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A New Understanding of the Pathogenesis of Acne Vulgaris

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ORIGINAL ARTICLE

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Do We Really Need Topical Antibiotics in Our New Treatment Paradigm of Acne Vulgaris? A Novel Question to Consider Based on an Updated Model of Pathogenesis

Leon H. Kircik MD

The understanding of the nature of inflammation in acne vulgaris (AV) has evolved with a greater understanding of the sequences of inflammation, especially prelesional inflammation, over the life cycle of an acne lesion. *Propionibacterium acnes*, although not the primary inducer of acne pathogenesis, promotes multiple mechanisms of inflammation that correlate mostly with inflammatory lesions. An importrant caveat in the updated model of acne pathogenesis is that although the microcomedone remains as an early precursor lesion, a specific folliculocentric pattern of innate inflammation occurs before or along with follicular hyperkeratinization.[1,2] In addition, inflammation persists during the resolving macular phase after inflammatory lesions flatten toward the end of their life cycle, even with treatment.The clinical translation based upon this updated model is that anti-inflammatory effects, comedolytic activity, and reduction in *P acnes* are all important components in acne treatment to help suppress initial lesion formation, and to decrease the intensity and duration of inflammation in visible acne lesions.[3,4]

From a therapeutic standpoint, the use of benzoyl peroxide (BP) and a topical retinoid suppresses several components of acne pathogenesis, including reduction in *P acnes* and comedolysis by BP, and reduction in follicular hyperkeratinization, decrease in innate inflammation, and inhibition of dermal matrix degradation by the topical retinoid.[2-4]This supplement also depicts how specific biomarkers of inflammation are upregulated in AV, with discussion of how therapies such as topical adapalene and BP may provide augmented therapeutic activity as compared with the indidual agents alone. Although some topical antibiotics also reduce *P acnes* and may exhibit some anti-inflammatory properties, they can induce antibiotic-resistant *P acnes* strains, an unwanted sequelae that does not happen with BP.[2] Hence, the question arises: Do we really need topical antibiotics in our new treatment paradigm for acne vulgaris?

I want to thank my friend and colleague, Dr. Jim Del Rosso, who carefully studied the currently available basic science and clinical data, conceptualized the overall pathophysiologic process of AV, and presented it to Galderma at their request as a consultant, and to colleagues in 2012. These efforts served as the fundamental framework both for this supplement and for my article entitled "The Role of Benzoyl Peroxide in the New Treatment Paradigm for Acne", published in a June 2013 supplement (Stein Gold L, Weiss J, Kircik L. *Decoding Acne: Genetic Markers, Molecules, and Propioniacterium Acnes. J Drugs and Dermatol* 2013;12(Supplement): S61-S78.)

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Disclosures

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The Updated Model of Acne Pathogenesis: Does it Bring Anything of Value to the Table?

James Q. Del Rosso DO FAOCD

I was very appreciative to be invited by Dr. Kircik and the *Journal of Drugs in Dermatology* to participate in this supplement on the updated model of acne pathogenesis. I am also thankful to the acne team at Galderma for requesting my services as a consultant starting almost 2 years ago to assist in integrating more recent research results and updating the overall conceptualization of acne pathophysiology. Although I am not a basic scientist, I have thoroughly explored the research on acne pathogenesis over several years as I believe an understanding of this information elevates our abilities as both clinicians and therapeuticians.

I hope this supplement provides information that is as helpful to you in clinical practice as it has been to me, as my understanding and appreciation of acne has been broadened substantially. I recommend reading this supplement more than once. I hope you enjoy it and find it beneficial.

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 ORIGINAL ARTICLE Journal of Drugs in Dermatology

The Sequence of Inflammation, Relevant Biomarkers, and the Pathogenesis of Acne Vulgaris: What Does Recent Research Show and What Does it Mean to the Clinician?

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ABSTRACT

Acne vulgaris (AV) remains one of the most common skin disorders seen in dermatology practices worldwide. Despite an abundance of publications, AV continues to be a formidable therapeutic challenge due to its complex pathogenesis and chronicity. Regarding the sequence of AV lesion formation, the traditional model teaches that the primary lesion is the microcomedone, a subclinical lesion caused by follicular hyperkeratinization. From the microcomedone, visible AV emerges with development of comedonal ("noninflammatory") and inflammatory lesions. Research published over the past decade has provided information about inflammatory mechanisms that warrant us reconsidering the traditional model of AV pathogenesis. More specifically, there is evidence that specific cascades of inflammation occur early during the initial subclinical formation and visible emergence of AV lesions, later during progression, and finally during resolution including scarring. It has also been shown that subclinical inflammation occurs before or concurrently with microcomedone formation. This article reviews an updated model of acne lesion development and its progression based on a literature review that highlights the role of inflammatory mediators, cellular infiltration patterns, and expression of receptors that signal specific immunologic and inflammatory responses. Clinical relevance related to this updated model is also addressed.

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INTRODUCTION

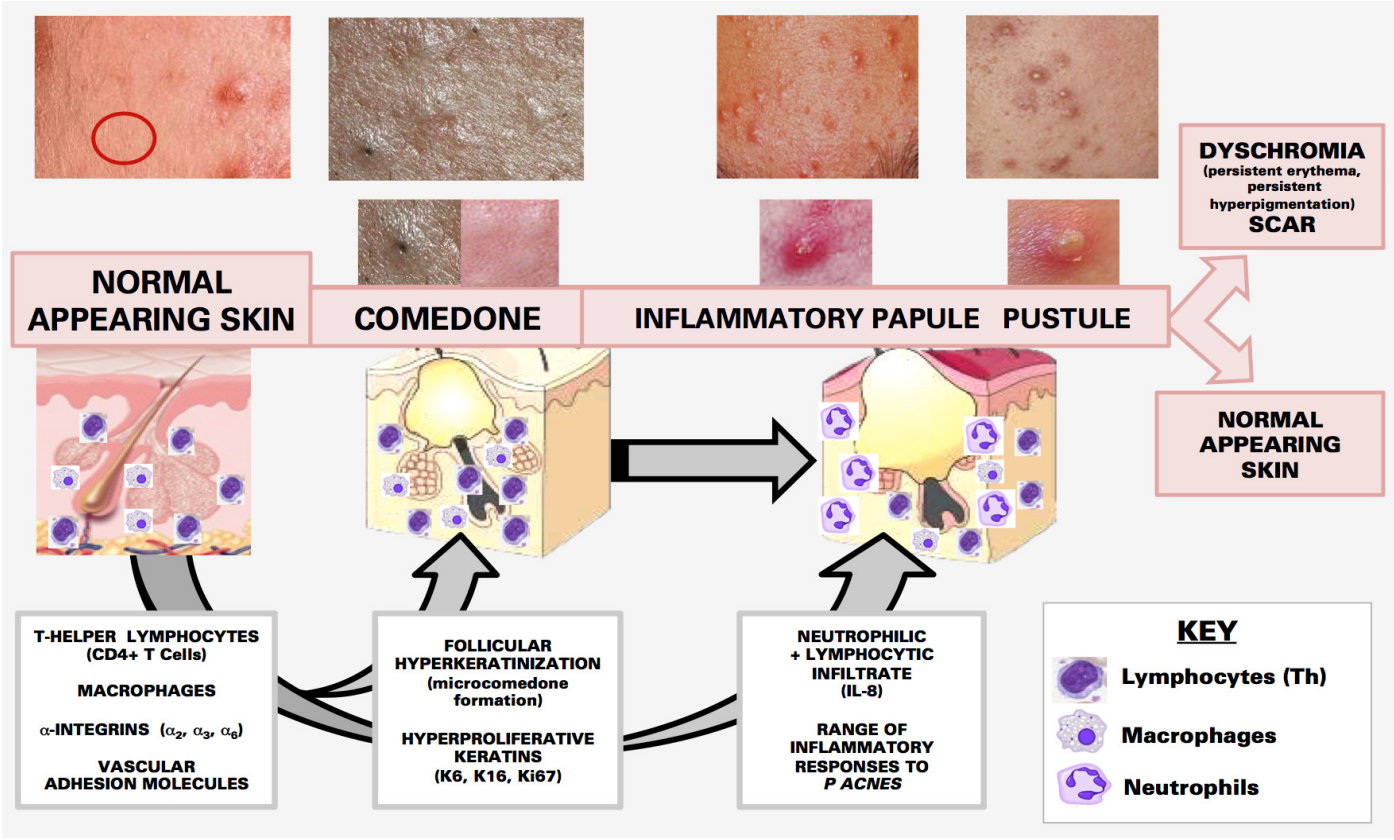
Acne vulgaris (AV) is the most common skin disorder encountered in dermatology practice in the United States, regardless of race.[1] Based on the 2009 National Ambulatory Medical Care Survey, AV accounted for 10.2% and 0.4% of non-Federal office-based visits to dermatologists and non-dermatologists, respectively.[2] Estimated to affect up to 50 million people in the United States, AV occurs commonly during adolescence, affecting up to 95% of individuals between 12 and 18 years of age.[1,3,4]

Many preteens and teenagers with AV experience a protracted course into their postadolescent years that can vary in severity and frequency of exacerbations.[4-7] Preteen and postadolescent AV are both common.[4,6-11] Although AV can sometimes "burn out" inexplicably after the teenage years, approximately 50% and 12% of women, and 40% and 3% of men, are reported to have AV in their thirties and in their forties, respectively.[4] Postadolescent AV is a subset that is rising in prevalence, with a notable increase in dermatology visits for adult women with AV observed over the past decade.[8,10,11]

The depth and progression of our traditional understanding of AV pathogenesis has been well described and correlated with clinical and laboratory findings, including histologic studies.[12-15] The predominant pathogenic factors associated with AV development and/or severity are follicular hyperkeratinization, excess sebum production, proliferation of *Propionibacterium acnes,* and cutaneous inflammation induced by upregulated proinflammatory mediators.[6,7,12-15] Literature review shows that the current understanding of AV pathogenesis evolves as valid and relevant research findings emerge.[14-20]

The *traditional model of acne pathogenesis,* better described as acne lesion development and progression, states that follicular hyperkeratinization (microcomedone formation) is the first step in the life cycle of an AV lesion.[12-15,20] A fully developed microcomedone and abnormal desquamation produces an intrafollicular keratinous plug behind which sebum accumulates. As follicular enlargement, hyperkeratinization, and excess sebum production progress, a microcomedone may transcend to form an open or closed comedone, which remain visibly noninflammatory.[13,20] An individual comedone may then remain at this stage until resolution, or may progress to form an inflammatory lesion (ie, papule, pustule). Although not often stressed in discussions of the traditional model, inflammatory lesions may also arise from visibly normal skin, possibly from a precursor microcomedone that bypasses the visible comedonal stage (Figure 1).[17] Subsequent to the microcomedone, a sequence of events may occur that lead to either superficial or deep inflammatory lesions, with *P acnes* proliferation contributing a variety of pathophysiologic effects. Many of these effects are proinflammatory and initiate or propagate inflammatory cascades in AV, and are explained by the genome of strains of *P acnes.*[14-18,20-23]

FIGURE 1. Development and emergence of lesions of acne vulgaris. Formation and progression of acne lesions correlated with sequence of underlying profiles of inflammation. (Profiles characterized by specific patterns of cellular infiltration, biomarkers, and histolologic changes).[14-20,27,28,35]



More recent data suggest that AV lesions often begin with a specific pattern of innate inflammation before or with follicular hyperkeratinization.[15-20,24-26] Figure 1 depicts the formation and progression of AV lesions sequentially correlated with underlying profiles of inflammation.[15-18] Various testing methods have demonstrated increased expression of specific proinflammatory cytokines, chemokines, enzymes, adhesion molecules, and receptors that function collectively in AV to promote cascades of inflammation. These inflammatory mediators play more important roles in AV than what was previously appreciated. In addition, their roles appear to be directed, sequenced, related to the time course of their active contributions to AV pathogenesis, and possibly correlating to patterns of upregulated gene expression and other biologic markers found at different time points in AV lesion development and progression.[15-20,26-29] Although expression of genes and biomarkers does not definitively confirm their role in disease pathogenesis, there appears to be a collective "menu" of relevant and dedicated inflammatory mediators that are not simply "bystanders," but rather are operative during the evolution, progression, and resolution of an individual AV lesion. In addition, methodical facial lesion tracking has confirmed that an inflammatory AV lesion may progress from a comedone; however, in approximately 28% of cases they arise directly from visibly uninvolved skin.[30]

Updated Model of Acne Pathogenesis: Where Does it Come From?

Research published in 1988 and the ensuing decade provided a sequential view of events in AV lesion formation with emphasis on its earlier stages.[27,28] These studies supported the concept of early *subclinical inflammation* prior to emergence of visible AV lesions, an observation that opened the door for new research directions on pathogenesis and therapy. Histologic and immunohistochemical evaluations completed in these studies showed that the earliest pattern of cellular infiltration in AV was lymphocytic, rather than a neutrophilic pattern as previously believed.[27,28] Lesion-directed neutrophilic infiltration develops later in the "AV lesion life cycle," especially with inflammatory lesions.

In 2003, a landmark article by Jeremy et al provided relevant scientific insights that advanced our knowledge about early subclinical inflammation in AV.[18] This report showed that a subclinical folliculocentric inflammatory process occurs with initial development and subsequent visible emergence of an AV lesion and appears to occur before or concurrently with follicular hyperkeratosis (microcomedone formation).[15-20,27,28] A variety of inflammatory mediators and cascades have been shown to participate in the subclinical and early pathogenic process, including upregulated cytokines, chemokines, enzymes, adhesion

TABLE 1.

Major Pathogenic Biomarkers of Inflammation Upregulated in Acne Vulgaris[12-20,24-29,31-35,37,38,40,41]

Biomarker	Pathophysiologic Activity in Acne Vulgaris	Comments
TLR-2	Upregulated pattern recognition receptor stimulated by *P acnes* ligand with signaling of innate inflammation	Active early in inducing prelesional inflammation
IL-1	"Jump start" cytokine from keratinocytes involved in early signaling of innate inflammatory response; reported to trigger follicular hyperkeratinization (comedogenesis)	Upregulated during prelesional inflammation, ie, stimulate lymphocytic infiltration (CD4+ T cells)
Integrins (α_2, α_3, α_6)	Markers for vascular adhesion (assist tracking of inflammatory cells to affected follicles forming acne lesions) and epidermal differentiation	Upregulated during prelesional inflammation (folliculocentric homing of T-lymphocytes)
hBD (1, 4)	Epidermal antimicrobial peptides increased in inflammatory papules and promote inflammation	Upregulation induced by *P acnes*
IL-8	Mediator of inflammation upregulated in inflammatory papules	Neutrophil and lymphocyte chemoattractant; can be induced by *P acnes*
MMPs	Extracellular matrix remodeling including collagen and elastic tissue degradation and repair; some promote inflammation	Upregulated MMP-1, MMP-3, others; active in inflammatory lesions; some may play an early role; many can be induced by *P acnes*

hBD, human β-defensin; IL, interleukin; MMP, matrix metalloproteinase; TLR, toll-like receptor.

molecules, and proliferation markers coupled with increased expression of specific cellular receptors (Table 1).[14-20,24-29,31-35]

The sequence of findings on AV pathogenesis support that early subclinical folliculocentric inflammation is present within individual follicles before or concurrently with follicular hyperkeratosis (microcomedone formation). These early cascades of inflammatory response eventually progress to form acne lesions. In addition, the research data demonstrate a progression of inflammatory patterns throughout the acne lesion life cycle, including during the resolution phase, which in some cases includes scar formation.[18,27,28] This defined progression of AV inflammation is reflected by sequenced changes in patterns of cellular infiltration, upregulation of specific biomarkers, augmented expression of certain genes, and the presence of several "messengers, mediators, and receptors" with known biologic activities in inflammatory processes (Table 1).[15-20,24-29] As noted in the traditional model, the presence of sebum and early proliferation of *P acnes* within the affected pilosebaceus unit can further amplify follicular inflammation. Additional research adds to the growing list of inflammatory mechanisms that this complex bacterium may initiate, many of which appear to be operative in AV (Figure 2).[14-20,22,23,31-36]

Sequence of Inflammatory Events

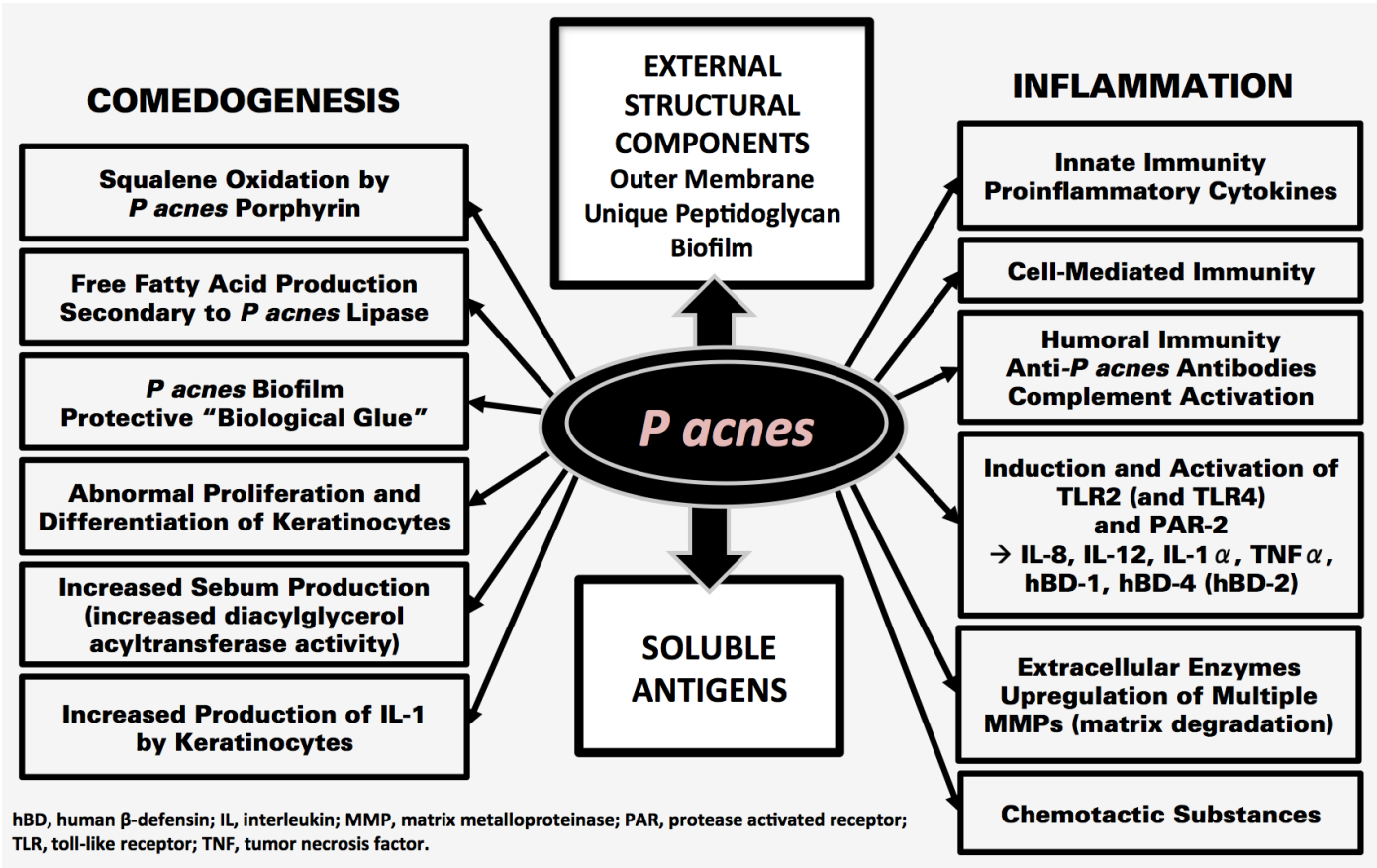
The study by Jeremy et al evaluated the timing of inflammatory events in acne lesion development, with qualitative and quantitative assessment of inflammatory cell types and various biomarkers known to modulate pathways of inflammation (ie, interleukins [ILs], vascular adhesion molecules).[18] In patients with AV, biopsies were taken from the back of uninvolved skin (n=20) and early papules present for ≤6 hours (n=12), with results compared with those seen in normal skin of subjects without AV (n=10). The study outcomes demonstrated a *prelesional folliculocentric inflammatory phase* as evidenced by markedly increased (1) numbers of CD4+ T lymphocytes (above the expected surveillance level noted in normal skin in non-AV subjects); (2) numbers of macrophages; (3) upregulated expression of perifollicular IL-1; and (4) upregulation of epidermal expression of α-integrins in both normal skin and early papules of AV subjects as compared with normal skin of those without AV. In addition, the magnitude of increases noted with the aforementioned cell types and biomarkers was greater in AV papules than in the normal skin of AV subjects, reflecting their relative participation in AV lesion development. Furthermore, in this study, the prelesional inflammation preceded follicular hyperkeratinization and the presence of microcomedones, although the number of subjects was small and the possibility of identifying the concurrent presence of microcomedones with additional tissue cuts cannot be entirely excluded. Nevertheless, the presence of early prelesional folliculocentric inflammation was documented in this study, consistent with results from later studies that provide additional support for the early subclinical inflammation in AV.

"Acne vulgaris continues to be a formidable therapeutic challenge due to its complex pathogenesis and chronicity."

Gene Array Profiling

Jeremy et al opened the door to rethinking AV pathogenesis by questioning the dogma of microcomedone formation being the primary precursor process. Sequenced patterns of inflammatory cell infiltration and specific biomarkers that demonstrate a subclinical folliculocentric pattern of innate immune response, upregulation of vascular adhesion to promote trafficking of T-lymphocytes (mostly CD4+ cells), and an increase in macrophages

FIGURE 2. Potential pathophysiologic roles of *Propionibacterium acnes* from lesion emergence through lesion progression in acne vulgaris.[15,16,35,56,57]



was shown.[18] Over the ensuing decade, other studies have evaluated biomarkers and gene expressions in AV, with emphasis on inflammatory papules and comparisons to unaffected skin.[29,37,38]

In one study, gene array expression profiling was analyzed from inflammatory acne papules (n=6), normal skin from AV subjects (n=6), and normal skin from subjects without AV (n=6).[29] The results demonstrated upregulation of 211 genes in tested inflammatory papules, most of which correlate with promotion of inflammatory processes and extracellular matrix remodeling. Importantly, gene upregulation does not necessarily translate to biologic or disease-related activity.[39] In order to contribute to AV pathogenesis, a given upregulated gene must actively signal the downstream production of the respective biologically active proteins as opposed to being present only as an epiphenomenon without clinical relevance.

Predominant pro-inflammatory upregulated genes that appear to be operative in AV are specific matrix metalloproteinase (MMP) enzymes (MMP-1, MMP-3), proinflammatory cytokines (IL-8, IL-1 [family 5,9]), antimicrobial peptides (human β-defensin 4 [hBD-4], granzyme B), and vascular adhesion molecules (lymphocyte adhesion molecule-1 [selectin L]).[29] The outcomes of this study are in agreement with Kang et al in demonstrating increased expression of MMPs (ie, MMP-1, MMP-3), and cytokines, especially IL-8 (a T-lymphocyte and neutrophil chemoattractant) in inflammatory acne lesions, and with Chronnell et al who reported an increase in hBD-1 and hBD-4 (formerly hBD-2) in AV.[29,38,40] These data are also consistent with the independent observation that distinct *P acnes* strains elicit expression of hBD-4 and IL-8.[41]

Interestingly, in one of 6 biopsies of normal skin in subjects with AV, perifollicular inflammation was noted using immunohistochemical analysis, suggesting subclinical inflammation associated with a clinically unapparent AV lesion.[29] Although no differences were noted between normal skin from AV subjects and those without AV by gene array profiling, this may be due to inadequate detection by the methodology as limited foci of inflammation present within a 5 mm punch specimen contribute minimally to overall gene expression.[29] In addition, a gene cluster analysis was completed and showed a separation into 2 distinct gene clustering patterns, with one cluster corresponding to involved skin from inflammatory AV papules and another corresponding to normal-appearing skin from the same 6 AV subjects. Further research is warranted in this area. Ultimately, these data are consistent with other evaluations using various technologies that demonstrate upregulation of MMPs, pro-inflammatory cytokines (including IL-8, which is a neutrophil chemoattractant), and vascular adhesion

molecules that contribute collectively to AV pathophysiology, and increase quantitatively as visible inflammatory lesions emerge.

The Role of *Propionibacterium acnes* in the Pathogenesis of Acne Vulgaris: Where Are We Now?

Although not the primary initiator of acne lesion formation, *P acnes* appears to play an integral role in the propagation of AV both early and late in the pathophysiologic process. Older literature discusses several mechanisms including production of chemotactic factors, extracellular enzymes, and cytokines; increased free fatty acids from breakdown of sebum; elicitation of a cell-mediated immune response; and the stimulation of humoral responses including complement fixation and antibodies to *P acnes.*[12-14,21] Over time, the role of *P acnes* in AV pathogenesis has been further elucidated by additional research discussed below. To summarize, certain strains of *P acnes* appear to utilize structural characteristics of its outer wall, receptor interactions, and secretion of various enzymes and other chemical messengers to induce various cascades of inflammation; however, the toll-like receptor-2 (TLR2) interaction appears to be central to the elicitation of innate immune response early in the process of AV lesion formation.[13-17,33,35]

Pattern Recognition Receptors

Available evidence suggests that *P acnes*–induced release of pro-inflammatory cytokines is dependent on interaction with the pattern recognition receptor (PRR) TLR2, with activation of inflammation also dependent on CD14, a PRR for lipid-containing ligands such as lipopolysaccharide found on the outer surface of some bacteria.[16,17,19,26,33-35] It has been suggested that the TLR2 ligand is the *P acnes* peptidoglycan, although more research is needed. All TLRs elicit conserved innate inflammatory pathways that activate the transcription factors, nuclear factor kappa-B (NF-kB) and activator protein-1 (AP-1), which modulate intracellular signaling cascades, regulation of pro-inflammatory cytokines (ie, tumor necrosis factor-α [TNF-α], IL-1b, IL-8), and MMP expression.[29,38] These data suggest that an important mechanism whereby *P acnes* signals production of innate inflammatory response in AV is via TLR2 activation, which triggers a pro-inflammatory cytokine pattern shown in other AV studies.[15,26,33,35,38]

Protease Signaling

P acnes produces various exogenous proteases that elicit cellular responses, at least in part, via protease-activated receptor 2 (PAR-2), with PAR-2 signaling shown to mediate inflammation and immune response.[32] One study investigated whether proteases from *P acnes* could activate PAR-2 on keratinocytes and signal production of pro-inflammatory cytokines, antimicrobial peptides (AMPs), and MMPs.[32] Results showed that protease activity and PAR-2 expression were increased in acne lesions. Also, protease activity was increased in lesional epithelium relative to perilesional epidermis in AV subjects (n=4), with PAR-2 highly expressed in the comedones of AV compared with those in nevus comedonicus (n=2), which are devoid of inflammation and do not progress through a life cycle. The *P acnes* culture supernatant induced PAR-2 signaling in keratinocytes with increased mRNA expression of IL-1α, IL-8, TNF-α, hBD-2 (hBD-4), LL-37, MMP-1, MMP-2, MMP-3, MMP-9, and MMP-13, and with inhibition shown using a selective PAR-2–specific antagonist. These results suggest a pathophysiologic role in AV for PAR-2 signaling by *P acnes,* and describe another potential pathway whereby this organism increases the same upregulated pattern of pro-inflammatory cytokines, AMPs, and MMPs as shown in other independent evaluations.[15,26,32,33,35,38,42]

Persistence of Inflammation Throughout Lesion Formation and Resolution

In older AV studies, early inflammatory events were generally conducted after clinical presentation, with inflammation believed to occur subsequent to microcomedone formation and visible emergence of a comedonal lesion.[27,28] The studies by Jeremy et al and others have brought forward the concept of early preclinical inflammation in AV. Not only may inflammation be an early event in AV, but it typically persists throughout the acne lesion life cycle.[33,35] Inflammatory mediators and cellular infiltrates persist after the resolution of acne lesions, including through scarring, with inflammatory cell infiltrates found in 77% of atrophic scars.[16,42] Persistent inflammatory hyperpigmentation (affecting darker skin) and persistent inflammatory erythema (affecting fair skin), although both often referred to erroneously as "postinflammatory," are the hallmarks of the AV resolution phase as palpable lesions flatten to form focally dyschromic macules that fade slowly over time.[43] After palpable AV lesions flatten, follicular inflammation does not disappear instantly. Rather, the dyschromic macules are inflammatory visibly and histologically, likely for several weeks to months, even with acne therapy. This observation may be partially related to the slow degradation of non-viable *P acnes* present within the follicle with the outer structure of this bacterium still capable of triggering innate inflammation.[33,35] From a clinical perspective, the pitfall to avoid is the practitioner withdrawing therapies during the macular resolution phase after palpable lesions flatten, thinking that inflammation is no longer present. On the contrary, it is suggested overall that optimized acne therapy be maintained until there is a good clinical sense that persistent inflammation has resolved and emergence of new AV lesions is well controlled.[44]

Types of Propionibacterium acne

Some pieces of the puzzle on *P acnes* and AV pathogenesis remain unknown, including the impact of different strains and phylogenetic types. Two phylogenetically distinct types of *P acnes* have been identified, type 1 and type 2, with type I subdivided into type 1A and type 1B.[32,45,46] Type 1A *P acnes* isolates have been reported as predominant in AV, with the greatest effect on AMPs and proinflammatory cytokine production.[41] As *P acnes* types exhibit biochemical and antigenic variability,

variations between type 1 and type 2 *P acnes*, or between type 1A and type 1B subtypes, may correlate with qualitative and quantitative differences in how AV pathogenesis is modulated.

Clinical Correlation of the Evolution of Acne Pathogenesis

The management of AV has focused on using therapies that target specific components of AV pathogenesis. With the traditional model emphasizing microcomedo formation prior to inflammation, topical retinoid therapy was emphasized for comedonal AV or mixed AV with some inflammatory lesions.[13,47] A topical retinoid is recommended from the outset of AV therapy to counter microcomedone and comedone formation, and induce certain anti-inflammatory effects (ie, reduced expression of TLR-2, inhibition of AP-1 pathway).[13,47,48] However, use of a benzoyl peroxide (BP)-containing formulation early in AV treatment is also suggested, especially in pediatric literature.[9] In reality, the "battle" to identify which specific product to routinely use "first line" is not definitively supported by published guidelines or studies, as there are many options, although certain approaches are suggested. Multiple clinical studies of AV patients being treated topically from the outset with a topical retinoid and a "leave on" BP-containing formulation have shown a faster onset of efficacy and a greater magnitude of inflammatory and comedonal lesion reduction overall as compared with retinoid monotherapy, at least over the 12 weeks used in most trials.[49-51] This observation has been correlated directly to greater severity of AV at baseline.[51] When AV of even greater severity is encountered, this combined topical approach can be used in combination with an oral antibiotic.[44,52] Use of a topical retinoid and a BP-containing formulation is a rational approach from the outset of AV treatment with the retinoid reducing follicular hyperkeratinization, MMP-induced dermal matrix degradation, and expression of TLR2.[13,45,52,53] Benzoyl peroxide used from the outset offers additive benefit via suppression of *P acnes* and reduction of both inflammatory and comedonal lesions.[13,54]

An ex vivo pilot study assessed the effects of adapalene (adap) (1 μM) and BP (10 μM), both separately and combined, on various inflammatory biomarkers in AV.[37] Five biopsies (papules n=4; acne-free n=1) were taken from back skin of subjects with AV (n=7). Lesional skin biopsies were incubated in culture media and activities of BP alone, adap alone, and combination adap and BP were assessed. Multiple inflammatory biomarkers were overexpressed in inflammatory skin (papules) relative to uninvolved skin including TLR-2, hBD-4, IL-8, integrins (α_2, α_3, α_6), and Ki-67 (proliferation marker). Relative to individual components, combination adap and BP was superior to each individual monad in suppressing several biomarkers in lesional skin, including hBD-4, IL-8, integrins (α_2, α_3, α_6), and Ki-67. Neither monad markedly suppressed hBD-4 or IL-8. Both adap with and without BP suppressed TLR-2 (BP alone showed no suppressive effect). Combination adap and BP produced greater ex vivo suppression of several upregulated biomarkers in inflammatory AV papules compared with adap alone and BP alone. If these effects on biomarkers are confirmed in vivo, combined retinoid and BP use would exhibit an augmented ability to normalize epidermal proliferation/differentiation, decrease adhesion and trafficking of inflammatory cells, inhibit *P acnes*–stimulated innate inflammation, and reduce *P acnes* counts.[29,37,55] The greater effects of the combination of a topical retinoid (such as adap) and BP may more effectively counter the prelesional inflammation, the emergence of AV lesions, and persistent inflammation after lesion resolution, the latter hopefully reducing inflammation that is associated with scarring.[37] As this study used ex vivo methodology, additional studies are needed to confirm these effects in vivo, including the impact of various therapies on specific biomarkers operative in AV.

Final Caveats

The information brought to light by the updated model reaches beyond academic interest and fascination. The following caveats correlate these research outcomes with clinical relevance.

(1) Although inflammation may not be visible when clinically examining comedonal lesions or early acne papules, specific patterns of inflammation are present and increased in quantity and/or activity. These early inflammatory patterns serve as therapeutic targets to intercept lesions early.[15-20,26-29,35]

(2) The similarity of inflammatory patterns in early papules and uninvolved skin in AV strongly supports the concept of early subclinical and sequential inflammation over the life cycle of AV lesions.[18]

(3) Skin biomarkers that correlate with AV lesions do not appear to be appreciably expressed in normal skin of those without AV. AV patients exhibit "acne prone" skin with a propensity to elicit subclinical folliculocentric inflammation in uninvolved skin marking the start of AV lesion development.[15,17,18,20,27-30]

(4) Combinations of agents can sometimes augment efficacy in AV through greater suppression of relevant biomarkers related to multiple modes of action.[13,44,47-55]

DISCLOSURES

Galderma had the opportunity to review the final version of the supplement and provide comments regarding accuracy of content; however, the authors maintained control over the content.

Dr. Del Rosso has served as a consultant, advisory board participant, clinical investigator, and speaker for Galderma, Allergan, Bayer HealthCare, Dermira, Eisai, Ferndale, Leo Pharma, Medicis (a Division of Valeant), Onset Dermatologics, Pharmaderm, Primus, Promius Pharma, Quinnova, Ranbaxy, Taro Pharmaceuticals, Tria-Beauty, Unilever, Valeant (Consumer Products), and Warner Chilcott.

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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