The pathogenesis of acne is not clearly understood, although primary contributory factors have been identified. Propionibacterium acnes, a commensal organism that plays an active role in acne vulgaris, thrives in the presence of excess sebum and has been shown to mediate inflammatory processes at the site of the sebaceous follicle, contributing to the formation of free radical species and generating pro-inflammatory cytokines. Coupled with faulty keratinization, excess sebum production and P. acnes colonization contribute to the formation of microcomedones, ultimately leading to development of the comedones, papules, pustules, and cysts characteristic of acne.

The presence of active acne lesions impacts the individual’s appearance, has negative effects on psycho-social function, and can be associated with potential physical discomfort. Scarring following acne is a significant risk and has been identified as the most devastating sequela to the patient. Acne is a chronic condition, similar in its impact and duration to atopic dermatitis. Patients may be subjected to protracted courses of therapy, during which they may be exposed to multiple different treatments in efforts to attain control of the inflammatory process. As such, management of acne can be associated with therapeutic inefficiency and escalating costs.

Initiation of effective therapy as early as possible within the disease course is associated with improved patient experiences, better outcomes, and long-term cost savings. Furthermore, data confirm that patient adherence is associated with better out-

Early Anti-inflammatory Topical Acne Therapy May Improve Outcomes and Reduce Bacterial Resistance

Cost-effective care is possible with the use of older and new treatments that confer efficacy and provide patient satisfaction.

By Leon H. Kircik, MD

Take-Home Tips. Acne is a chronic, inflammatory condition, similar in its impact and duration to atopic dermatitis. Initiation of effective therapy as early as possible within the disease course is associated with improved patient experiences, better outcomes, and long-term cost savings. Topical benzoyl peroxide is a relatively inexpensive and generally helpful agent in the management of acne vulgaris, though its efficacy as a monotherapy is typically limited. In light of the significant and growing problem of antibiotic resistance, current expert treatment guidelines for acne de-emphasize the use of systemic antibiotics. Dapsone 5% gel applied twice daily has been shown to decrease both the inflammatory and non-inflammatory lesions of acne vulgaris. It was well tolerated and shown to be compatible with topical benzoyl peroxide.
comes and lower long-term treatment costs. Selection of an effective, convenient, and well-tolerated regimen, then, is essential for successful, cost-effective care.

Treatment Options and Therapeutic Challenges
Acne is essentially an inflammatory disease. A better understanding of the pathophysiology of acne and associated scarring has been gained through recent in vivo research reporting a marked increase in inflammatory cytokine gene transcripts in active acne lesions, including TNF-α and IL-1β. Importantly, these pro-inflammatory cytokines amplify NF-kβ signaling pathways that originally led to their production while also stimulating nearby cells, according to the authors. This investigation also identified significant increases in IL-8 and IL-10 and showed that elevated Activator Protein-1 (AP)-1 in acne lesions leads to elevated matrix metalloproteinases, which degrade collagen—up to 2.5-fold compared to normal skin. Furthermore, the researchers noted that the inflammatory process is localized to the pilosebaceous unit.

The most common sequela of inflammatory acne, scarring often is devastating to patients. Most treatments for acne scarring confer minimal benefit, while the gold standard of scar revision, laser therapy, typically requires multiple treatments and is expensive. Preventing and treating inflammatory lesions as early as possible is the best way to prevent scarring. Also, any agent blocking (AP)-1, which increases matrix metalloproteinases that cause scarring via collagen degradation, will be useful in scar prevention.

Historically, management options for acne have targeted either P. acnes colonization or faulty keratinization. Topical treatments are by far the most common intervention for acne; options have included retinoids—tretinoin, adapalene, and tazarotene; antimicrobials, such as erythromycin and clindamycin; and benzoyl peroxide. Different combination formulations of retinoids, antibiotics, and benzoyl peroxide are also available. Oral treatment options include antibiotics and isotretinoin.

Although the P. acnes bacterium is pathogenic in acne vulgaris, acne is not an infectious process. Topical benzoyl peroxide is a relatively inexpensive and generally helpful agent in the management of acne vulgaris. It provides comparable efficacy at 2.5%, 5% and 10% concentrations, though higher concentrations tend to produce more cutaneous irritation. Benzoyl peroxide has the advantage of not being associated with developing bacterial resistance. However, its efficacy as a monotherapy is typically limited.

Topical and oral antibiotics reduce but do not eradicate P. acnes populations. Current consensus holds that systemic antibiotics confer effects more through their anti-inflammatory than their anti-infective properties. In light of the significant and growing problem of antibiotic resistance, current expert treatment guidelines for acne de-emphasize the use of systemic antibiotics.

Concern about antibiotic resistance in acne patients is not simply theoretical, as the 1980s produced the first reports of P. acnes resistance to antibiotics, and subsequent studies document acne treatment failure associated with resistance to topical antibiotics. Resistance is not limited to P. acnes; Researchers have documented resistant strains of Staphylococcus epidermidis and Streptococcus pyogenes. Both erythromycin and tetracycline have been associated with high rates of resistant acne.

Despite the well-known and recently re-affirmed role of inflammation in acne, no primarily anti-inflammatory topical therapy had been available for acne. Anti-inflammatory topical dapsone 5% gel (Aczone Gel 5%, Allergan) is now available for topical treatment of acne.

A New Option: Safety and Tolerability of Topical Dapsone
Dapsone’s strong anti-inflammatory effects have made it a very powerful treatment in several neutrophilic dermatoses (such as dermatitis herpetiformis), yet the mechanism of action of this effect is not well understood. Several in vitro studies show the anti-inflammatory effect of dapsone, and the successful use of oral dapsone in several sub-epi-
Dermal blistering diseases is associated with anti-inflammatory effects by the suppression of neutrophil and eosinophil functions, likely through dapsone’s inhibition of IL-8 release, seen in cultured human keratinocytes.19 Dapsone has been shown to have multiple effects that mediate cutaneous inflammation.20-24

Systemic dapsone has been associated with notable risks, including hemotoxicity (methemoglobinemia). Individuals with a glucose-6-phosphate dehydrogenase (G6PD) deficiency, methemoglobin reductase deficiency, or hemoglobin M disease are at highest risk for hemotoxicity, and the package insert for oral dapsone requires regular screening of full blood counts. However, topical dapsone is not associated with this risk, and no laboratory testing is required. In clinical trials, twice-daily topical application of dapsone as directed for the treatment of acne did not induce significant changes in hemoglobin or other hematologic indicators, even in G6PD-deficient patients.25-28 Continuous use of dapsone 5% gel is not associated with an increase in plasma concentrations of the drug.28 Concomitant use of topical benzoyl peroxide or adapalene has not been shown to affect the pharmacokinetic profile of dapsone 5% gel.26

Aczone gel is formulated with diethylene glycol monoethyl ether (DGME), which facilitates the permeation of active ingredients into the skin and helps undissolved dapsone to remain in the pilosebaceous unit, according to in vitro data.13 Specific properties of DGME help topical dapsone in this novel formulation to remain in the pilosebaceous unit and subsequently increases its efficacy in the treatment of acne vulgaris.

In clinical trials, topical dapsone treatment was well tolerated with similar reports of adverse events in the active and control groups (58.2 percent and 58.6 percent, respectively). Most events were of mild to moderate intensity, resolved during treatment, and did not result in treatment discontinuation. Just 0.6 percent of treated patients discontinued participation due to lack of efficacy, while 0.4 percent withdrew due to an adverse event. Treatment with dapsone 5% gel resulted in a reduction in oiliness from 18.6 percent at baseline to 5.6 percent at week 12 and reduction in erythema from 14.8 percent at baseline to 6.2 percent at week 12. Vehicle-treated patients also experienced 12-week reductions in oiliness and erythema (from 19.2 percent to 7.2 percent and 15.6 percent to 8 percent, respectively), suggesting that components of the vehicle contribute to these beneficial effects.27

It is important to clarify that, although its chemical structure is similar to that of the sulfonamide antibiotics, dapsone is distinctively different from the sulfonamides; It is classified as a sulfone.30 A history of allergic reaction to sulfonamide non-antibiotics or sulfonamide antibiotics or history of adverse reactions to sulfonamides does not predict cross-reactivity with other sulfa drugs.31

**Topical Dapsone Efficacy**

Dapsone 5% gel applied twice daily has been shown to decrease both the inflammatory and non-inflammatory lesions of acne vulgaris. In two 12-week, double-blind, randomized, parallel group, phase III studies conducted under identical protocols, a total of 3,010 patients age 12 or older were assigned to apply either dapsone gel 5% twice daily or vehicle gel to affected areas of the face.27 Pooled analysis of the data shows that treated patients experienced significantly greater reductions from baseline to 12 weeks in inflammatory, non-inflammatory, and total lesion counts com-
pared to controls; the greatest reduction was in inflammatory lesion counts—reduced by nearly half in treated patients (47.5 percent vs. 41.8 percent). Response to treatment was noted at week 2 and was maintained throughout the study. Treated patients achieved superior Global Acne Assessment Scores, regardless of whether baseline acne was more or less severe.

Long-term treatment is associated with similar efficacy and tolerability. In a one-year open-label, non-comparative trial of topical dapsone involving a total of 506 patients age 12 or older, patients applied dapsone twice daily for a mean of 253 days over the 12-month study period. Improvement in inflammatory lesions, evident by week 4, was more significant than improvement in non-inflammatory lesions. Lesion counts continuously decreased through month 6 and were maintained through 12 months. Twelve-month mean percent reduction in lesion counts from baseline was 58.2 percent for inflammatory lesions and 19.5 percent for non-inflammatory lesions. Although at month 3, 96 patients initiated concomitant systemic or topical acne therapy according to study protocols, ad hoc analysis of the data revealed no clinically apparent differences in lesion count reductions for this subpopulation at month 3 or 12. Treatment was well tolerated: 0.8 percent of patients withdrew due to lack of efficacy, while 2.2 percent withdrew due to an adverse event.

A combination trial compared dapsone alone to dapsone plus adapalene and dapsone plus benzoyl peroxide 4%, with the combination regimens found to provide greater mean percentage reduction in total lesion and in non-inflammatory lesion counts than dapsone alone. Of note, there was no statistically significant difference between topical dapsone alone versus the combination regimen for inflammatory lesions, indicating that topical dapsone alone is a powerful agent against inflammatory lesions. The use of topical dapsone along with topical adapalene was shown to provide a statistically significant reduction in the number of non-inflammatory lesions compared to dapsone plus benzoyl peroxide or dapsone plus vehicle, suggesting that the two agents work synergistically. Global Acne Assessment Score treatment success (defined as none or minimal disease) was significantly better for dapsone plus adapalene compared to dapsone plus vehicle.

Minimizing Costs and Maximizing Efficacy

Early and effective therapy for acne is essential to minimize the psychosocial impact of the disease and limit the risk for development of sequelae, such as scarring. At the same time, data confirm the need to identify treatment regimens that optimize efficacy and tolerability in order to promote therapeutic adherence. Additionally, the growing problem of bacterial resistance requires all healthcare providers to use antibiotics judiciously, particularly oral agents sometimes used for acne.

Given the chronicity of acne vulgaris, clinicians also have a responsibility to consider the costs of acne treatment to the individual patient as well as to the healthcare system overall. Costs to manage acne vulgaris are high. Just 10 years ago, five million prescriptions for oral antibiotics and 1.4 million prescriptions for isotretinoin were dispensed annually for the treatment of acne. Patient demand for acne therapy is expected to continue to increase in the coming years.

Topical and oral antibiotics are potentially low-cost and traditionally effective, but concerns about antibiotic resistance have limited their usefulness. The low financial cost of therapy may not justify the long-term cost to the healthcare system from increasing resistance.

Given these various practical and financial considerations, researchers have urged the development of non-antibiotic acne therapies, while data emphasize the importance of good tolerability. The relatively recent approval of dapsone gel may fulfill these therapeutic demands. The safety of topical dapsone is sufficiently obvious that the FDA has withdrawn the requirement for baseline blood monitoring (particularly G6PD screening). Trials confirm excellent tolerability of the new aqueous gel formulation, suggesting that patients will adhere to therapy and thus experience more
Topical Anti-inflammatory Therapy in Acne

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