Improved Understanding of Inflammation in Acne Pathophysiology:

Leading to New Developments in Treatment

New technologies have shown the presence of inflammatory pathways throughout all stages of acne lesion formation.

BY JAMES Q. DEL ROSSO, DO

Acne vulgaris (AV) is the most common skin disorder seen in ambulatory dermatology practices in the US. As a result, advances in pathophysiology that can lead to new therapies are always of high interest.

Our understanding of the pathophysiology of AV is evolving as new technologies have shown the presence of inflammatory pathways throughout all stages of acne lesion formation. As our understanding of the pathophysiology of AV increases, researchers can focus on targeting specific points in cascades of inflammation as they develop new therapies to treat AV.

Conventional View of Pathophysiology. The conventional pathophysiologic model of AV states an acne lesion is initiated subclinically as follicular hyperkeratosis, which leads to formation of a microcomedone. AV then becomes apparent as closed and/or open comedones emerge, both associated with a lack of visible inflammation.[1-3] Some AV lesions may progress to become visibly inflamed, appearing as papules, pustules, and/or nodules. Ultimately, AV evolves with some lesions remaining as comedones, while others progress to superficial or deep inflammatory lesions, eventually resolving with normal appearing skin, discoloration, or scarring. As each follicle goes through its own independent pathophysiologic "life cycle," most patients present at any given point in time with a mixture of AV lesions in various stages.[3]

Inflammation in Acne Pathophysiology. Advances in immunohistochemistry and other research techniques have brought forth new information on AV pathophysiology. Studies have included detailed analyses of cellular infiltrates, gene expressions, and chemical messengers (e.g., cytokines, chemokines) present at different stages of AV lesion formation, including before the emergence of visible lesions. It is now known that both follicular hyperkeratosis and perifollicular inflammation occur early during subclinical development of an AV lesion.[1-3] This subclinical inflammation is primarily a lymphocytic process at the outset and changes qualitatively and quantitatively as the life of the AV lesion progresses. An early inflammatory papule is associated with a greater density of lymphocytic infiltrate. Perifollicular inflammation may also be augmented with a greater infiltrate density that is more rich in neutrophils, presenting as a deeper papule, pustule, or a nodule. The latter occurs more often in association with follicular wall rupture. Although the cellular content and density of inflammation may be different among different AV lesion types, and the cellular mix

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and cytokines that present may change as lesions progress, inflammation is a constant and central part of an AV lesion throughout its entire life cycle.[1,3]

Targets of Acne Treatment. It is well recognized that pathophysiologic targets for acne treatment include comedogenesis, sebum production, androgenic mechanisms, and inflammatory pathways. Important information has been gleaned over the past decade on AV pathophysiology that may translate to development of newer therapeutic approaches. An example includes the role IL-1β in AV lesion initiation and development. IL-1β is believed to play an important role in the initiaton of AV lesions, including comedogenesis, and in the propagation of inflammation in AV.[4]

There is also newer information on the complex interrelationship between *Propionibacterium acnes*, a bacterium of the normal flora which inhabits and inflammation in AV. Different subtypes of *P acnes* exist, with only some strains more commonly associated with the presence of AV.[5] Proinflammatory strains of Pacnes are known to induce major inflammatory cytokines IL-1, IL-8 and IL-12 in human monocytes and IL-6 in human keratinocytes, findings that support reduction in colony counts of as one of the approaches used to treat AV.[6] Reduction in *P acnes* has been directly correlated with clinical improvement in AV.[7]

Current Approaches to Non-Antibiotic Topical AV Therapy. The major prescription topical agents used to treat AV are benzoyl peroxide (BP), retinoids, and antibiotics. BP has antimicrobial anticomedogenic properties, with its primary limitations being cutaneous irritation dryness and bleaching of colored fabric.[7,8] Retinoids have long been used to decrease comedone formation by inhibiting follicular hyperkeratosis and to help reduce inflammation directly through receptor inhibition.[8,9]

Antibiotic Therapy for Acne Vulgaris. Antibiotics are commonly used to treat AV, with mechanisms of action including *P acnes* reduction, and in some cases direct anti-inflammatory effects (eg doxycycline, minocycline).[7,8] Among topical antibiotics, clindamycin is the most commonly prescribed agent for AV. Doxycycline and minocycline comprise the majority of oral antibiotic use for AV. These agents, when utilized with proper patient selection and in combination with other agents for AV, are effective. However, a major disadvantage associated with antibiotic use for AV is antibiotic resistance, not just with *P acnes*, but with other strains of bacteria found on the skin.[10] This perpetuates the need to develop antimicrobial drugs that do not induce antibiotic resistance in microorganisms.

Nitric Oxide: A Potential Therapy for Acne Vulgaris. Nitric Oxide (NO) is a diatomic, short-acting molecule that is naturally present in the human body. It functions biologically as a signaling molecule that is involved in many different physiologic processes. Its primary role is to provide vascular relaxation, immunomodulation, and direct antimicrobial activity against several bacteria.[11,12] The therapeutic potential for NO in treatment of AV includes both direct antimicrobial and anti-inflammatory properties.

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Several companies are pursuing topical delivery of NO for the treatment of acne. Patented technology from Novan, Inc for packaging NO as part of an engineered macromolecule has enabled the creation of a topical gel (SB204) that is under development for the treatment of AV. Pharmacokinetic (PK) study of systemic exposure to the topically applied NO-releasing formulation showed that SB204 8%, applied twice daily over 17 percent body surface area for five days, did not increase plasma nitrate concentrations and created no changes in hematologic indices, methemoglobin levels, or chemistry panels as compared to vehicle gel.[13]

With favorable PK and safety profiles verified, a Phase 2, multicenter, randomized, double-blind, vehicle-controlled, parallel-group, three-arm study of topical SB204 was completed.[14] Subjects >12 years of age with AV were randomized to twice daily treatment with SB204 1% gel (n=51), SB204 4% gel (n=50), or vehicle gel (n=52). Subjects treated with SB204 4% showed a significantly greater reduction in both inflammatory and non-inflammatory (comedonal) lesions at week 12 as compared to both the SB204 1% and the vehicle.[14] (See Figures 1-3.) Changes in facial sebum measurements using Sebutape measurements were also obtained during the study. Subjects treated with SB204 gel with a net decrease in total sebum also had a mean reduction of inflammatory lesions of 60 percent, suggesting a potential correlation between reduction in sebum and reduction in inflammatory lesions.[14] Overall, participants in the study experienced favorable cutaneous tolerability and safety, with the majority of adverse events being mild in severity.

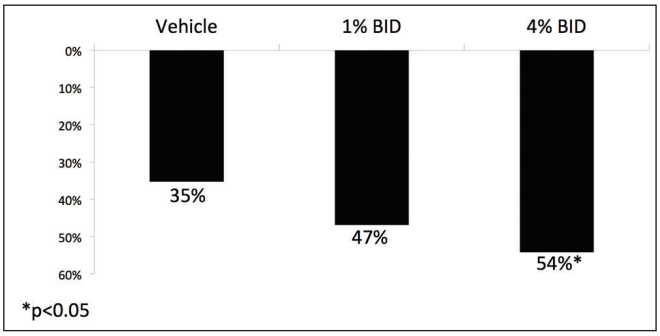

Figure 1. Inflammatory Lesions
% Reduction from Baseline at Week 12 (End of Study)

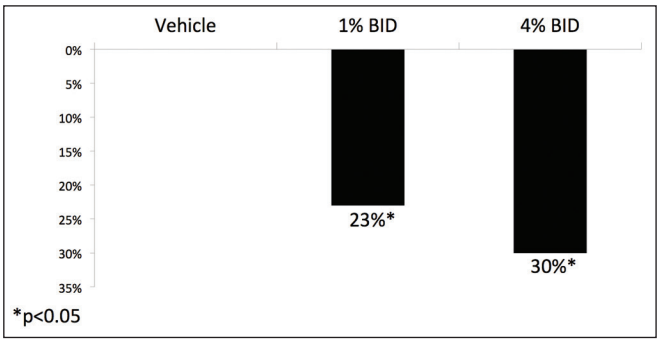

Figure 2. Non-inflammatory Lesions
% Reduction from Baseline at Week 12 (End of Study)

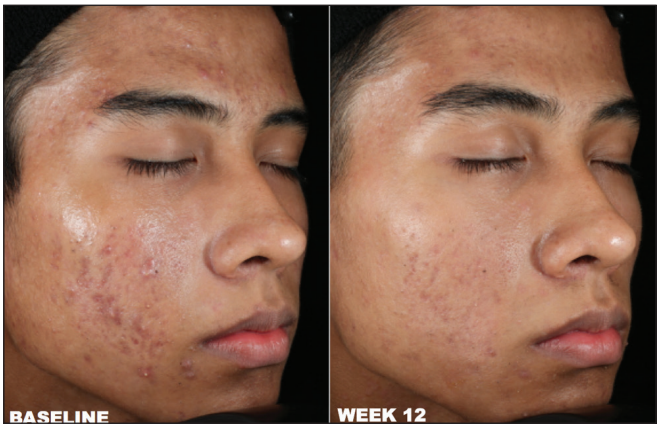

Figure 3. Subject treated with SB204 4% Gel BID at Baseline and at Week 12 (End of Study)

An additional Phase 2 trial evaluated the safety and efficacy SB204 1% gel, SB204 4% gel, and vehicle gel once-daily or twice-daily, and in a larger study population. Researchers reported in March 2016 at the American Academy of Dermatology Annual Meeting similar positive results with the SB204 4% formulation, with the important clarification that once-daily application was as effective as twice-daily dosing.[15] The results of these PK and Phase 2 studies are very encouraging, and a Phase 3 study evaluating SB204 4% gel for treatment of AV is underway.

EXCITING AND WELCOME DEVELOPMENTS

Overall, the development of new treatments that address multiple components of AV pathophysiology, incorporate novel mechanisms of action, are effective and safe, and avert antibiotic resistance is exciting and welcome. It is hopeful that new agents will soon become part of our therapeutic armamentarium.

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