Rethinking the Pathogenesis and Treatment of Acne Vulgaris

Recent findings raise questions about the order in which pathogenic factors occur in acne.

BY JOSHUA ZEICHNER, MD

Data in recent years have led to the discovery of several new variables in the pathogenesis of acne. Where the simpler, more traditional dogma of acne pathogenesis holds that both closed and open comedones lead to papular/pustular lesions, the emerging model of acne lesion progression is much more complex. We now know, for instance, that subclinical inflammation precedes the formation of microcomedones, and this inflammation persists during acne lesion progression. As comedonal lesions are histologically characterized by the presence of inflammatory cells, perhaps they should no longer be labeled as "non-inflammatory." In addition, formation of inflammatory lesions may bypass the "comedonal step," and inflammatory lesions may arise directly from clinically normal appearing skin. Finally, inflammatory mediators persist even after the resolution of primary acne lesions, as persistent inflammation has been demonstrated in scars.1-9

Several studies question the order in which pathogenic factors occur in acne. A 2003 biopsy study examining clinically normal skin in acne patients as well as patients with early inflamed acne lesions found that clinically normal skin showed elevated levels of CD4+ T cells, macrophages, vascular adhesion molecules, and pro-inflammatory cytokines.10 The authors concluded that inflammation occurs before the formation of microcomedones and that clinically normal appearing skin in acne patients is in fact not normal at all. Another study using photographic tracking of acne lesions using software designed to track stars found that inflammatory lesions are preceded by comedones in 54 percent of patients, normal-appearing skin in 28 percent of patients, erythematous macules in 12 percent of patients, and scars in six percent of patients.11

TREATMENT PEARLS

These findings hold certain implications for care. For example, they implicitly suggest the importance for treating the field from the beginning rather than spot treating. In addition, it is important to continue to treat the patient after acne resolves because of persistent inflammation. We also now must deal with the question of whether post-inflammatory erythema or pigmentation should really be referred to as "persistent" rather than "post-inflammatory."
“Despite the lack of new molecules in the acne space, combination options have opened up new avenues in managing our patients’ acne.”

Combination Approaches. In recent years, published reports (most notably the Global Alliance Acne treatment algorithm) have found enhanced therapeutic benefits in treating acne by combining agents with different but complementary mechanisms of action. A 2011 *in vitro* study assessed the modulatory effects of adapalene and benzoyl peroxide on skin obtained through surgery (see box on right). The study involved five biopsies (four on acne papules and one on acne-free skin) from each of seven patients. The skin was incubated in culture media, the individual drugs or the combination of both agents combined.12 Multiple inflammatory biomarkers were over-expressed in acne skin, and the combination of adapalene and benzoyl peroxide had a synergistic effect on TLR-2 and integrins a2, a3, a6 in inflamed skin relative to the individual components. Similarly, adapalene and benzoyl peroxide in combination had a synergistic effect on TLR-2 and hBD4 relative to adapalene and benzoyl peroxide individually.12

Moisturizers in Prescription Regimens. Given the associated inherent epidermal abnormalities with acne vulgaris, clinicians should consider the impact of acne on barrier function and whether topical therapies alter the structural and/or functional integrity of the epidermal barrier.13 The skin of acne patients has been demonstrated to be deficient in ceramides.14 Moreover, given that some topical acne medications are inherently irritating, should we recommend moisturizers in our prescription regimens?

In one study, patients with mild to moderate acne were given a moisturizer to apply in the evening, 20 minutes prior to use of tazarotene 0.1% (Tazorac, Allergan) cream.15 Patients receiving the combination regimen experienced a 57 percent reduction in inflammatory lesions, compared to 46 percent in the tazarotene alone group, and a 50 percent reduction in non-inflammatory lesions, compared to 48 percent in the tazarotene alone group. There was also consistently less dryness during all study points in the moisturizing arm (with statistical significance at week two), as well as a trend for non-statistical-

ly significant lower levels of peeling and erythema in the moisturizing arm.15

Another open-label study followed patients receiving a regimen of a ceramicate-containing moisturizing followed by benzoyl peroxide 2.5%clindamycin phosphate gel 1.2% (Acanza, Medicis) and a ceramicate-containing moisturizer in the morning followed by micronized tretinoin 0.05% (Atralin, Medicis) gel in the evening. A success rate of clear or almost clear was achieved in 60 percent of patients.16 These data suggest that moisturizing before medication does not interfere with efficacy and may also help to reduce cutaneous adverse events.

CONCLUSION

As new research continues to shed light on the pathogenesis of acne, it is incumbent upon clinicians to consider the ways in which our improved understanding of acne should affect the treatment regimens we prescribe. Despite the lack of new molecules in the acne space, combination options have opened up new avenues in managing our patients’ acne.

Dr. Zeichner has served as a consultant or investigator for Allergan, Beiersdorf, Galderma, L’Oreal, Medicis, Onset, Pharmaderm, Promius, and Valeant.

Joshua Zeichner, MD, FAAD is an Assistant Professor and Director of Cosmetic and Clinical Research in the Department of Dermatology at Mount Sinai Medical Center in New York.