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EDITORIAL

ORIGINAL ARTICLES

Evolving Concepts in the Pathogenesis of Acne Vulgaris

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Acne is perhaps the most prevalent skin disease in Western societies,[1] yet our understanding of it still remains largely incomplete. We know that the primary pathogenic factors in acne vulgaris are increased sebum production, faulty keratinization, inflammation, and bacterial colonization by *Propionibacterium acnes*;[2,3] yet the precise influence of these elements and their interactions is questioned.

However, we now have some well accepted facts:

- Acne vulgaris is not an infectious disease
- Acne vulgaris is primarily an inflammatory disease
- The role of *P. acnes* is more inflammatory than infectious
- The presence of inflammation is continuous throughout the disease process from beginning to end—if there is an end—causing postinflammatory erythema, hyperpigmentation, and scarring
- Finally, acne vulgaris is a chronic disease requiring ongoing therapy

The chronic inflammatory nature of acne has become an important consideration in treatment, which should be aimed not only at eradicating existing lesions but also preventing long-term sequelea such as scarring or postinflammatory hyperpigmentation. This treatment goal can only be achieved by preventing new lesion formation. Therapeutic options targeted at rapidly reducing inflammation by optimizing therapy with a combination of anti-inflammatory agents, and thus decreasing the disease burden, will reduce the likelihood of unwanted adverse effects.

We have now learned that the old way of "dubbing the medicine on the pimples" is not going to work, and that treating both lesional and non-lesional normal appearing skin is the key to successful management of acne vulgaris. This treatment style reflects an understanding of the concept of "subclinical inflammation" in acne vulgaris, which has been clearly elucidated. Unfortunately, this message in itself is very challenging. I myself find that patients have difficulty in accepting treatment for something that is not there and that they do not see.

Next, this leads us to the maintenance therapy of acne vulgaris, where long-term use of antibiotics as monotherapy without benzoyl peroxide contributes to the development of antibiotic resistance. Antibiotic resistance is described as "a global public health challenge" and "a major health security challenge of the 21st century" by global health authorities.[4,5] Antibiotic stewardship is a multidisciplinary initiative promoted by Centers for Disease Control, which assures that patients receive: "The right dose of the right antibiotic at the right time for the right duration"[6,7] It is notable that dermatologists represent 1% of all healthcare providers, and yet they prescribe approximately 4.9% of antibiotics.[8] Therefore, the use of benzoyl peroxide in combination with topical or oral antibiotics to prevent antibiotic resistance or avoid the use of monotherapy antibiotics should now be part of our regimen for the management of acne vulgaris. Hopefully, this will fulfill our specialty's commitment to antibiotic stewardship.

The pages ahead will explore my perspective, as well as that of my colleagues Dr. Whitney Bowe and Dr. Andrew Alexis, on the novel findings related to acne vulgaris and the development of a new treatment paradigm that emphasizes the importance of antibiotic stewardship.

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Re-evaluating Treatment Targets in Acne Vulgaris: Adapting to a New Understanding of Pathophysiology

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ABSTRACT

Two primary factors are changing current approaches to the management of acne vulgaris (AV): the continuously evolving role of *Propionibacterium acnes* in the pathophysiology of AV and recent evidence of an inflammatory basis for AV via innate immunity. The developing concepts emphasize that acne is primarily an inflammatory disease. The emerging concept of subclinical inflammation and its effect on development and progression of acne lesions correlating with the sequence of the underlying inflammation process has been a major change in our understanding of acne pathogenesis. Thus, inflammation has become the major feature of the disease process from onset to resolution, including postinflammatory erythema, postinflammatory hyperpigmentation, and scarring. Our treatment targets may also need to be reconsidered, with more emphasis on anti-inflammatory treatments.

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INTRODUCTION

Two primary factors are changing current approaches to the management of acne vulgaris (AV): the continuously evolving role of *Propionibacterium acnes* in the pathophysiology of AV and emerging evidence of an inflammatory basis for AV. The developing concepts emphasize that acne is primarily an inflammatory disease. Recent research has confirmed that inflammation is the hallmark of all acne lesions, from the microcomedo to so-called "noninflammatory" lesions (open and closed comedones), to inflammatory lesions (papules, pustules, nodules, and "cysts"), to "postinflammatory" erythema and hyperpigmentation and scarring.

The pathophysiology of acne and associated scarring were elucidated with reports of marked elevations in inflammatory cytokine gene transcripts in active acne lesions, including tumor necrosis factor (TNF)-α and interleukin (IL)-1β, leading to an amplification of nuclear factor (NF)-kB signaling pathways. There were also significant increases in IL-8 and IL-10 and elevated activator protein (AP)-1 in acne lesions. This leads to elevated matrix metalloproteinases, which degrade collagen up to 2.5 fold compared with normal skin. Moreover, this inflammatory process was localized to the pilosebaceous unit.[1]

Given these findings, clinicians are re-evaluating their therapeutic targets in the pathogenesis of AV and exploring optimal regimens that reduce inflammation without contributing to antibiotic resistance.

A History of Inflammation

There was no doubt that inflammation played an important role in the development of inflammatory lesions, such as papules and pustules, or that *P. acnes* played a role leading to secondary inflammatory processes in those stages of acne development. Recent research has elucidated the role of inflammation in the pathogenesis of acne and, more precisely, the contribution of *P. acnes* to drive inflammation.[1-9] It was already well established that acne is not an infectious process.[2] *P. acnes* is now shown to drive the inflammation of AV via various different pathways throughout the course of the disease process, one of the most important is via the activation of innate immunity.[3] *P. acnes* is thought to instigate an inflammatory cytokine response via activation of toll-like receptor (TLR)-2,[3] which triggers a pro-inflammatory cytokine pattern.[1-7]

However, we are now discovering that subclinical inflammation is present at the onset of disease and it is not only driven by *P. acnes*. Studies by Jeremy et al and others have shed light on the concept of early preclinical inflammation in acne[8] that typically persists throughout the acne lesion life cycle.[6-7] They have documented a prelesional folliculocentric inflammatory phase of acne, evidenced by markedly increased numbers of CD4+ T lymphocytes; numbers of macrophages; upregulated expression of perifollicular IL-1; and upregulation of epidermal expression of α-integrins. These mediators are elevated in both normal skin and early papules of subjects with acne compared with normal skin of subjects without acne. Additionally, in subjects with acne, lesions had increased inflammatory mediators relative to uninvolved skin. Those mediators are also part of the immune system activation. More importantly, they were able to show that prelesional inflammation preceded follicular hyperkeratinization and the presence of microcomedones.[8] These findings suggest that the so-called

"non-inflammatory lesions" (microcomedo, open and closed comedones) are actually inflammatory in nature. More supporting evidence is that lipid peroxide levels, which are also a marker of inflammation, are elevated in early comedones and microcomedones, as well as in all subsequent acne lesions.[4]

Inflammation persists throughout the course of lesion development and resolution. Persistent inflammatory hyperpigmentation and erythema are evidence of the inflammatory processes occurring throughout the acne lesion cycle.[9] Kang et al confirmed that acne scars are mediated by inflammation.[1] Additionally, 10 inflammatory genes are upregulated in the skin of acne patients.[10] Researchers showed a prominent role of matrix metalloproteinases, inflammatory cytokines, and antimicrobial peptides in acne lesions. Some of those biomarkers, such as IL-1 and integrins, may be involved with prelesional inflammation early on in the disease process.[11]

The conventional teaching that the microcomedone is the mother of all acne lesions is losing its validity. The notion of sequencing of all inflammatory lesions from so-called "non-inflammatory" lesions is being replaced by the new concept of inflammatory lesions possibly rising from normal appearing skin, scar, or just erythematous macules. With computer assisted alignment and tracking of acne lesions, Do et al were able to demonstrate that 28% of all inflammatory lesions arise directly from visibly normal skin.[6] This means that 28% of papules and pustules did not follow comedones as was conventionally considered.

New research into the *P. acnes* microbiome confirms that the bacteria is not infective; in fact, certain strains of *P. acnes* were enriched in healthy skin, while other strains were more likely to be associated with the development of acne.[12] Two phylogenetically distinct types of *P. acnes* have been identified: type 1 and type 2. Type I is subdivided into type 1A, type 1B, and type 1C.[12-13] Type 1A *P. acnes* isolates have been reported as predominant in AV and, of the various subtypes, they have the greatest effect on antimicrobial peptides and proinflammatory cytokine production.[10,12-13]

Reconsidering Therapeutic Targets

Systemic antibiotics used in acne therapy are known to confer anti-inflammatory effects, and mostly anti-inflammatory actions appear to account for the efficacy of antibiotics in acne therapy.[14] In light of documented antibiotic resistance associated with antibiotics used to treat acne,[15-16] guidelines for acne management published in the last decade discourage long-term use of antibiotics and emphasize the use of topical antimicrobials and retinoids.[17] Remarkably, evidence shows that oral antibiotics remain the most commonly prescribed treatments for acne, accounting for 41% of all prescriptions written for acne.[18] A 2009 update of the recommendations emphasizes the use of oral or topical antibiotics in combination with benzoyl peroxide (BPO),[19] avoiding the use of oral or topical antibiotics as monotherapy, concurrent use of oral and topical antibiotics, and discontinuation of antibiotics when there is only slight or no improvement. The guidelines also highlight the critical role of topical retinoids in long-term acne maintenance treatment. Benzoyl peroxide is a potent oxidizing agent that generates reactive oxygen species that physically destroy the bacteria. In addition to antimicrobial properties, BPO is also shown to have comedolytic and anti-inflammatory effects.[19]

Benzoyl peroxide's efficacy as a monotherapy was traditionally considered to be limited; however, the agent is readily used in fixed-dose combinations with antibiotics or topical retinoids, providing documented benefit.[20-22] Like BPO, retinoids are being shown to have multiple effects. While the anti-comedogenic effect is the hallmark of topical retinoids, we now know that they also have anti-inflammatory properties.[21] The fixed combination formulation of adapalene 0.1% and BPO 2.5% has established efficacy, safety, and tolerability.[23-24] Pooled analysis from 3 double-blind controlled trials of similar design including 3,855 subjects shows that adapalene/BPO gel has synergistic effects. The fixed combination of adapalene 0.1%/BPO 2.5% has early anti-inflammatory benefits. Synergy was observed for reduction in inflammatory lesions through week 4 and for non-inflammatory lesions through week 8.[25]

"The guidelines also highlight the critical role of topical retinoids in long-term acne maintenance treatment."

Acne vulgaris is a chronic disorder, suggesting a need for continuous and long-term use of antibiotics. Yet such antibiotic use contributes to the major health problem of antibiotic resistance and poses a great challenge to maintenance treatment of the disease. In the past, Thiboutot et al had shown positive results for adapalene 0.1% gel in maintenance therapy of severe acne after stopping doxycycline,[26] and Leyden et al had similarly shown that tazarotene 0.1% gel plus minocycline is not better than minocycline alone in sustaining acne improvement.[27]

In view of this above challenge, adapalene 0.1%/BPO 2.5% gel has been studied in long-term management of severe acne after stopping 3 months' use of oral antibiotics. A randomized, vehicle-controlled, multicenter, double-blind study evaluated the efficacy and safety of the fixed-dose combination adapalene 0.1%/BPO 2.5% gel with doxycycline hyclate 100mg once daily in the treatment of severe AV for the first 12 weeks, followed by just topical treatment vs vehicle for 6 months. A total of 459 participants were randomized in a 1:1 ratio to receive oral doxycycline hyclate 100mg once daily and either adapalene/BPO or

vehicle once daily for 12 weeks. As early as week 2, total, inflammatory, and noninflammatory lesion counts were reduced in the topical combination arm compared with the vehicle arm. At week 12, topical combination therapy plus doxycycline was statistically significantly superior to vehicle plus doxycycline in reducing total, inflammatory, and non-inflammatory lesion counts. A rapid reduction in *P. acnes* in the adapalene/BPO plus doxycycline group vs the doxycycline alone group—particularly within the first 4 weeks—was demonstrated through the use of digital UV fluorescence photography.[28]

The second portion of this study, which was also double-blind, randomized, and controlled, enrolled the subjects who had achieved at least 50% global improvement in the previous 12-week treatment. Subjects were randomized to receive adapalene/BPO gel or its vehicle once daily for 24 weeks. At week 24, subjects using adapalene/BPO had a significantly higher rate of lesion maintenance success (at least 50% improvement in lesion counts achieved in initial treatment) for all types of lesions. Fifty-seven percent of subjects receiving adapalene/BPO had maintained 100% of the effect at week 24 following discontinuation of oral antibiotics. That number of subjects was 74% for the 70% of the effect at week 24.

Another open label study by Leyden has demonstrated that adaplene 0.1%/BPO 2.5% gel was able to reduce effectively skin colonization by antibiotic sensitive and antibiotic resistant *P. acnes* over 4 weeks in healthy volunteers.[29]

New Perspectives

Acne vulgaris has long been known to be an inflammatory disease rather than an infective one. However, the emerging concept of subclinical inflammation and its effect on development and progression of acne lesions correlating with the sequence of the underlying inflammation process has been a major change in our understanding of acne pathogenesis. Thus, inflammation has become the major feature of the disease process from onset to resolution, including postinflammatory erythema, postinflammatory hyperpigmentation, and scarring. Therefore, this new paradigm may even necessitate change of nomenclature, such as from postinflammatory hyperpigmentation and postinflammatory erythema to persistent hyperpigmentation and persistent erythema, since there is no end of inflammation in this disease process. Additionally, the term "noninflammatory" lesions should be eliminated, since we now know that all lesions are of an inflammatory nature, albeit subclinically.

Therefore, our treatment targets may also need to be reconsidered, with more emphasis on anti-inflammatory treatments.

DISCLOSURES

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

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Acne Vulgaris in Skin of Color: Understanding Nuances and Optimizing Treatment Outcomes

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ABSTRACT

According to the United States national survey data, acne vulgaris is the leading dermatologic diagnosis among African Americans, Hispanics/Latinos, and Asians/Pacific Islanders. This patient population, collectively referred to as having skin of color, exhibits clinical and therapeutic nuances that are relevant in the management of acne. Understanding the nuances in clinical presentation, safety considerations, cultural factors, and desired treatment endpoints is key to ensuring successful outcomes.

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INTRODUCTION

Epidemiology

Published practice and community-based survey studies have reported that acne is the most frequent dermatologic condition in 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] Arab-Americans (in Southeast Michigan),[5] and South-Asian Americans (in New York, NY).[6] In a global study, unilateral facial photographs of 2,835 females (10 to 70 years of age) from 4 cities (Los Angeles, USA; London, UK; Akita, Japan; and Rome, Italy) were examined for clinical features of acne. The prevalence of acne was found to be 37%, 32%, 30%, 24%, and 23% in African Americans, Hispanics, Asians, Caucasians, and Continental Indians, respectively.[7]

Clinical Nuances

Increased constitutive pigmentation and labile melanocyte responses to inflammation are key characteristics of skin of color. As a result, inflammatory disorders of the skin, such as acne, are typically complicated by the presence of postinflammatory hyperpigmentation (PIH). Acne-associated PIH is characterized by hyperpigmented macules typically ranging from 2 mm to 4 mm in size arising at sites of resolved or resolving acne lesions (Figure 1). Although spontaneous remission is expected, PIH generally lasts from several weeks to several months after an acne lesion has resolved, depending on the severity.

Patients frequently refer to PIH as "uneven skin tone" or "acne scars," and may have the misconception that the lesions are permanent if left untreated. In many instances, PIH is of greater concern to the patient than the acne itself; it is often the driving force for acne patients with skin of color to seek a dermatologist consultation. In the setting of excoriation or other traumatic manipulation of acne lesions by the patient, PIH tends to be more severe and longer lasting (Figure 2). A harsh skin care regimen (eg, vigorous scrubbing, or excessive use of exfoliating products, strong toners, or astringents, etc) can also contribute to PIH. In cases of severe excoriation or "acne excoriée," hypopigmented macules with angulated hyperpigmented borders can be observed (Figure 3).

Populations with skin of color (especially those of sub-Saharan African ancestry) have a higher prevalence of keloids and hypertrophic scars.[8] This is due to a genetic predisposition toward heightened fibroblast responses to injury and inflammation. Inflammation from acne, particularly in cases of severe truncal involvement, can therefore lead to the formation of keloids in individuals who are so predisposed. As such, moderate to severe acne in populations with skin of color is associated with a higher risk of disfiguring and persistent raised scars, which are most frequently observed on the chest, upper back, and jawline.

There are a number of cultural skin and hair care practices that can in some instances exacerbate acne.[9] One example is the more frequent use of cocoa butter lotions and creams among African Americans.[10] This is due to a widely held perception in this population that cocoa butter helps to even skin tone and improve scars. Therefore, in an effort to reduce the hyperpigmentation and perceived "scars" of PIH, many patients with skin of color (particularly African Americans) may apply cocoa butter liberally to the face. This in turn can exacerbate acne due to its comedogenicity.

Another cultural practice that can contribute to worsening acne is the frequent use of thick, oil-based hair products among populations of African ancestry with afro-textured hair. In this population, the application of hair products designed to add sheen, prevent dryness, and improve manageability is a common practice. Historically, thicker products containing petrolatum or mineral oil have been used and these have

FIGURE 1. Acne and associated postinflammatory hyperpigmentation.

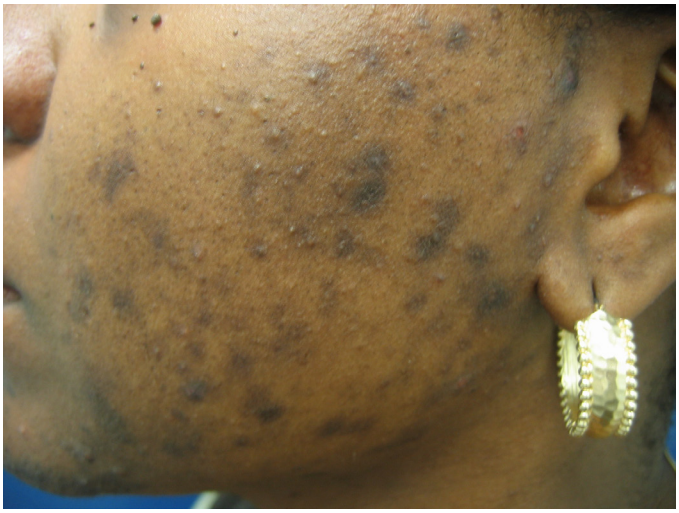
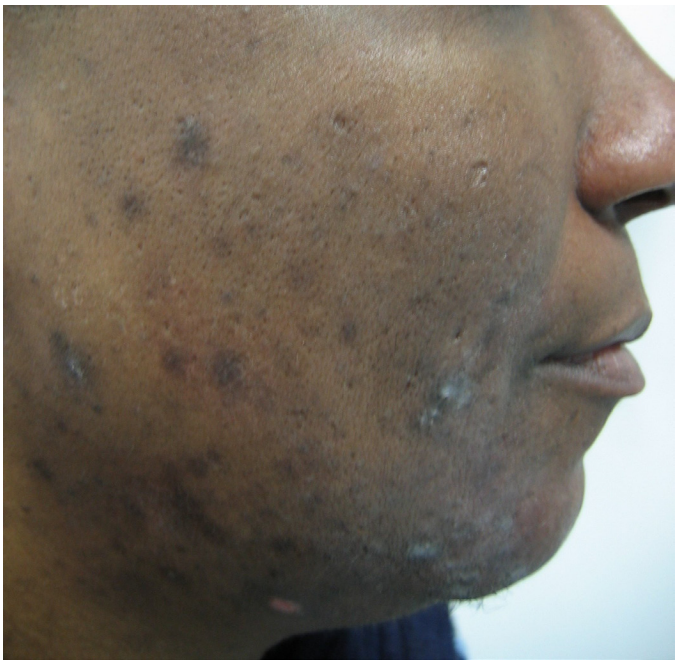


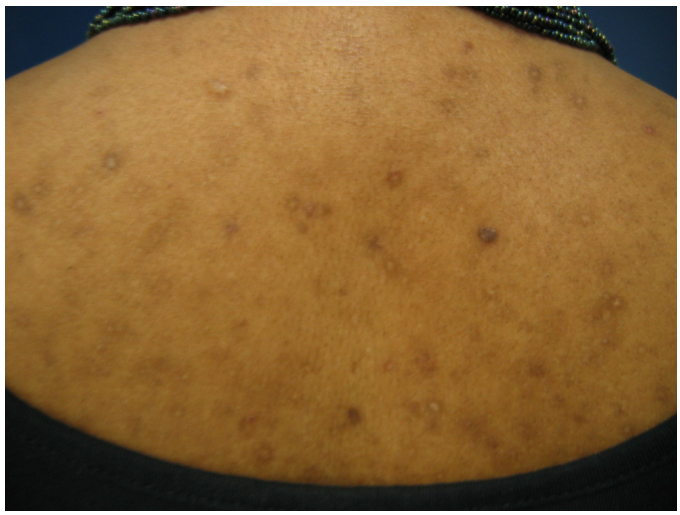
FIGURE 2. Acne with excoriation.



been associated with pomade acne.[11] This variant of acne is less common today than when it was first described over 4 decades ago due to shifts in consumer preferences toward lighter, less greasy hair products. However, it can still be observed and, when it is identified, patients should be counseled on using alternative hair products that are less likely to cause acne, such as silicone-based hair serums (containing cyclomethicone or dimethicone).[9,12]

The use of over-the-counter topical skin lightening or skin bleaching creams is not uncommon among patients with skin of color, many of whom try such products as a treatment of

FIGURE 3. Acne excoriée with hypopigmented macules and hyperpigmented borders.



PIH and other dyschromias before seeking a dermatology consultation.[9] In addition to hydroquinone-based products, some skin lightening creams sold at ethnic beauty supply stores and via the internet illegally contain prescription-strength corticosteroids, such as clobetasol and bethamethasone valerate.[13] As such, steroid acne can be seen in this context. Clinical clues to this diagnosis include an acute flare of acne with monomorphous inflamed papules and pustules in association with facial hypopigmentation and atrophy. Patients are generally unaware that such bleaching creams may contain potent corticosteroids and often do not consider mentioning these products to their physician unless asked directly. Therefore, the diagnosis rests on the dermatologist having a clinical suspicion when presented with the aforementioned signs and symptoms. Requesting that the patient bring in all their skin care products is a useful way to detect the inadvertent long-term use of corticosteroids on the face, or other products that may contribute to acne.

The Role of Inflammation

It has been well established that inflammation plays an integral role in the pathogenesis of acne, particularly in the context of papules, pustules, nodules, and "cysts." However, only recently has the role of inflammation as an early and subclinical event in the development of acne been elucidated.

In a 1996 study, Halder et al[14] examined 30 black females with acne, obtaining punch biopsies of lesional skin. Histopathological signs of inflammation were found to be out of proportion to clinical inflammation and extended beyond the boundaries of clinically inflamed lesions. Moreover, even clinically non-inflamed lesions (ie, comedones) exhibited inflammation histopathologically. This subclinical inflammation likely contributes to the high propensity toward PIH in acne patients with darker skin (including those with mild to moderate acne).

However, more recent evidence supports the notion that subclinical inflammation is not unique to skin of color, but rather a pathogenic feature of acne in general. In an immunohistochemical study examining biopsies of clinically normal perifollicular skin, clinically inflamed acne lesions, and control samples from subjects without acne, Jeremy et al[15] found that levels of interlekin-1 (a proinflammtory cytokine) were upregulated in perifollicular skin. In addition, numbers of CD3+, CD4+ T-lymphocytes were increased in perifollicular skin compared with controls.[15] Taken together, inflammatory responses may be a primary event in the pathogenesis of acne and can precede the development of clinically detectable acne lesions.

Subclinical inflammation in acne is of particular importance to skin of color given the risk of postinflammatory pigment alteration. Inflammatory mediators including prostaglandins and leukotrienes have been shown to stimulate melanocyte pigment production.[16] Therefore, it is plausible that effective control of inflammation (both clinical and subclinical) may reduce the severity and number of hyperpigmented macules associated with acne in skin of color.

An important driver of inflammatory responses associated with acne is the bacterium, *Propionibacterium acnes*. There is evidence that *P. acnes* activates innate immunity via toll-like receptor 2 (TLR-2) leading to release of interleulin (IL)-1α from keratinocytes, which in turn stimulates follicular hyperkeratinization and the formation of the microcomedo.[17] It has recently been shown that *P. acnes* activates inflammasomes leading to the production of IL-1β by monocytes, which could contribute to increased inflammation.[17,18] Targeting *P. acnes* is therefore a core strategy in the management of acne and its associated inflammatory responses.

"To maximize tolerability, patients should be counseled to avoid harsh scrubs, toners, and exfoliating cleansing routines that can increase the risk of irritation from prescription therapies."

Implications for Treatment

The greater tendency toward dyspigmentation and keloid scarring in patients with skin of color has important therapeutic implications.

1. Early and aggressive control of acne-associated inflammation is imperative. This can be accomplished with the use of a well-rounded treatment regimen that targets multiple factors in the pathogenesis of the disease and includes agents with anti-inflammatory properties. Acne treatments with anti-inflammatory effects include topical retinoids, the oral tetracycline antibiotics, topical dapsone, and azelaic acid. Among the retinoids, the anti-inflammatory activity of adapalene has been the most studied. Adapalene has been shown in vitro and in vivo to decrease expression of toll-like receptor (TLR)-2 (a receptor of the innate immune system) and IL-10 (an anti-inflammatory cytokine). (Zuliani T et al. *Exp Dermatol*. 2011;20:850-853.) In addition, adapalene increases expression of CD1d – a cell surface glycoprotein that plays a role in antigen presentation and induction of cutaneous inflammatory responses. Other anti-inflammatory effects of adapalene include inhibition of arachadonic acid metabolism, neutrophil chemotaxis, and free radical production.[19] Benzoyl peroxide (BPO), through its microbicidal effects, indirectly reduces inflammation by killing *P. acnes* – a trigger of acne-associated inflammation.

   A well rounded regimen includes a multi-pronged approach to address the multiple pathogenic factors associated with acne, including follicular hyperkeratinization, *P. acnes* inflammation, and increased sebum production. Therefore, combination topical regimens that include a topical retinoid, a BPO, and/or an immunomodulating agent (eg, dapsone, azelaic acid) tend to be the most effective.

   Under-treatment of acne in patients with skin of color should be avoided, given the greater risk of dyspigmentation and keloidal scarring (in more severe cases). As such, the threshold for using oral antibiotics (for their anti-inflammatory and anti-*P. acnes* effects) in the appropriate patient is low. Regimens that initially include oral doxycycline or minocycline in combination with a topical retinoid followed by maintenance with a topical retinoid is a well-established long-term treatment strategy in the general acne population,[20,21] and is particularly well suited to patients with skin of color.

   Oral isotretinoin should also be considered for the appropriate patient with severe inflammatory acne who is at risk for scarring, as well as for patients who fail oral antibiotics. It has been reported based on U.S. National Ambulatory Medical Care Survey data that isotretinoin is less frequently prescribed to blacks than to whites; cost may contribute to this disparity, but patient and provider biases as well as racial differences in severity cannot be ruled out.[22] When warranted, oral isotretinoin should be considered early in the course of nodulocystic or other severe forms of acne in patients with skin of color.

   In cases of severely inflamed papules or nodulocystic lesions, the use of intralesional corticosteroid injections (typically triamcinolone acetonide 2.5 mg/mL to 3.3. mg/mL) to rapidly reduce local inflammation is an effective

short-term measure. However, overly aggressive intralesional injections using higher concentrations can lead to corticosteroid-induced hypopigmentation in darker skinned patients.

2. Avoiding iatrogenic PIH from medication-induced irritation is essential. Special considerations need to be made regarding specific therapeutic agents, concentrations, and vehicles in order to select a regimen that is well tolerated by a given patient. While all Food and Drug Administration (FDA)-approved topical acne treatments can safely be used in patients with skin of color, individual variations in sensitivity exist and should be accounted for when selecting a regimen for any given patient. Erring on the side of increased tolerability is a prudent approach for patients with skin of color, given that any irritant reactions can lead to pigmentary alterations (hyper- or hypo-pigmentation). While such treatment-related dyschromias are generally self-limited, they tend to cause considerable patient anxiety and loss of confidence in the prescriber on the part of the patient.

   Tolerability considerations are especially important when selecting topical retinoids. While all FDA-approved topical retinoids can safely be used in patients with skin of color, adapalene 0.1% is associated with the least irritation potential[23-26] and has been studied in numerous populations with skin of color – including studies conducted in South Africa,[27,28] Japan,[29] China,[25] Singapore,[26] and Mexico.[30] Tretinoin is best tolerated in a branded microsphere formulation or an aqueous gel. However, when generic tretinoin formulations are used, it is advisable to initiate treatment with the lowest concentration (0.025%), titrating up to higher concentrations in the appropriate patient.[10] Tazoratene is best tolerated as a cream; initiating this at the lowest concentration (0.05%) and titrating to higher concentrations and/or gel formulations in the appropriate patient is the preferred approach.[10]

   When BPOs are used on the face, vehicle and concentration considerations are important with respect to maximizing tolerability. When treating facial acne, 2.5%-5.5% BPO formulations in aqueous gels, microsphere cream, or emollient foam are generally well tolerated and strongly preferred over products in ethanolic gels or those with higher concentrations. However, concentrations up to 10% found in BPO cleansers or a short-contact emollient foam preparation are generally well tolerated on the trunk.

   Several meta-analysis studies investigating the comparative safety and efficacy of topical acne formulations between higher and lower Fitzpatrick skin types, as well as investigations into specific racial/ethnic groups, have recently been published. Most recently, a subgroup analysis evaluating the efficacy and safety of adapalene 0.1%/BPO 2.5% gel in 238 black subjects was published. Adapalene/BPO gel was well tolerated in this cohort, and no cases of treatment related PIH were observed.[31] A previous study demonstrated comparable tolerability of adapalene/BPO gel in subjects with Fitzpatrick skin types I to III and IV to VI.[32] A similar study involving clindamycin phosphate 1.2%/BP gel found no differences in cutaneous irritation in Fitzpatrick skin types I to III vs IV to VI.[33] This formulation was also investigated in Hispanic subjects in a post-hoc analysis, in which Hispanic patients were not found to be more sensitive to treatment-related cutaneous irritation. A small pilot study found clindamycin phosphate 1.2% and tretinoin 0.025% gel to be well tolerated in 33 patients with Fitzpatrick skin types IV to VI.[34] In a subset analysis of a community-based trial of combination therapy with clindamycin 1%/BPO 5% gel and topical tretinoin microsphere or adapalene gel 0.1%, treatment was well tolerated with a trend toward better resolution of hyperpigmentation with clindamycin/BPO gel in combination with tretinoin microspere gel 0.04%.[35] In a comparative meta-analysis, adapalene 0.1% in black patients vs white patients was associated with a low incidence of irritation (erythema, scaling, and dryness).

   To maximize tolerability, patients should be counseled to avoid harsh scrubs, toners, and exfoliating cleansing routines that can increase the risk of irritation from prescription therapies.[36] Initiating therapy with every other night dosing of retinoids and applying a non-comedogenic moisturizer immediately after topical prescriptions are useful strategies for maximizing tolerability and minimizing dryness/peeling. In patients with extremely dry, sensitive skin, applying a moisturizer prior to the retinoid can be helpful.[37]

3. Designing a treatment regimen that helps to reduce PIH is a strategy that increases patient satisfaction. This involves selecting products that have dual efficacy–treating both acne and hyperpigmentation (such as retinoids and azelaic acid), as well as adjunctive therapies that specifically target PIH (including hydroquinone and chemical peels).[9,38] The topical retinoids are particularly useful in the management of both acne and PIH in skin of color. Tretinoin,[39] adapalene,[27,28] and tazarotene[40] have all been shown to reduce PIH in studies involving patients with skin of color. A fixed dose of triple combination therapy has also been shown to improve PIH. (Galderma data on file, study report HDTL 043 A-B). To align the dermatologist's treatment endpoint with patient expectations, follow-up evaluations should be continued until the clearance of both active acne lesions and PIH. Thus, the time course to achieving a treatment success is on average longer in a patient with skin of color, typically spanning 6 months or more.

4. Identifying and eliminating potentially exacerbating factors that are more prevalent in specific populations (discussed above) is an important step toward ensuring favorable treatment outcomes.

CONCLUSION

The treatment of acne in skin of color patients involves selecting a regimen that ensures early and sustained control of inflammation; avoidance of irritation to prevent iatrogenic dyspigmentation; treatment of both acne lesions and associated PIH; and identification of potential cultural factors that can exacerbate or contribute to acne.

DISCLOSURES

Andrew F. Alexis MD MPH has served as a consultant for Galderma, Allergan, Estée Lauder, Johnson & Johnson Consumer Companies Inc, L'Oréal, and SkinMedica.

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Antibiotic Resistance and Acne: Where We Stand and What the Future Holds

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ABSTRACT

Antibiotic resistance is described as "a global public health challenge" and a "major health security challenge of the 21st century" by global health authorities,[1] and there is a growing need for dermatologists to counteract it in their treatments of acne.[3,4] Antibiotic limiting regimens, such as a combination of topical retinoids and benzoyl peroxide, have shown effectiveness in the treatment of acne; and topical probiotics could also play a needed role.

J Drugs Dermatol. 2014;13(suppl 6):s66-s70.

INTRODUCTION

Antibiotic resistance has become a global priority, and the science ministers of the G8 countries have deemed it to be a "major health security challenge of the 21st century."[1] The World Health Organization has also identified antibiotic resistance as a "rapidly evolving health issue extending far beyond the human health sector," emphasizing the urgent need for a cross-sectoral approach.[2]

Although dermatologists account for approximately 1% of the physicians in the United States, they prescribe 4.9% of the antibiotics (Figure 1).[3] Dermatologists regularly prescribe antibiotics for acne vulgaris (AV) and other long-term inflammatory dermatoses; but antibiotic resistance has led to a decreased sensitivity of certain bacterial organisms, such as *Propionibacterium acnes*, to antibiotics.[4]

For example, Ross et al collected phenotypes and genotypes of 73 antibiotic-resistant strains of *P. acnes* that were acquired from the skin of acne patients in the United Kingdom, United States, France, Germany, Australia, and Japan, and found that most erythromycin-resistant isolates were cross-resistant to clindamycin.[5] Tetracycline-resistant isolates had differing degrees of cross-resistance to doxycycline and minocycline, and isolates from the United States had higher cross-resistance to minocycline than isolates from other countries.[5] The investigators also found resistant strains in which mutations could not be identified, which suggests that uncharacterized resistance mechanisms have evolved.[5]

DISCUSSION

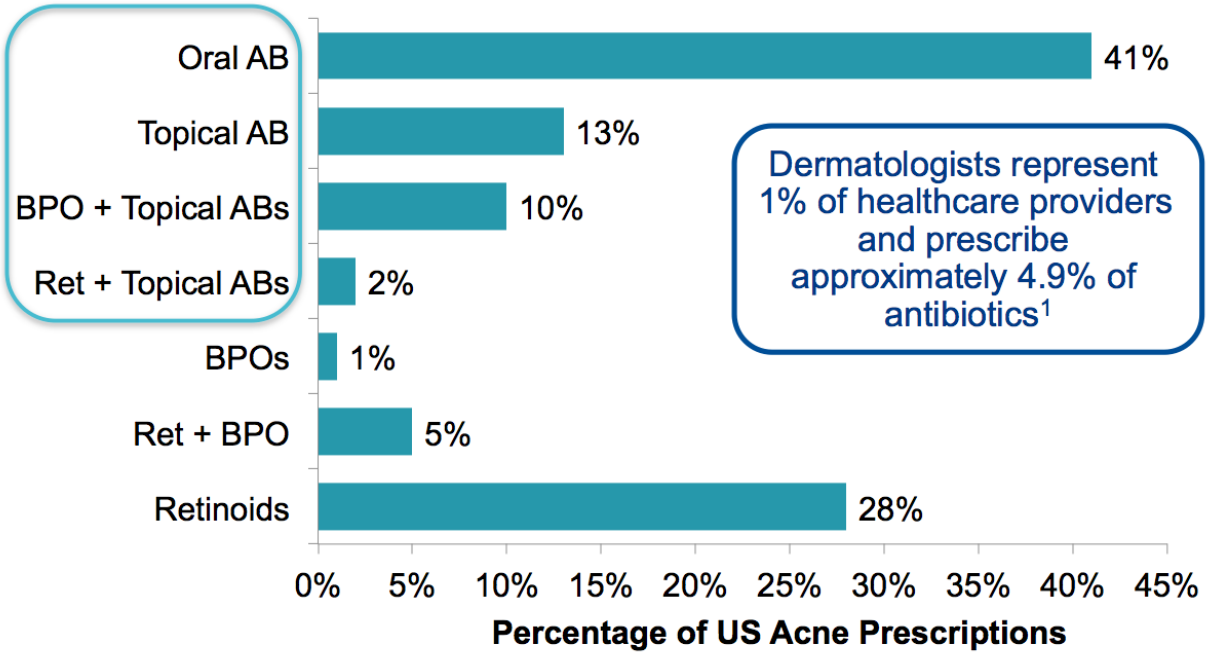
As the sensitivity of *P. acnes* to several oral and topical antibiotics has decreased, the efficacy of oral tetracyclines and erythromycin has also noticeably decreased, which has led to an escalation in the prescribing of doxycycline, minocycline, and other antibiotics for *P. acnes*.[6] Additionally, changing patterns of antibiotic sensitivity and the escalation of more virulent pathogens, such as community-acquired methicillin-resistant *Staphylococcus aureus,* macrolide-resistant *staphylococci* and *streptococci,* and mupirocin-resistant *S. aureus,* have led to major changes in clinicians prescribing patterns of antibiotics.[7]

Although most of the time clinicians are responding to these new resistance patterns in an appropriate fashion, it is important to note that both correct and incorrect use of antibiotics can promote antimicrobial resistance. Oral and topical antibiotics account for 54% of all prescriptions written for acne in the field of dermatology, and approximately 66% of antibiotic use in dermatology is for acne.[7] Even when dermatologists use antibiotics responsibly, we are contributing to resistance. However, when used inappropriately, resistance rates grow at an even more rapid rate. Antibiotic monotherapy, long-term administration of antibiotics, and dosing below the recommended levels especially promote the development of bacterial resistance.[8] Not only do these practices result in *P. acnes* resistance and acne treatment failures, but they have also resulted in the spread of resistance to other organisms colonizing the skin.[8] Long-term use of antibiotics has even yielded systemic consequences, including an increased risk of upper respiratory tract infections.[8]

Studies have demonstrated that antibiotic limiting regimens, such as a combination of topical retinoids and benzoyl peroxide (BPO), can be highly effective for the treatment of acne.[8,9,10] The ACCESS I and ACCESS II trials have shown that topical retinoids with BPO are effective for both the primary and maintenance treatment of *P. acnes* (Figure 2).

ACCESS I was a randomized, vehicle-controlled, multicenter, double-blind study that assessed the efficacy and safety of combination therapy using doxycycline and an adapalene 0.1% and BPO 2.5% combination gel (Epiduo®) for the treatment of

FIGURE 1. Acne prescription profiles in dermatology.[1]



[1]Symphony Health PHAST Monthly Prescription

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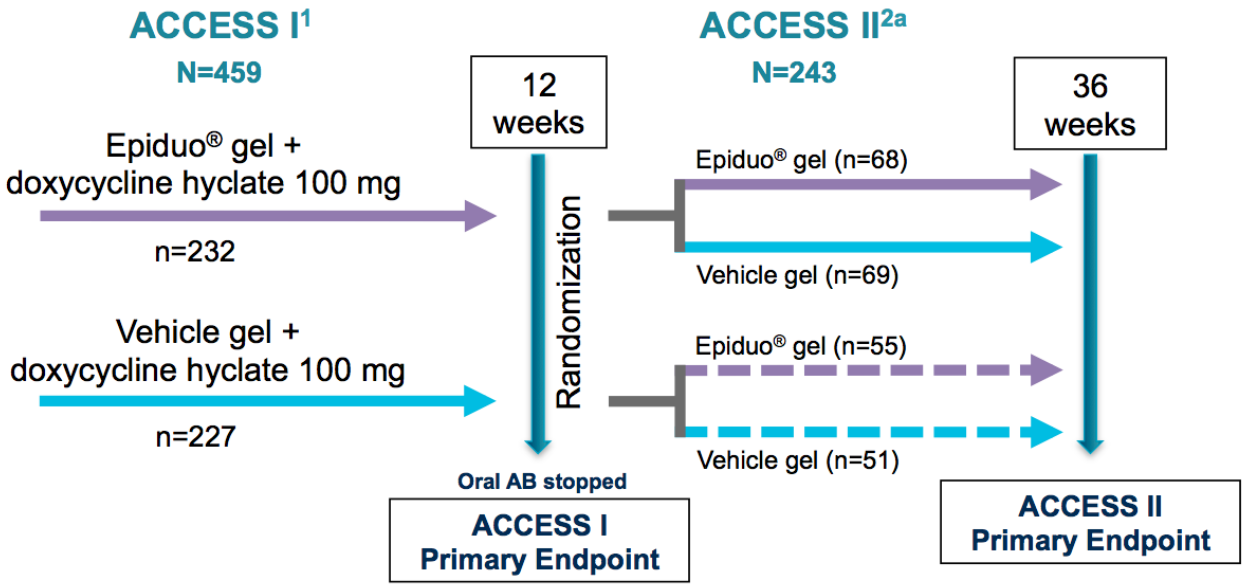
AB, antibiotic; BPO, benzoyl peroxide; Ret, retinoids.

FIGURE 2. Adapalene/benzoyl peroxide in patients with severe acne: the ACCESS study.



[a]First 280 patients who completed the previous study, ACCESS I, and had obtained at least a "Good" improvement, defined as about 50% improvement from baseline or better (grade 0, 1, 2, or 3) were eligible for ACCESS II enrollment.
AB, antibiotic.

[1]Stein Gold 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.

[2]Poulin Y, Sanchez NP, Bucko A, et al. A 6-month maintenance therapy with adapalene-benzoyl peroxide gel prevents relapse and continuously improves efficacy among patients with severe acne vulgaris: results of a randomized controlled trial. *Br J Dermatol.* 2011;164(6):1376-1382.

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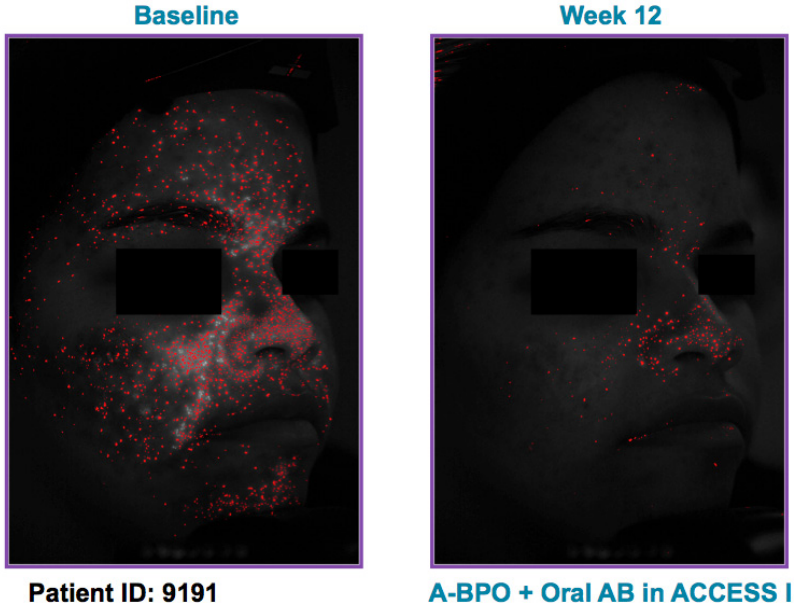
FIGURE 3. UV fluorescence of Propionibacterium acnes through ACCESS I.



UV digital fluorescence photographs from a phase 4, multicenter, randomized, double-blind, vehicle-controlled, parallel-group study of adapalene 0.1%/benzoyl peroxide 2.5% fixed-dose combination with oral doxycycline vs. vehicle gel with oral doxycycline for 12 weeks, followed by adapalene 0.1%/benzoyl peroxide 2.5% or vehicle gel for an additional 24 weeks, in patients with severe acne vulgaris (N=243).

A, adapalene; AB, antibiotic; BPO, benzoyl peroxide.
Data on file, Galderma Laboratories, L.P.

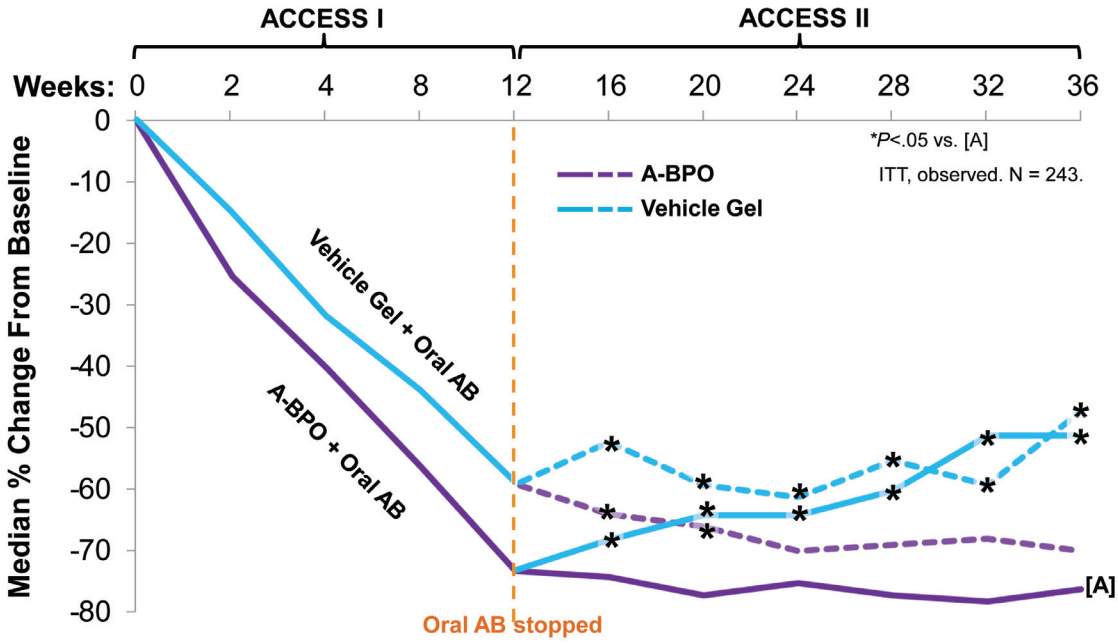
severe AV.[9] A total of 459 subjects were randomized in a 1:1 ratio to receive for 12 weeks oral doxycycline once daily or either Epiduo or a vehicle gel once daily. The efficacy of doxycycline and Epiduo was demonstrated by week 2 compared with the vehicle arm for total inflammatory and noninflammatory lesions.[9] By week 12, the doxycycline and Epiduo group was superior to vehicle in reducing total inflammatory and noninflammatory lesion counts and for global success and overall participant satisfaction.[9] Digital UV fluorescence photography also showed an expeditious and efficacious reduction to *P. acnes* in the doxycycline and Epiduo group (Figure 3).[9]

Whereas ACCESS I focused on the primary treatment of acne with Epiduo, ACCESS II evaluated the safety and efficacy of Epiduo for maintenance therapy or relapse prevention.[10] ACCESS II was a 24-week, multicenter, double-blind, randomized extension of ACCESS I that compared Epiduo with vehicle in 243 subjects. After the randomized subjects were treated for 12 weeks in ACCESS I, and had experienced at least a 50% global improvement in their AV, they were randomized to receive Epiduo gel or its vehicle once daily for 24 weeks.[10] By week 24, when Epiduo was compared with vehicle, it yielded a significantly higher lesion maintenance success rate for all lesions; and a significantly greater number of subjects who had been administered Epiduo had an equivalent or superior Investigator's Global Assessment score at week 24 than at baseline.[10] In ACCESS II, Epiduo resulted in further decrease of lesion counts, and 45.7% of subjects were "clear" or "almost clear" at week 24 (Figure 4).[10,11]

"It is our responsibility to take whatever measures we can to limit the development of further antibiotic resistance, and those measures are reviewed here."

Leyden et al evaluated the effectiveness of adapalene and BPO combination gel in the reduction of antibiotic-sensitive and resistant strains of *P. acnes* on the facial skin. This 4-week, open-label, single-center study included 30 healthy adults with high facial *P. acnes* populations that were resistant to one or more of the following antibiotics: erythromycin, tetracycline, clindamycin, minocycline, and doxycycline.[12] Although all of the subjects had *P. acnes* strains resistant to one or more of the 5 antibiotics at baseline, the total *P. acnes* counts decreased by 1.1 logs after 2 weeks of treatment and by 1.6 logs after 4 weeks.[12] In addition to reducing population densities of *P. acnes*, adapalene and BPO combination gel completely eradicated antibiotic resistant strains in some subjects.[12]

FIGURE 4. Total lesion reduction in ACCESS II.



Tan J, Stein Gold L, Schlessinger J, et al. Short-term combination therapy and long-term relapse prevention in the treatment of severe acne vulgaris. *J Drugs Dermatol.* 2012;11(2):174-180.

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AB, antibiotic; A-BPO, adapalene/benzoyl peroxide.

The Global Alliance to Improve Outcomes in Acne has recommended several strategies for the prevention of *P. acnes* antibiotic resistance that limit antibiotics and use a topical retinoid and BPO. Antibiotics should be limited to the shortest duration possible and never be used as a monotherapy.[13] The number of patients still filling prescriptions for antibiotics in the absence of a BPO topical treatment is astounding. Whether or not these patients are being advised to use the two concurrently, or they stop using the BPO independently despite counseling to the contrary, remains unclear. But it is our responsibility to our patients to emphasize the importance of using BPO every time an oral or topical antibiotic is prescribed or refilled. Moreover, dermatologists should discontinue antibiotics when there is no further improvement or the improvement is only slight.[13] Oral antibiotics should ideally be used for 3 months, but 6 to 8 weeks into treatment might be an appropriate time point at which to assess the response to antibiotics. Lastly, the concurrent use of oral and topical antibiotics, particularly if chemically different, should be discontinued.[13]

Antibiotics should also be avoided for maintenance therapy. In lieu of antibiotics, maintenance therapy should include the use of a topical retinoid and BPO to limit antibiotic resistance. Benzoyl peroxide reduces the likelihood of antibiotic-resistant *P. acnes* emerging, and rapidly reduces the number of sensitive and resistant strains of *P. acnes* at the site of application. Benzoyl peroxide should be used either concomitantly or pulsed as an anti-resistance agent, and it may be helpful to use BPO for a minimum of 5 to 7 days between antibiotic courses. As studies continue to further validate the efficacy of BPO, and validate its essential role in the fight against antibiotic resistance, it will continue to assume a larger role in the practice of dermatology.

Topical Probiotics

While thought leaders in the fields of public health, infectious disease, and dermatology continue to explore ways to maintain the efficacy of our antibiotic armamentarium and prevent further resistance from developing, other researchers are searching for novel therapeutic options. Topical probiotics have the potential to be a treatment of interest for acne. While studies are still very preliminary, they do show some promising results.[14]

Probiotics are healthy strains of bacteria that potentially improve the health of their host, and there are 3 means by which probiotics can benefit a patient via topical administration. First, if a live culture is actually capable of surviving on the skin's surface, that strain could potentially provide a protective shield on the patient's skin, blocking colonization by possibly harmful organisms.[14] Second, some probiotics are capable of producing and secreting antimicrobial substances into their environment; so one can envision an antimicrobial alternative to antibiotics that works via a unique mechanism.[14]

Third, when certain probiotic strains are placed in contact with epithelial cells, they are capable of inhibiting inflammatory pathways and thus the production of inflammatory cytokines.[14] As chronic inflammation plays a major role in acne, a natural immunomodulator could play a needed role.

CONCLUSION

Antibiotics have played a leading role in the treatment of acne for decades. However, recent issues surrounding resistance force us to question how much longer we can count on these drugs, and whether or not they will maintain their front-line role as safe, effective treatments. It is our responsibility to take whatever measures we can to limit the development of further antibiotic resistance, and those measures are reviewed here. While we fight to maintain the clinical value of antibiotics, we must also continue to search for novel approaches to the treatment of acne. An ongoing search for unique treatments that can be used in concert with or as alternatives to antibiotics will allow us to best prepare ourselves for what the future has in store.

DISCLOSURES

Whitney P. Bowe MD has served as a consultant for Johnson & Johnson Consumer Companies Inc, on an advisory panel for Galderma Labs, and as a consultant for Procter and Gamble.

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