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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