The Building Blocks to Better Acne Treatment

The importance of the vehicle in protecting the skin barrier and maximizing the benefits of acne therapy.

BY EMIL A. TANGHETTI, M.D.

Approximately 85% of individuals between the ages of 12 and 24 years will experience acne vulgaris, the most common dermatological disorder. The disease also affects 8% of adults aged 25 to 34 years and 3% of persons 35 to 44 years of age. Although acne vulgaris affects an estimated 17 million people in the United States, more than 50 million people are estimated to be affected by some form of acne.[1,2]

ACNE TREATMENTS SHOULD BE BOTH EFFECTIVE AND WELL TOLERATED

Because of the prevalence and chronicity of acne, as well as its psychological impacts,[3] the availability of effective, well-tolerated treatments is critical. Although an acne treatment's efficacy may be foremost in the minds of dermatologists, its tolerability cannot be overlooked. Burning, dryness and peeling caused by acne treatments may be as bothersome to some patients as the acne blemishes themselves, and may result in non-compliance. This decreased compliance can lead to decreased efficacy.[4] The goal in acne therapy should be to identify the most effective regimen that is also well tolerated and easy to use, thereby promoting maximal patient compliance and an optimal outcome.

The use of specific vehicle excipients may improve the tolerability of standard acne treatments.[5,6] Certain moisturizing excipients improve treatment outcomes by addressing problems with barrier integrity — problems that are caused not only by ongoing disease, but also by the various acne treatments.[7] In this article, we'll discuss the role of specific moisturizing-vehicle excipients to improve barrier function and outcomes of acne treatment.

THE IMPORTANCE OF BARRIER FUNCTION

In the early 1950s, Irvin Blank conducted research that showed water was more important than oil content in maintaining the flexibility of the cornified epithelium.[8] Therefore, keeping skin healthy requires maintaining adequate water content in the stratum corneum.

Skin feels normal and healthy when the water content in the stratum corneum is 20% to 35%. However, when water content falls below 10%, xerosis develops. Xerosis is characterized by a stratum corneum that is thicker than normal, fissured, and disorganized. Lamellar bodies may play a key role in barrier function, providing the environment for maintaining essential intercellular lipids — sphingolipids, free sterols and fatty acids — to prevent excess water loss through evaporation.[9]

The epidermal barrier can be disrupted in several ways, including through the normal pathogenesis of acne. Extreme cold, low humidity or sunburn can affect the barrier, as can the use of soaps and surfactants. Diseases of the epidermis (atopic dermatitis, psoriasis) can be disruptive to the barrier. Linoleic acid deficiency, which is an important component in the pathogenesis of acne, also might cause barrier impairment. Downing proposed that when the follicular epithelium barrier was impaired by linoleic acid deficiency, other free fatty acids (products of bacterial lipase and sebocyte metabolism) were allowed to enter the epithelium and induce localized essential fatty acid deficiency.[10] Decreased levels of linoleic acid may also be implicated in the development of inflammatory damage and ductal hypercornification, and these acids may cause the influx of water that leads to increased colonization by *P. acnes*.[11,12,13]

Barrier integrity can be disrupted by acne treatments. For example, topical all-trans retinoic acid causes irritation of the skin. In fact, retinoic acid impairs the water barrier function of the stratum corneum, as evidenced by increased transepidermal water loss (TEWL).[7] Nonretinoid acne treatments may also impact barrier function. Irritation, burning, dry skin, and peeling associated with some of these treatments.[5,14,15,16]

BARRIER REPAIR REQUIRES INCREASING MOISTURE CONTENT

In order to repair the epidermal barrier, signals are transmitted to the intracellular machin-

The Pathogenesis of Acne

The multifactorial pathogenesis of acne involves:

(1) excess sebum production brought about by hormonal changes (primarily because of increased production of androgens just prior to the onset of puberty),
(2) abnormal desquamation of follicular keratinocytes,
(3) proliferation of *Propionibacterium acnes* within the follicle, and
(4) inflammation and immune responses caused by the production of proinflammatory molecules, including chemoattractants released by P acnes, which cause the migration of lymphocytes and neutrophils.[1,2]

Because of its ability to target the many factors that underlie acne pathogenesis, combination therapy has become a mainstay of acne treatment.

ery, initiating repair through four remoisturizing steps: (1) initiation of barrier repair, (2) alteration of the skin-surface moisture partition coefficient, (3) diffusion of moisture from the dermis to the epidermis, and (4) intercellular lipid synthesis. TEWL is the trigger for the physiological signaling that initiates lipid synthesis.[9]

Reconditioning of the epidermal barrier can occur by creating conditions that allow the stratum corneum to increase moisture content. Two mechanisms commonly used to rehydrate the stratum corneum are attracting water from viable skin layers through the use of humectants, and trapping moisture through the use of occlusives.[9]

HUMECTANTS

Humectants function by drawing water from the deeper layers of the epidermis and dermis into the stratum corneum. Naturally occurring humectants include glycosaminoglycans, such as hyaluronic acid; glycerin is an example of a synthetic humectant. Humectants alone are ineffective because they actually increase TEWL, especially when applied to skin with a damaged epidermal barrier. Humectants used in combination with occlusives provide optimal moisturization.[9]

OCCLUSIVES

Occlusives function by retarding the evaporation of water. In general, occlusives are oily substances that vary considerably in their effectiveness and tolerability. Although petrolatum is the most efficacious humectant, it is less tolerable than others because of its greasiness. Lanolin is also less tolerable because of its characteristic odor and the possibility of allergic contact dermatitis. Although mineral oil is frequently used, it reduces TEWL by only 30% and its greasiness makes it a poor option for acne patients already concerned about oily skin.[9]

The newest and most popular category of occlusive moisturizers is silicone, which includes the agents dimethicone and cyclomethicone. These occlusive agents are popular because they are hypoallergenic, noncomedogenic and lack any strong odor. Silicone is also used in combination with petrolatum because of petrolatum's efficacy and silicone's ability to reduce the greasiness of petrolatum.[9]

OCCLUSIVE/HUMECTANT COMBINATION

Because the pathogenesis of acne — and in some cases, the acne treatment itself — leads to barrier impairment, the most advantageous dermatologic vehicle should aid in the reconditioning of the epidermal barrier. The humectant glycerin and the occlusive dimethicone are excipients capable of helping to recondition the epidermal barrier.[9] There is now available a clindamycin 1%/benzoyl peroxide 5% with a vehicle that contains these excipients (Duac). This formulation has been tested for its effect upon the tolerability of acne treatments.[5,17]

VEHICLE MAKES A DIFFERENCE

Two reports examined the tolerability of two water-based clindamycin 1%/benzoyl peroxide 5% gels that were identical except for the vehicle. Fagundes et al reported the findings of a randomized, evaluator-blinded, split-face study comparing the tolerability of 1% clindamycin/5% benzoyl peroxide/glycerin/dimethicone with 1% clindamycin/5% benzoyl peroxide (BenzaClin). As called for in each product's prescribing information, 1% clindamycin/5% benzoyl peroxide/glycerin/dimethicone was used once daily in the evening, and 1% clindamycin/5% benzoyl peroxide was used twice daily, once in the morning and once in the evening. There was a 2-week washout period and a 1-week treatment period. Of the 62 enrolled subjects, 61 completed the study. Local tolerance (erythema, peeling and dryness) was graded on a scale of 0 to 3 by a blinded evaluator at baseline and after 1 week. In addition, subjects used a questionnaire after the first and last applications to rate local tolerance symptoms of burning, stinging, and itching, as well as product preference.[5]

The formulation containing the glycerin and dimethicone moisturizers was better tolerated. There was significantly less peeling ($p = 0.045$), dryness ($p = 0.059$) (based on blinded evaluator scores), and burning ($p = 0.034$) (based on patient questionnaire responses; data not shown) compared with 1% clindamycin/5% benzoyl peroxide without moisturizers.

In another study, the local tolerability of a retinoid was compared with the local tolerability of the retinoid tazarotene (Tazorac) plus a 1% clindamycin/5% benzoyl peroxide/glycerin/dimethicone. In this multicenter, randomized, double-blind, parallel-group study, 121 subjects were evaluated throughout a 12-week period. The efficacy of the combination therapy was statistically superior. The group receiving the combination regi-

Steps Toward Remoisturization

1. **Initiation of barrier repair.**
2. **Alteration of the skin-surface moisture partition coefficient.**
3. **Diffusion of moisture from the dermis to the epidermis.**
4. **Intercellular lipid synthesis.**

Table1: Patients With Adverse Events Probably or Definitely Related to Study Treatment

Adverse Events	Tazarotene alone (N =61)	Tazarotene + clindamycin/benzoyl peroxide (N =60)	Between-group significance
Peeling	\\\\\\\\\\ (18%)	\\\\\ (10%)	NS
Burning	\\\\\\\ (13%)	\\\\\\\ (13%)	NS
Redness/erythema	\\\\\\ (12%)	\\\\\\\ (13%)	NS
Dryness	\\\\\\ (12%)	\\\\\ (8%)	NS
Facial discomfort	\\ (3%)	\\\ (5%)	NS
Itching/pruritus	\\ (3%)	\\\ (5%)	NS
Oiliness	\ (2%)	\ (2%)	NS
Facial irritation	(0%)	\ (2%)	NS

NS =not significant.

men demonstrated equal, if not better, tolerability as well, which was an unexpected result: investigators anticipated seeing increased dryness and skin irritation when combining these two agents. The incidence of most local side effects was about equal (≤2% difference), but the incidence of peeling and dryness was lower (although not statistically significantly so) at 12 weeks with the combination than with the retinoid alone (10% versus 18% for peeling and 8% versus 12% for dryness.) [18] *(See Table 1).* A post-hoc subanalysis of the study data found that the incidence of peeling was significantly less ($p < 0.05$) in the combination treatment group than in the monotherapy group at week four, a time when retinoid-associated dryness and irritation is typically highest.[19] Thus, the combination therapy would likely improve patient compliance, especially at this critical time in the treatment cycle.

PROTECTING THE BARRIER

The epidermal barrier can become impaired through the normal pathogenesis of acne and can become damaged as a result of acne treatment.[7] The reconditioning of the epidermal barrier of the stratum corneum requires alteration of the environment to retard TEWL. Such an environment can be created by using humectants in combination with occlusives.[9]

Currently, combination therapy is the favored approach for acne treatment. Knowledge of the combined agents' interactions and tolerability is critical, especially during the maintenance phase of treatment. Local side effects caused by disruption of the epidermal barrier may discourage treatment compliance, leading ultimately to treatment failure. By including moisturizing excipients in topical therapy formulations, barrier integrity is improved, tolerability is maximized, and treatment outcome can be optimized. ■

Dr. Tanghetti is a Clinical Professor at the University of California Davis and practices dermatology and laser surgery.

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