesions, on the other hand, refer to open and closed comedones. The term "non-inflammatory" is still used by convention, but it is in reality a misnomer. Recent data suggest that subclinical perifollicular inflammation actually precedes formation of the microcomedone. This means that comedones are in fact inflammatory lesions. In one 2003 study, investigators took biopsies from clinically normal appearing skin in acne patients. They discovered that while no clinical lesions were observed, sub-clinical elevation of CD4+ T cells, macrophages, vascular adhesion molecules, and pro-inflammatory cytokines were present.[19] Moreover, inflammatory lesions may arise from clinically normal appearing skin. Using photographic star tracking software, investigators in another study followed acne lesions on the face during a 30-day period. Inflammatory lesions developed from comedones in 54% of patients, but from normal-appearing skin in 28% of patients.[20] Regardless of nomenclature, comendones are in fact inflammatory lesions.

Consensus guidelines recommend combination therapy for the treatment of all but the mildest comedonal acne.[21] Enhanced therapeutic benefits can be achieved by combining agents with different but complementary mechanisms of action. The following review will discuss topical medications, alone and in combination, for the treatment of AV, both traditional inflammatory lesions and inflammatory comedonal lesions.

Topical Treatment Options

An algorithmic approach may be used to select the proper acne therapy based on lesion type, severity, and extent of body surface area affected. Topical therapies may be used as a first-line approach for mild to moderate acne or in combination with orals for more severe disease. Prescription topical options include benzoyl peroxide (BPO), topical antibiotics, topical retinoids, and topical dapsone. These are frequently prescribed in various combinations to suit the specific needs of the patient. In general, simpler regimens improve outcomes, as patients

have been shown to have greater adherence to regimens with fewer steps.[22] For this reason, fixed-dose combination topical drugs have become popular options in treating acne rather than applying each of the monotherapies twice daily. Combinations include BPO-antibiotics, BPO-topical retinoids, and topical retinoids - topical antibiotics in various generic and branded formulations.

Benzoyl Peroxide

Benzoyl peroxide has at the same time anti-microbial, anti-inflammatory, and keratolytic properties. It is a recommended component of almost all combination regimens for treating acne.[21,23] BPO is directly toxic to *P. acnes*, and to date there are no reports of *P. acnes* resistance.[24] BPO is thought to work by inhibiting the metabolism of *P. acnes*' interference with protein synthesis and mitochondrial function, and lead to DNA damage.[25] It is commonly used alongside topical antibiotics to prevent the development of bacterial resistance, and acne improvement has been noted after BPO was given to patients with previously known *P. acnes* resistance.[26] By killing *P. acnes* and preventing its subsequent production of pro-inflammatory mediators, BPO is indirectly anti-inflammatory.[21] Moreover, BPO has keratolytic properties. Statistically higher concentrations of corneocytes have been shown to be removed by tape-strip analysis after application of BPO 2% cream compared with vehicle cream or untreated skin.[27]

"An algorithmic approach may be used to select the proper acne therapy based on lesion type, severity, and extent of body surface area affected."

The most common adverse events (AEs) that patients associate with BPO are concentration-dependent irritant dermatitis. True allergic contact dermatitis is quite rare.[28,29] In fact, studies have shown that not only are lower concentrations of BPO less irritating than higher concentrations, but they also demonstrate similar efficacy to higher concentrations.[30] In one study, twice-daily application of BPO 2.5% resulted in a 97% and 99% reduction in *P. acnes* counts after 1 week and 2 weeks respectively.[31] While products are vehicle- and formulation-dependent and generalizations cannot be made blindly, in general lower BPO concentrations may be preferred because they cause less potential skin irritation.

Topical Antibiotics

Antibiotics have both anti-microbial and anti-inflammatory effects on the skin. They reduce the levels of *P. acnes* bacteria within the sebaceous follicles. Some (eg, erythromycin and tetracyclines) also have direct anti-inflammatory properties, reducing pro-inflammatory chemotactic factors and lipase levels at concentrations lower than the mean inhibitory concentrations needed for *P. acnes* killing.[32] Lipophilic antibiotics are considered best for acne because they can most easily penetrate the lipid-filled, sebaceous environment. These include macrolides (eg, erythromycin), clindamycin, tetracyclines (eg, doxycycline, minocycline), and trimethoprim.[33]

Clindamycin and erythromycin are the 2 most commonly used topical antibiotics in the United States for the treatment of acne.[34] Topical erythromycin has largely fallen out of favor with most experts because of high levels of resistance by *P. acnes*.[35] Clindamycin is widely used as an individual agent combined with a separate BPO-containing preparation or as an ingredient in one of many fixed-dose BPO/clindamycin combination products.

Besides being antimicrobial, clindamycin's anti-inflammatory properties play an important role in its therapeutic effect. Clindamycin has been shown to lower *P. acnes*-related inflammatory factors, decreasing lipase production and the subsequent release of free fatty acids. In addition, it has been shown to inhibit leukocyte chemotaxis, reducing perifollicular inflammation. Clindamycin has also been shown to reduce levels of pro-inflammatory cytokines IL1-β, IL-6, INF-ɣ, TNF-α, and GM-CSF.[36,37]

While tetracyclines are used orally, there are no topical versions currently available in the US. Minocycline, however, has been successfully stabilized in a topical foam formulation and is currently in development stages. This drug will be reviewed in a subsequent section.

With the growing awareness of bacterial resistance to antibiotics, monotherapy with topical (or oral) antibiotics is not recommended for the treatment of acne.[38] The first reports of bacterial resistance to topical clindamycin came in the 1970's and were the result of mutations in 23S ribosomal RNA, conferring cross-resistance to both erythromycin and clindamycin.[39] Resistance has been demonstrated in clinical studies. In one trial, clindamycin as monotherapy for the treatment of acne for 16 weeks resulted in *P. acnes* counts increasing by more than 1600% compared with baseline. This effect was blocked with the addition of BPO.[40] Current guidelines recommend the concurrent use of BPO with topical antibiotics to reduce the risk of developing resistance.[26]

Topical Retinoids

Retinoids are a class of drugs similar in structure to Vitamin A. Vitamin A interacts with nuclear receptors to stimulate processes related to cell growth and differentiation. Three topical retinoids are available by prescription in the US: tretinoin, tazarotene, and adapalene (ADA).[41] Collectively these drugs

have keratolytic and anti-inflammatory properties. They are also comedolytic, enhancing cellular differentiation and proliferation, normalizing desquamation and keratinization, and reducing cell cohesiveness within the follicle.[21,26] Retinoids may be used as monotherapy or in combination with other topicals for both comedonal and inflammatory disease. Moreover, they are commonly used as maintenance therapy after initial control has been obtained over the acne.[21,26] While effective, application site reactions such as dryness, peeling, redness, burning, and stinging are especially common in the first few weeks of therapy, a period known as "retinization."[42] Various approaches have been taken to minimize these AEs, including initial intermittent use and application of moisturizers.[43]

Topical Dapsone

Dapsone is a sulfone antibiotic with anti-inflammatory properties. Topical dapsone 5% gel is approved by the US Food and Drug Administration (FDA) and commercially available to treat acne. While similar in name, the sulfone dapsone is structurally different to sulfonamide antibiotics. As such there is no allergic cross reactivity with sulfonamides, and a higher likelihood of someone with a known sulfa allergy being allergic to penicillin rather than to dapsone.[44] The exact mechanism of action in treating acne is not clear. In vitro, dapsone has been demonstrated to inhibit neutrophil chemotaxis and release of lysosomal enzymes that promote inflammation and oxygen-free radicals. While dapsone is antimicrobial in treating leprosy, no activity has been shown against *P. acnes*.[45] Data from the pivotal phase 3 clinical trials revealed that twice-daily use of topical dapsone was effective in treating both inflammatory and comedonal lesions (though with greater efficacy in inflammatory lesions), and it also had an extremely favorable tolerability profile.[46] Moreover, topical dapsone has been successfully combined with other medications, such as topical retinoids and BPO.[47,48]

Newly Approved Topical Therapies

In the past year, 2 new fixed-dose combination topical products have been brought to market for the treatment of AV. Both demonstrate efficacy and tolerability across a variety of acne lesion types. The following summarizes the latest data on fixed-dose BPO 3.75%/clindamycin phosphate (CP) 1.2% gel and BPO 2.5%/ADA 0.3% gel.

Benzoyl Peroxide 3.75% /Clindamycin Phosphate 1.2% Gel

In November 2014, BPO 3.75%/CP 1.2% gel received FDA approval for the treatment of AV in patients 12 years of age and older. The vehicle is an aqueous gel with humectant properties and free from alcohol and preservatives.[49] CP is the water soluble ester of clindamycin, which is fully dissolved in the aqueous gel base and readily available when applied to the skin. BPO is both microdispersed in the gel as well as micronized. It is evenly distributed in each metered dose, and 90% of the BPO particles are less than 10 microns in diameter.[50] (As a point of reference, the hair follicle diameter for vellus hairs is estimated to be in the range of 130 microns.[51])

In the phase 3, pivotal clinical trial, 498 subjects were enrolled in a 12-week multi-center, double-blind, vehicle-controlled study. Patients were randomized 1:1 to receive either active drug or vehicle, which was applied once daily to the face. Standard washout periods for previous prescription and over-the-counter (OTC) products were enforced. Enrolled patients had a baseline Evaluator's Global Severity Score (EGSS) of moderate or severe (EGSS = 3 or 4) and mean baseline lesion counts of 27 and 37.8 inflammatory and comedonal lesions, respectively.[52]

The drug was shown to be efficacious and statistically better than vehicle for all efficacy treatment variables. At week 12, the absolute change in inflammatory lesions was -16.3 lesions compared with baseline, while the comedonal lesions were reduced by 19.2 lesions. There was a 51.8% and 60.4% mean reduction in comedonal and inflammatory lesions, respectively. 35% of patients were considered a treatment success at week 12, with a 2-grade improvement in EGSS. 29% of patients were a treatment success with a greater than 2-grade EGSS improvement. In this case, for example, a patient would have had a baseline score of a 4 (severe) and improved at least 3 grades to 1 or 0 (almost clear or clear). A severe patient (EGSS = 4) who improved 2 grades to mild (EGSS = 2) was not included in this endpoint.[52]

BPO 3.75%/CP 1.2% gel was well tolerated. The most common AEs in the study, which occurred in less than 0.5% of subjects treated with the active drug, were application site reactions including burning, contact dermatitis, pruritus, and rash. No subjects in the active treatment arm discontinued the study due to an AE or a lack of efficacy. Cutaneous tolerability was similar between the active drug and the vehicle.[49,52]

Post-hoc analyses of the phase 3 data and phase 4 studies have provided additional data on BPO 3.75%/CP 1.2% gel. In one analysis, the drug was found to be effective and well-tolerated in the severe subpopulation of acne patients in the study. 55.1% of severe patients had at least a 2 grade improvement in EGSS at week 12, and 30.6% of severe patients were clear or almost clear.[53] Additionally, it was found to be effective in adult women[54] and in adolescents.[55] Finally, BPO 3.75%/CP 1.2% gel was shown to have excellent cosmetic compatibility with facial foundation makeup in adult women.[56]

Benzoly Peroxide 2.5%/Adapalene 0.3% Gel

BPO 2.5%/ADA 0.3% fixed-dose combination gel received FDA approval for the treatment of acne in July 2015.[57] This antibiotic-free option is the next generation of BPO 2.5%/ADA 0.1% gel that was approved for acne in 2009.[58,59] An in vitro absorption study was performed comparing the fixed-dose combination gel to separate application of the monad drugs. The fixed-dose

combination gel yielded superior ADA release into the skin. Moreover, the BPO 2.5%/ADA 0.3% gel was *not* found to be bioequivalent to different regimens of monad formulations.[60]

In the pivotal phase 3 study, efficacy and safety of BPO 2.5%/ADA 0.3% gel were compared with that of vehicle gel in patients with moderate to severe acne. A subpopulation of severe patients was also evaluated. The safety and tolerability of BPO 2.5%/ADA 0.3% was compared with BPO 2.5%/ADA 0.1%. The study was not designed or powered to compare efficacy of the 0.3% vs 0.1% formulations. A total of 503 patients were enrolled in the multicenter, randomized, double-blinded, parallel-group, vehicle- and active-controlled study. Subjects were randomized 3:3:1 to receive 0.3% drug, 0.1% drug, or vehicle gel. At baseline, patients were required to have an acne severity of moderate or severe (Investigator's Global Assessment (IGA) = 3 or 4). The study medication was applied once daily for 12 weeks.[61]

BPO 2.5%/ADA 0.3% gel reached its co-primary efficacy endpoints. Treatment success rate was defined as at least a 2-grade improvement on IGA at week 12 compared with baseline. 33.5% of patients on the 0.03% drug were considered a treatment success, compared with 11.5% in the vehicle arm (P=.001). In addition, there was a 66.4% reduction in inflammatory lesions at week 12 (with a baseline mean lesion count of 39.2 lesions) in the active treatment arm. A greater degree of efficacy was observed in the severe acne subpopulation. 31.3% of patients achieved treatment success at week 12 vs 13.3% in the vehicle arm (P=.029), and there was a 71.8% reduction in inflammatory lesions vs 28.6% in the vehicle arm (P<.001).[61]

The drug was well tolerated, albeit with slightly more cutaneous AEs than reported in the BPO 2.5%/ADA 0.1% gel arm. There were a total of 15 AEs in the 0.3% drug group vs 2 AEs (both occurring in the same patient) in the 0.1% drug group. No AEs were reported in subjects on the vehicle. One subject in the 0.3% gel group discontinued from the study because of an AE (a flare of atopic dermatitis). There were no serious AEs during the study. Overall the mean tolerability scores in the 0.3% gel arm were less than mild, on a 4 point scale where 0 = none and 3 = severe.[61]

On the Horizon

While we currently have 2 new formulations of previously existing molecules, there are also several new chemical entities in development for the treatment of acne. In addition, new concentrations and novel delivery systems for some of our current medications will further add to the armamentarium of drugs available to treat acne. In the next few years there will be several new and different options available for use.

Topical Dapsone

Clinical trials for a new concentration of dapsone topical gel have been completed. This formulation is designed for once daily application.[62] Further details on the efficacy and safety of the drug are not publicly available.

DRM01

DRM01 is a new chemical entity in development for the treatment of acne. It is an inhibitor of coenzyme-A carboxylase, the enzyme responsible for the first and rate-limiting step in the production of fatty acids. In vitro, it has demonstrated a dose-dependent inhibition of lipid synthesis, and shown to decrease sebaceous gland size in an animal model.[63]

A phase 2a, first-in-human study has been completed evaluating safety, tolerability, and preliminary efficacy of the drug compared with vehicle. Patients with moderate to severe acne were enrolled in the study and randomized 1:1 to apply active drug or vehicle twice daily for 12 weeks. Patients were then followed post-therapy through week 16. Numerical improvements were noted at week 4, and statistical significance was achieved for all efficacy endpoints at week 12. A significantly greater mean reduction in both inflammatory (64% vs 46%; P=.0006) and comedonal (48% vs 29%; P=.0025) lesion counts were observed in the active drug compared with vehicle. Moreover, a statistically greater number of patients (almost 25%) in the active arm achieved a treatment success (>2 grade improvement in the IGA score) at week 12 compared with vehicle (P=.0070). The drug was well-tolerated and similar between the DRM01 and vehicle groups. Most local skin reactions were none to mild. Five subjects in the DRM01 group experienced a severe local skin reaction, which included severe erythema (1 subject) and severe burning/stinging (4 subjects).[64]

FMX101

Minocycline is commonly prescribed as an oral therapy for the treatment of AV and soft tissue infections. Because of stability issues, challenges have previously arisen in attempts to formulate it as a topical preparation. FMX101 is a topical minocycline foam currently in development for the treatment of acne. A phase 2, multicenter, randomized, double-blind trial has been completed at 3 study centers in Israel. One hundred and fifty patients with moderate to severe acne were enrolled and treated with once-daily application of either a 1% or 4% minocycline foam or vehicle. By week 12, a 72% (P<.001) and 73% (P<.05) reduction in inflammatory and comedonal lesions, respectively, were observed in the FMX101 4% group, which was statistically superior to vehicle. Moreover, 53% of patients using FMX101 4% were clear or almost clear vs 19.6% in the vehicle arm (P<.05). In addition, 36.2% of patients on the 4% drug were clear or almost clear along with a greater than 2 grades improvement, compared with 15.2% on vehicle (P<.05). There were no reported treatment-related AEs.[65]

SB204

Nitric oxide is a naturally occurring molecule in the body that possesses both anti-microbial and anti-inflammatory

properties. SB204 is a topical nitric oxide-releasing gel currently being developed. Its active ingredient, NVN1000, is anti-inflammatory, has demonstrated antimicrobial activity against *P. acnes*, and inhibited lipogenesis in an in vitro model. A phase 2, multi-center, randomized, double-blind, vehicle-controlled study treating moderate to severe acne has been completed in Latin America. Enrolled subjects were randomized to receive either SB204 1%, SB204 4%, or vehicle for 12 weeks. There was a 57% and 25% reduction in inflammatory and comedonal lesions, respectively, at week 12 in the 4% drug arm. Moreover, in a sebum analysis using sebutapes, 80% les sebum was measured from the skin in both the high and low concentration SB204 groups compared with the vehicle group. A concentration-dependent decrease in squalene and free fatty acids was observed. The drug was well tolerated, and only mild local skin reactions were reported.[66]

SEB002

Photodynamic therapy is a commonly used treatment for various skin conditions such as actinic keratoses. Its use in AV has been reported, but efficacy has been limited by the ability of the photosensitizer and light source to penetrate deep enough into the sebaceous glad where the pathology in acne occurs.[67] SEB002 is a suspension of gold-coated silica microparticles that can be delivered into the sebaceous gland using mechanical vibration. Subsequent activation using a light source leads to selective targeting and destruction of the sebaceous glands. Preliminary results are promising, with an excellent tolerability profile. In one European study, 48 patients were randomized to receive 3 treatments at 2-week intervals or to treat the skin initially with an OTC face wash for 12 weeks, then crossed over to the SEB002 treatment. At the week 28 evaluation, subjects treated initially with SEB002 experienced a 61% reduction in inflammatory lesions, while the cross-over group achieved a 50% reduction. The procedure was well tolerated. No anesthetic was used during the procedure, and most subjects reported only mild to moderate pain. Mild erythema was not uncommon, and it subsided within 30 to 60 minutes of the procedure.[68]

CONCLUSION

Acne vulgaris is a multifactorial skin condition that dermatologists treat on a daily basis. The clinical picture ranges from mild comedones to severe nodular cystic disease. However, recent data suggest that all acne lesions are in fact inflammatory despite the frequently used term "non-inflammatory" rather than "comedonal" lesions. Consensus guidelines recommend combination therapy using drugs with different, complimentary mechanisms of action. There is a variety of individual agents that may be combined to suit the individual patient's needs. The newest formulations offer enhanced efficacy with minimal irritation. These, along with several novel acne drugs in the pipeline, will continue to improve the landscape of topical anti-acne therapies.

DISCLOSURES

Dr. Zeichner has worked as an Advisory Board Member, Consultant, and Speaker for Allergan, Galderma, and Valeant and an Advisory Board Member for Foamix.

REFERENCES

1. Pawin H, Chivot M, Beylot, et al. Living with acne. A study of adolescents' personal experiences. *Dermatology*. 2007;215(4):308-314.
2. James WD. Clinical practice. Acne. *N Engl J Med*. 2005;352(14):1463-1472.
3. Thiboutot DM. Overview of acne and its treatment. *Cutis*. 2008;81(suppl 1):s3-s7.
4. Burton JL, Cunliffe WJ, Stafford I, Shuster S. The prevalence of acne vulgaris in adolescence. *Br J Dermatol*. 1971;85(2):119-126.
5. Mallon E, Newton JN, Klassen A, Stewart-Brown SL, Ryan TJ, Finlay AY. The quality of life in acne: a comparison with general medical conditions using generic questionnaires. *Br J Dermatol*. 1999;140(4):672-676.
6. Baldwin HE. The interaction between acne vulgaris and the psyche. *Cutis*. 2002;70(2):133-139.
7. Gupta MA, Gupta AK. Depression and suicidal ideation in dermatology patients with acne, alopecia areata, atopic dermatitis and psoriasis. *Br J Dermatol*. 1998; 139(5):846-850.
8. Plewig G, Fulton JE, Kligman AM. Cellular dynamics of comedo formation in acne vulgaris. *Arch Dermatol Forsch*. 1971;242(1):12-29.
9. Thiboutot D. Regulation of human sebaceous glands. *J Invest Dermatol*. 2004;123(1):1-12.
10. Vowels BR, Yang S, Leyden JJ. Induction of proinflammatory cytokines by a soluble factor of Propionibacterium acnes: implications for chronic inflammatory acne. *Infect Immun*. 1995;63(8):3158-3165.
11. Guy R, Green MR, Kealey T. Modeling acne in vitro. *J Invest Dermatol*. 1996;106(1):176-182.
12. Vowels BR, Yang S, Leyden JJ. Induction of proinflammatory cytokines by a soluble factor of Propionibacterium acnes: implications for chronic inflammatory acne. *Infect Immun*. 1995;63(8):3158-3165.
13. Guy R, Kealey T. Modelling the infundibulum in acne. *Dermatology*. 1998;196(1):32-37.
14. Holmes RL, Williams M, Cunliffe WJ. Pilo-sebaceous duct obstruction and acne. *Br J Dermatol*. 1972;87(4):327-332.
15. Burkhart CG, Burkhart CN. Expanding the microcomedone theory and acne therapeutics: Propionibacterium acnes biofilm produces biological glue that holds corneocytes together to form plug. *J Am Acad Dermatol*. 2007;57(4):722-724.
16. Marples RR, Downing DT, Kligman AM. Control of free fatty acids in human surface lipids by Corynebacterium acnes. *J Invest Dermatol*. 1971;56(2):127-131.
17. Kim J, Ochoa MT, Krutzik SR, et al. Activation of toll-like receptor 2 in acne triggers inflammatory cytokine responses. *J Immunol*. 2002;169(3):1535-1541.
18. Kim J. Review of the innate immune response in acne vulgaris: activation of Toll-like receptor 2 in acne triggers inflammatory cytokine responses. *Dermatology*. 2005;211(3):193-198.
19. 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.
20. Do TT, Zarkhin S, Orringer JS, 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.
21. Gollnick H, Cunliffe W, Berson D, et al. Management of acne: a report from a Global Alliance to Improve Outcomes in Acne. *J Am Acad Dermatol*. 2003;49(suppl 1):s1-s37.
22. Yentzer BA, Ade RA, Fountain JM, et al. Simplifying regimens promotes greater adherence and outcomes with topical acne medications: a randomized controlled trial. *Cutis*. 2010;86(2):103-108.
23. Tanghetti EA, Popp KF. A current review of topical benzoyl peroxide: new perspectives on formulation and utilization. *Dermatol Clin*. 2009;27(1):17-24.
24. Leyden JJ, Preston N, Osborn C, Gottschalk RW. In-vivo effectiveness of adapalene 0.1%/benzoyl peroxide 2.5% gel on antibiotic-sensitive and resistant Propionibacterium acnes. *J Clin Aesthet Dermatol*. 2011;4(5):22-26.
25. Burkhart CG, Burkhart CN. Antibacterial properties of benzoyl peroxide in aerobic and anaerobic conditions. *Int J Dermatol*. 2006;45(11):1373-1374.
26. 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):s1-s50.
27. Waller JM, Dreher F, Behnam S, et al. 'Keratolytic' properties of benzoyl peroxide and retinoic acid resemble salicylic acid in man. *Skin Pharmacol Physiol*. 2006;19(5):283-289.

28. Morelli R, Lanzarini M, Vincenzi C, Reggiani M. Contact dermatitis due to benzoyl peroxide. *Contact Dermatitis.* 1989;20(3):238-239.
29. Sagransky M, Yentzer BA, Feldman SR. Benzoyl peroxide: a review of its current use in the treatment of acne vulgaris. *Expert Opin. Pharmacother.* 2009;10(15):2555-2562.
30. Dosik JS, Vamvakias G. Comparative irritation potential of two combination acne products: a randomized controlled, subject- and evaluator-blind, comparative study in healthy volunteers. *Am J Clin Dermatol.* 2008;9(5):313-317.
31. Mills OH Jr, Kligman AM, Pochi P, Comite H. Comparing 2.5%, 5%, and 10% benzoyl peroxide on inflammatory acne vulgaris. *Int J Dermatol.* 1986;25(10):664-667.
32. Sapadin AN, Fleischmajer R. Tetracyclines: nonantibiotic properties and their clinical implications. *J Am Acad Dermatol.* 2006;54(2):258-265.
33. Leyden JJ, Del Rosso JQ. Oral antibiotic therapy for acne vulgaris: pharmacokinetic and pharmacodynamic perspectives. *J Clinical Aesthet Dermatol.* 2011;4(2):40-47.
34. Toyoda M, Morohashi M. An overview of topical antibiotics for acne treatment. *Dermatology.* 1998;196(1):130-134.
35. Leyden JJ, Wortzman M, Baldwin EK. Antibiotic-resistant Propionibacterium acnes suppressed by a benzoyl peroxide cleanser 6%. *Cutis.* 2008;82(6):417-421.
36. 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.
37. Whitney KM, Ditre CM. Anti-inflammatory properties of clindamycin: a review of its use in the treatment of acne vulgaris. *Dermatology.* 2011;4:27-41
38. Guay DR. Topical clindamycin in the management of acne vulgaris. *Expert Opin Pharmacother.* 2007;8(15):2625-2664.
39. Del Rosso JQ, Kim G. Optimizing use of oral antibiotics in acne vulgaris. *Dermatol Clin.* 2009;27(1):33-42.
40. Cunliffe WJ, Holland KT, Bojar R, Levy SF. A randomized, double-blind comparison of a clindamycin phosphate/benzoyl peroxide gel formulation and a matching clindamycin gel with respect to microbiologic activity and clinical efficacy in the topical treatment of acne vulgaris. *Clin Ther.* 2002;24(7):1117-1133.
41. Bikowski JB. Mechanisms of the comedolytic and anti-inflammatory properties of topical retinoids. *J Drugs Dermatol.* 2005;4(1):41-47.
42. Draelos ZD, Ertel KD, Berge CA. Facilitating facial retinization through barrier improvement. *Cutis.* 2006;78(4):275-281.
43. Zeichner JA, Patel RV, Haddican M, Wong V. Efficacy and safety of a ceramide containing moisturizer followed by fixed-dose clindamycin phosphate 1.2%/benzoyl peroxide 2.5% gel in the morning in combination with a ceramide containing moisturizer followed by tretinoin 0.05% gel in the evening for the treatment of facial acne vulgaris. *J Drugs Dermatol.* 2012;11(6):748-752.
44. Strom BL, Schinnar R, Apter AJ, et al. Absence of cross-reactivity between sulfonamide antibiotics and sulfonamide nonantibiotics. *N Engl J Med.* 2003;349(17):1628-1635.
45. Zhu YI, Stiller MJ. Dapsone and sulfones in dermatology: overview and update. *J Am Acad Dermatol.* 2001;45(3):420-434.
46. 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.
47. Fleischer AB, Shalita A, Eichenfield LF, et al. Dapsone gel 5% in combination with adapalene gel 0.1%, benzoyl peroxide gel 4%, or moisturizer for the treatment of acne vulgaris: a 12-week, randomized, double-blind study. *J Drugs Dermatol.* 2010;9(1):33-40.
48. Tanghetti E, Dhawan S, Green L, et al. Clinical evidence for the role of a topical anti-inflammatory agent in comedonal acne: findings from a randomized study of dapsone gel 5% in combination with tazarotene cream 0.1% in patients with acne vulgaris. *J Drugs Dermatol.* 2011;10(7):783-792.
49. Onexton [prescribing information]. Bridgewater, NJ: Valeant Pharmaceuticals North America LLC; 2014.
50. Bucks DAW, Pillai RS, McCall-Perez F. Advances in formulation technologies: creating highly effective and well-tolerated topical dermatologicals. *Skin & Aging.* 2010;(suppl):s4-s6.
51. Lee MS, Kossard S, Wilkinson B, and Doyle JA .Quantification of hair follicle parameters using computer image analysis: a comparison of androgenetic alopecia with normal scalp biopsies. *Australas J Dermatol.* 1995;36(3):143-147.
52. Pariser DM, Rich P, Cook-Bolden FE, Korotzer A. An aqueous gel fixed combination of clindamycin phosphate 1.2% and benzoyl peroxide 3.75% for the once-daily treatment of moderate to severe acne vulgaris. *J Drugs Dermatol.* 2014;13(9):1083-1089.
53. Stein Gold L. Efficacy and tolerability of a fixed combination of clindamycin phosphate (1.2%) and benzoyl peroxide (3.75%) aqueous gel in moderate and severe acne vulgaris subpopulations. *J Drugs Dermatol.* 2015;14(9):969-974.
54. Zeichner JA. The efficacy and tolerability of a fixed combination clindamycin (1.2%) and benzoyl peroxide (3.75%) aqueous gel in adult female patients with facial acne vulgaris. *J Clin Aesthet Dermatol.* 2015;8(4):21-25.
55. Cook-Bolden FE. Efficacy and tolerability of a fixed combination of clindamycin phosphate (1.2%) and benzoyl peroxide (3.75%) aqueous gel in moderate or severe adolescent acne vulgaris. *J Clin Aesthet Dermatol.* 2015;8(5):28-32.
56. Bhatia N, Pillai R. Randomized, observer-blind, split-face compatibility study with clindamycin phosphate 1.2%/benzoyl peroxide 3.75% gel and facial foundation makeup. *J Clin Aesthet Dermatol.* 2015;8(9):25-32.
57. Epiduo Forte [prescribing information]. Fort Worth, TX: Galderma; 2015.
58. Thiboutot DM, Weiss J, Bucko A, et al. Adapalene-benzoyl peroxide, a fixed-dose combination for the treatment of acne vulgaris: results of a multicenter, randomized double-blind, controlled study. *J Am Acad Dermatol.* 2007;57(5):791-799.
59. Gollnick, HP, Draelos Z, Glenn MJ, et al. Adapalene-benzoyl peroxide, a unique fixed-dose combination topical gel for the treatment of acne vulgaris: a transatlantic, randomized, double-blind, controlled study in 1670 patients. *Br J Dermatol.* 2009;161(5):1180-1189.
60. Sevin K, Osman-Ponchet H, Gaborit A, et al. Fixed-combination adapalene 0.3%/benzoyl peroxide 2.5% gel provides optimal percutaneous absorption compared to monad formulations of these compounds: a bioequivalence study. Poster presented at the Fall Clinical Dermatology Conference. Las Vegas, NV. October 2014.
61. Weiss J, Stein-Gold L, Tanghetti E. et al. Efficacy and safety of adapalene 0.3%/benzoyl peroxide 2.5% topical gel versus vehicle in moderate and severe acne vulgaris. Poster presented at the Fall Clinical Dermatology Conference. Las Vegas, NV. October 2014.
62. Safety and efficacy study of dapsone gel in patients with acne vulgaris. https://clinicaltrials.gov/ct2/show/record/NCT01974323. Accessed November 28, 2015.
63. Hunt DWC, Hofland HEJ. DRM01, a novel acetyl conenzyme A carboxylase (ACC) inhibitor, reduces sebum production. Poster presented at the Society for Investigative Dermatology Annual Meeting; Albuquerque, NM. May 2014.
64. Bissonnette R, Poulin Y, Drew J, et al. Early onset of action in a randomized, vehicle-controlled phase 2a study of DRM01, a novel topical sebum inhibitor, in subjects with acne vulgaris. Poster presented at the Fall Clinical Dermatology Conference. Las Vegas, NV. October 2014.
65. Stein-Gold L, Shemer A, Sprecher E, et al. A phase 2 randomized trial of a new minocycline foam for the treatment of moderate to severe acne vulgaris. Poster presented at the South Beach Dermatology Symposium. Miami, FL. Feburary 2014.
66. Rico J, Quiring J, Hollenbach S, et al. Phase 2 study of efficacy and safety of SB204 in the treatment of acne vulgaris. Poster presented at the Annual Meeting of the Society for Investigative Dermatology. Albuquerque, NM. May 2014.
67. Nestor MS, Gold MH, Kauvar AN. The use of photodynamic therapy in dermatology: results of a consensus conference. *J Drugs Dermatol.* 2006;5(2):140-154.
68. Paithankar DY, Sakamoto FH, Farinelli WA, et al. Acne treatment based on selective photothermolysis of sebaceous follicles with topically delivered light-absorbing gold microparticles. *J Invest Dermatol.* 2015;135(7):1727-1734.

AUTHOR CORRESPONDENCE

Joshua A. Zeichner MD
E-mail:.....joshua.zeichner@mountsinai.org

CME Post-Test: For fastest results, please complete this activity online by scanning the QR code below or visiting www.JDDonline.com in the Medical Education Library, where you will be able to receive your CME certificate immediately upon achieving the passing score. Successful completion of the Post-Test is required to earn *1.0 AMA PRA Category 1 CME Credits™*. You must earn a passing score of at least 70% and complete the activity evaluation form in order to complete the course, and receive a certificate for *1.0 AMA PRA Category 1 CME Credits™*. You can take the test online as many times as you require to achieve the passing score. Alternatively, you may select your best answer for each of the following questions and insert them into the Answer Grid found on the Evaluation/Certificate Request Form on page s18, and return your completed Evaluation/Certificate Request Form to JDD by fax to (718) 407-0898, or by mail to 377 Park Avenue South, 6th Floor, New York, NY 10016.

1. Acne vulgaris is an
   a. Infectious disease
   b. Inflammatory disease
   c. Autoimmune disease
   d. None of the above

2. The most common cause of dermatophyte infections worldwide is/are:
   a. True
   b. False

3. 100% of all papules and pustules evolve from:
   a. Open comedones
   b. Closed comedones
   c. Normal skin
   d. None of the above

4. Which of the following plays in important role in acne vulgaris:
   a. TLR2
   b. TLR3
   c. TLR4
   d. TLR7

5. Which of the following lesions is not inflammatory in nature:
   a. Papules
   b. Pustules
   c. Open comedones
   d. None of the above

6. Acne vulgaris is an infectious disease:
   a. True
   b. False

7. Which of the following statements regarding benzoyl peroxide 3.75%/clindamycin 1.2% gel is correct:
   a. The benzoyl peroxide in the formulation is both microdispersed and micronized
   b. The vehicle contains humectants and is free of preservatives and alcohol
   c. Efficacy has been demonstrated in special populations including adult women, severe patients, and adolescents
   d The drug has been shown to be compatible with facial foundation makeup
   e. All are correct

8. Which of the following statements is incorrect:
   a. Topical retinoids are keratolytic, comedolytic, and anti-inflammatory
   b. High levels of bacterial resistance have been reported to topical erythromycin
   c. Topical dapsone is effective at killing *Propionibacterium acnes* bacteria
   d Benzoyl peroxide is keratolytic and indirectly anti-inflammatory through its killing of *Propionibacterium acnes* and prevention of subsequent production pro-inflammatory cytokines
   e. No resistance of *Propionibacterium acnes* to benzoyl peroxide has been reported

9. Benzoyl peroxide 2.5%/adapalene 3% has been shown to be more effective in treating severe acne patients than moderate acne patients:
   a. True
   b. False

10. Once-daily application of a fixed-dose combination topical drug is as efficacious as applying the monotherapies separately twice daily:
   a. True
   b. False

 CME

Evaluation Form

Inflammatory Acne Vulgaris: Current Concepts In Pathogenesis And Management

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. **For fastest results, please complete this form online at JDDonline.com** in the Medical Education Library. ***You must complete and submit this form or complete the CME activity online to receive credits for completing this activity. There is no fee for this CME activity.*** You must earn a passing score of at least 70% and complete the activity evaluation form in order to complete the course and receive a certificate for 1.0 *AMA PRA Category 1 CME Credits*™. Alternatively, you may return this form to JDD by fax to (718) 407-0898, or by mail to 377 Park Avenue South, 6th Floor, NY, NY 10016.

Request for Credit

Name _____ Degree _____

Organization _____ Specialty _____

Address _____

City _____ State _____ ZIP _____

Telephone _____ Fax _____

Email _____

Signature _____ Date _____

I am registered on JDDonline.com

☐ Yes ☐ No

If yes:

User Name _____ Password _____

Post-test Answer Key

1	2	3	4	5	6	7	8	9	10	11	12	13	14

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

☐ I participated in the entire activity and claim 1.0 *AMA PRA Category 1 Credits*™.

Please answer the following questions by circling the appropriate rating:

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

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:

_____

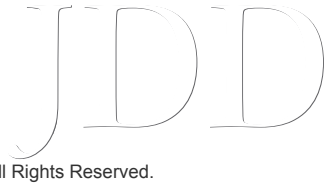
Name one thing you intend to change in your practice as a result of completing this activity:

_____

Additional comments about this activity:

_____

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



JOURNAL OF DRUGS IN DERMATOLOGY
JDD
DRUGS • DEVICES • METHODS

JO0116