Acne Vulgaris and the Epidermal Barrier

Is Acne Vulgaris Associated with Inherent Epidermal Abnormalities that Cause Impairment of Barrier Functions? Do Any Topical Acne Therapies Alter the Structural and/or Functional Integrity of the Epidermal Barrier?

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Abstract

Acne vulgaris is a common dermatological disorder that predominantly affects teenagers, but can also affect preadolescents and post-teen individuals. Despite the fact that acne vulgaris is the most common skin disorder encountered in ambulatory dermatology practice in the United States, there has been limited research on the epidermal permeability barrier in untreated skin of people with acne vulgaris and also after use of acne therapies. This article reviews the research results and discusses the available literature on this subject area. The importance of proper skin care as a component of the management of acne vulgaris is supported by the information that is currently available.

Background

Unlike in atopic dermatitis, epidermal barrier dysfunction is not what usually comes to mind when one is asked to describe or list cutaneous abnormalities associated with acne vulgaris (AV). Although more studies are needed, there is a body of literature that supports the concept that AV is associated with inherent abnormalities in epidermal barrier functions. In addition, some therapies used to treat AV can induce alterations within the epidermis that can lead to changes that disrupt some of the normal physiological functions of the epidermis, including the stratum corneum (SC). In the case of AV, one needs to also consider the follicular epithelial barrier, which is directly involved with changes that occur during both comedogenesis, and in stages of inflammation, especially with follicular rupture.

Is There a Connection Between Specific Alterations in the Follicular Epidermis and the Development of Acne Lesions?

Alterations in follicular keratinization are integral components of the pathogenesis of AV and occur in the subclinical stages of acne lesion formation (microcomedo formation).[1] Filaggrin is a key protein in epidermal differentiation and contributes to the structural and functional integrity of the SC. Within acne lesions, there is an increase in filaggrin expression in keratinocytes lining the follicle wall.[2] In addition, *Propionibacterium acnes* has been shown to increase filaggrin expression in cultured keratinocytes and also in explants of human skin.[3] Importantly, it is not known if the changes in filaggrin expression noted in AV are primary or secondary events.[4] An interesting hypothesis was raised by the results of a study examining filaggrin mutations in patients with xerosis.[5] Study subjects were queried for a history of skin disorders and signs and symptoms of dry skin. Whole blood samples were obtained with DNA extracted and analyzed for null mutations in filaggrin. The odds ratio of having AV was 0.3 in the subjects carrying one copy of the null mutation. Although this was not

statistically significant, and a history of AV was self-reported, the authors hypothesized that a null mutation in the filaggrin gene could be protective against AV.[4] An additional study tested this hypothesis in a cohort of Singaporean Chinese patients presenting with AV where they evaluated and performed screening for 22 types of filaggrin null mutations in 287 patients with AV and in more than 400 control subjects. A comparative analysis failed to identify a statistically significant negative association between AV and filaggrin mutations in this population. The suggested concept that a reduced ability to express filaggrin due to genetic mutation correlates directly with a lesser ability to form acne lesions is interesting; however, studies to date do not provide cogent evidence to clearly support this hypothesis.

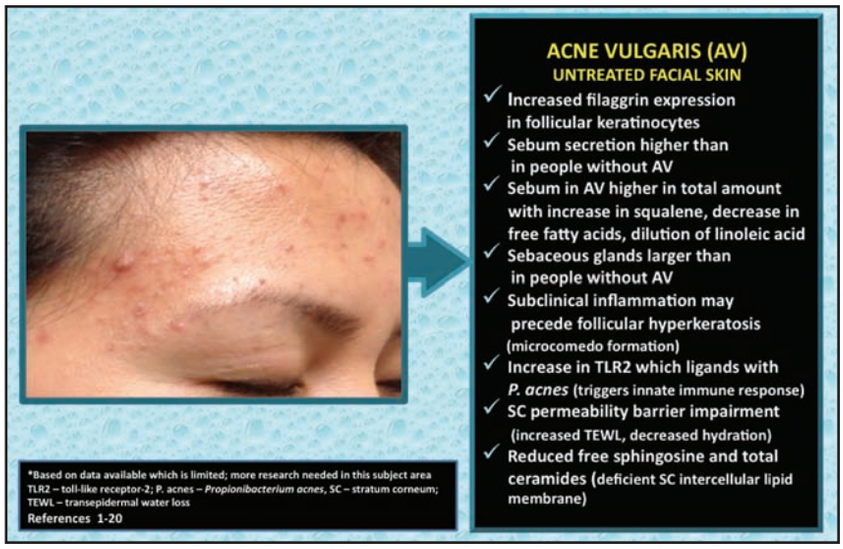

Figure 1. Observations in facial skin in acne vulgaris. Focus on findings that may impact epidermal barrier functions*

Epidermal Permeability Barrier Characteristics and Acne Vulgaris

In AV, the barrier functions of both the epidermis of the exposed skin surface and that which comprises the follicular epithelial lining are significant to consider. Both may be involved in pathophysiological mechanisms associated with AV or with impaired physiological properties of the SC, such as regulation of water flux and/or epidermal hydration. Figure 1 depicts findings that may correlate with epidermal barrier functions in acne-prone facial skin of individuals with AV.

Surface epidermis. The facial skin of patients with AV differs from normal skin of people without AV in several ways. Although exceptions may exist, sebum production is higher and the size of sebaceous glands are larger in people with acne-prone facial skin who are already known to have AV as compared with the facial skin of people without AV.[6] In addition, the normal-appearing facial skin of patients with AV can exhibit specific perifollicular and follicular patterns of inflammatory cellular infiltration and inflammatory marker expression that are very similar to the patterns observed in early acne papules present for ≤6 hours.[7] These findings and the observations of others suggest that subclinical inflammation is present early in the emergence of acne lesion development even in the absence of follicular hyperkeratinization.[7–11] As more attention is now being given to the role of various barrier functions of the epidermis (especially the SC) in different disease states, it is important to know if there are any inherent structural or functional epidermal barrier aberrations in AV that may be important to address therapeutically, especially as certain medications used to treat AV can alter some epidermal properties.[12]

Yamamato et al[13] examined sebum secretion, SC lipids, transepidermal water loss (TEWL), and conductance within the SC of male patients with mild-to-moderate AV (n=36), age range 14 to 26 years, and age-matched male control subjects (n=29).[13] They found that the patients with AV exhibited markedly higher sebum secretion and greater TEWL and markedly decreased SC conductance (corneometry testing). The combined findings of higher TEWL and lower SC hydration (decreased conductance) noted in the patients with AV compared to controls supports SC permeability barrier impairment associated with AV. In addition, acne patients had significantly reduced free sphingosine and total ceramides in their SC, which is indicative of a deficient intercellular lipid membrane and correlates with impairment of the SC permeability barrier. The increase in TEWL and decrease in SC hydration (conductance) were of greater magnitude in patients with AV of moderate severity as compared to those with mild acne severity and

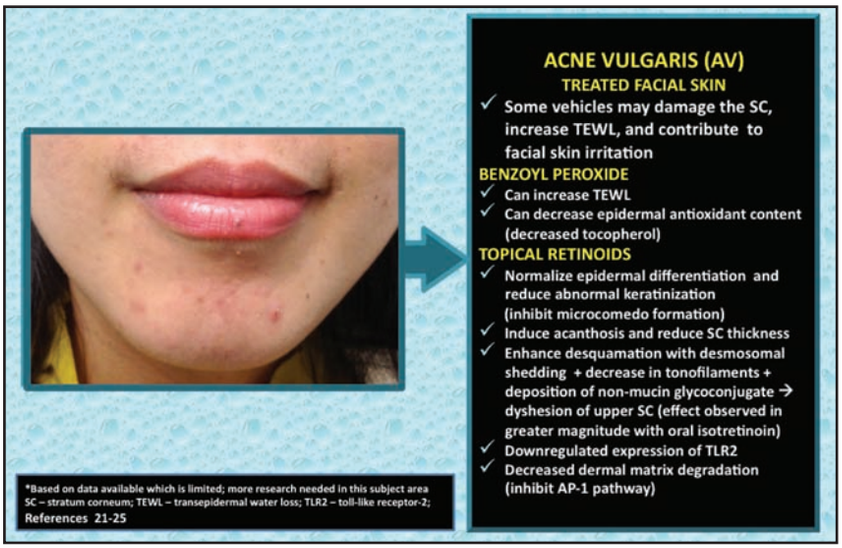

Figure 2. Observations in facial skin in acne vulgaris. Focus on findings that may impact epidermal barrier functions*

as compared to normal control subjects.[13] These latter findings suggest that the degree of SC permeability barrier impairment correlates directly with the severity of AV.[13]

Follicular epidermis (epithelium). In addition to the exposed epidermis of the integumentary surface, the follicular epithelium also contributes to cutaneous barrier functions. Loss of physical barrier integrity sometimes occurs when the intensity of inflammation reduces the strength of the follicular wall. In AV, the proliferation of *P. acnes* within the follicle initiates several inflammatory cascades related to innate, acquired, and humoral immunological responses; direct inflammatory effects of enzymes (i.e., lipases, matrix metalloproteases); and inflammation triggered by catalytic breakdown products.[14,15] When intrafollicular and perifollicular inflammatory processes markedly intensify, attenuation of the follicular wall can lead to various degrees of rupture with subsequent leakage of sebum, keratin, bacteria, and cellular debris into the dermis. The presence of these substances, which are foreign to the dermis, provokes further inflammation that is deeper, eventuating in the emergence of a nodular or nodulocystic acne lesion.

It is important to differentiate the lipids and other components of the intercellular lipid membrane of the SC, the core structural component of the epidermal permeability barrier, from the lipids and other components of sebum that reside in the pilosebaceous follicle. Lipids in sebum are distinct from the SC lipids.[12,16–18] Also, the content of sebum in patients with AV may be different from individuals without AV. In a small study of males, age range 15 to 25 years, with AV (n=9) and without AV (n=9), the sebum content differed between the two groups.[18] In the males with AV, the sebum quantity was 59-percent higher, squalene was increased approximately two-fold, and free fatty acids were decreased. A relative essential fatty acid deficiency has also been discussed related to pilosebaceous unit contents.[19,20] In AV, increased sebum flow dilutes linoleic acid resulting in a relative deficiency which may play a role in comedogenesis.

How Do Some Topical Acne Therapies Alter Epidermal Barrier Functions?

Some topical medications, systemic medications, and physical procedures used to treat AV and/or acne scarring can lead to alterations in SC permeability barrier function based on documentation of increased TEWL and in some cases visible signs of xerosis. Increases in TEWL have been reported with benzoyl peroxide, tretinoin, tazarotene, and isotretinoin.[21–25] See Figure 2, which depicts findings in acne-treated skin that can be related to epidermal barrier functions. Various efforts have been made to minimize impairments of the SC permeability barrier induced by acne therapies.

Benzoyl peroxide. Benzoyl peroxide (BP) has been used extensively for the treatment of AV for more than six decades, offering the ability to markedly reduce counts and suppress the proliferation of *P. acnes*, including inhibition of the emergence of antibiotic-resistant strains of the organism.[26–28]

It is well known that BP can cause cutaneous irritation in some patients, which appears to be dependent on concentration, vehicle formulation, type of adjunctive skin care, other concomitant acne medications, and the inherent skin sensitivity of the individual. Allergic contact dermatitis from BP is much less common than

irritant dermatitis. Despite the widespread use of BP over many years for AV in both prescription and over-the-counter formulations, there is a paucity of data on what epidermal effects BP may induce, although it has been shown to exhibit some "keratolytic" activity.[28]

In one study, investigators attempted to offset the 1.8-fold increase in TEWL from application of BP 10% by topical administration of alpha-tocotrienol, an isomer of vitamin E.[22] The changes induced by BP suggest that this agent induces damage to the SC lipid bilayer, which results in an increase in TEWL and also creates some impairment of the epidermal antioxidant barrier by reducing levels of vitamin E. Application of alpha-tocotrienol did mitigate BP-induced peroxidation of SC lipids, but did not offset the increase in TEWL.[22]

Topical retinoids. Since the availability of topical tretinoin in the United States in 1971, topical retinoid therapy has been a major part of the foundation of therapy for AV.[26,29] The subsequent availability of adapalene in 1996 and tazarotene in 1997, both in cream and gel formulations and in two different concentrations, expanded the choices available to clinicians when selecting a topical retinoid for treatment of AV. The efficacy and overall favorable safety of the available topical retinoids used to treat AV is well established, with use of a topical retinoid suggested from the outset when AV develops in the preteen or early teenage years, especially as many cases exhibit multiple comedonal lesions at this point in time. Application of a topical retinoid each day reduces microcomedo formation and stopping the topical retinoid leads to an increase in microcomedo formation within days to a few weeks. As more inflammatory lesions emerge over time, use of a topical retinoid is still suggested as these agents reduce both comedonal and inflammatory acne lesions related to multiple modes of action.[26–29] Depending on the severity of AV, use of a topical retinoid in combination with other topical agents, and also in combination with oral therapy for AV, supports the foundation of the global guidelines that have been published on acne management.[26,29]

The ability of a topical retinoid to inhibit microcomedo formation, decrease both comedones and inflammatory lesions of AV, interfere with dermal matrix dedradation, and promote remodeling of upper dermal collagen and elastic tissue reflect a variety of modulating effects on different cellular mechanisms in skin.[29–31] These include alterations in epidermal keratinization and differentiation, downregulation of toll-like receptor-2 (TLR2) expression, decrease in dermal matrix degradation that is promoted by chronic photodamage, and alteration of various transcription factors involved in patterns of cutaneous inflammation.[29–31] After initiation of treatment with a topical retinoid, many patients develop visible dermatitis changes (erythema, fine scaling, desquamation) usually within the first two weeks, referred to as "retinoid dermatitis." These skin changes are almost always transient and diminish with continued application over the first 2 to 4 weeks of use.

Topical retinoids have been shown to exhibit effects on various targets, cells, and pathways involved in the normal physiology of the epidermis and dermis and on mechanisms involved in the pathogenesis of AV. As a result of this broad range of effects in skin, it has been stated that the "separation of therapeutic from toxic effects of topical and systemic retinoids may be difficult, because the same cellular mechanisms are operative."[31] In both animals and humans, topical retinoids induce acanthosis, hypergranulosis, and a relative decrease in SC thickness, likely related to augmented cell turnover.[31] In mouse skin, topical retinoid application increased epidermal labeling index, with a plateau effect noted after approximately one week as acanthosis peaks. After approximately two weeks, acanthosis reverts partially toward baseline followed by the reaching of a steady-state equilibrium, which persists thereafter.[31] Interestingly, this 2- to 3-week time course of epidermal alteration prior to stabilization correlates with the time course of retinoid dermatitis. This observation suggests that the visible changes of retinoid dermatitis that occur early after starting topical retinoid therapy at least partially reflect the therapeutic mechanisms of action that the topical retinoid initiates within the epidermis.

As topical retinoids enhance desquamation with a reduction in SC thickness and function, alteration in permeability barrier function is a likely sequelae.[32] Concurrent moisturizer use to pre-emptively reduce the SC permeability barrier impairment induced by topical retinoid application has been evaluated with a reduction in signs and symptoms associated with retinoid dermatitis without an apparent loss of efficacy.[33] Moisturizer application to reduce the signs and symptoms of retinoid dermatitis after they develop has also been reported and is often self-initiated by patients.[34] In a study of tretinoin

cream 0.025% in women with photoaging (n=50) between the ages of 35 and 55 years, application of a moisturizer for two weeks before and during tretinoin treatment prevented an increase in TEWL.[21]

Topical retinoid application also induces desmosomal shedding within the stratum spinosum, a decrease in tonofilaments, and some deposition of nonmucin glycoconjugates, leading to SC loosening and upper epidermal dyshesion.[31] The magnitude of these effects are less than with oral retinoids, which are associated with a greater magnitude of skin fragility.[31] Nevertheless, the changes induced by topical retinoid use, which promote epidermal dyshesion, explain the superficial denudation of skin reported by patients who undergo tape striping-type techniques to remove unwanted hair usually on the upper lip or eyebrow region.

Changes in the SC permeability barrier associated with both topical and oral retinoid therapy do not appear to be related to any reduction in SC lipids comprising the intercellular lipid membrane of the SC.[31]

Topical and oral antibiotics. Alteration of the cutaneous flora by antibiotics, either topical or oral, changes the microbiome.[27] This can result in physiological changes within the epidermis as the spectrum of organisms comprising the skin flora is altered. The prevalence of resistant organisms, such as *P. acnes* and *Staphylococcus epidermidis* also increases, as does colonization of the nasopharyngeal region with bacteria that may potentially be pathogenic to the patient or others (i.e., *Streptococcus pyogenes*).[27]

Microdermabrasion. Although microdermabrasion is a superficial procedure and not a topical medication, it is included here as it is an office-based procedure that is commonly used in some clinical practices and also at spas and salons. Therefore, many patients who are using current treatment for AV may undergo the procedure and not be aware that it could potentially predispose the patient to cutaneous irritation associated with topical agents used for AV. Two studies have documented a transient increase in TEWL and increased SC hydration following microdermabrasion. TEWL evaluations were completed following microdermabrasion with either sodium chloride or aluminum oxide crystals.[35] Both TEWL and SC hydration were significantly increased 24 hours following microdermabrasion with both types of crystals. TEWL returned to baseline at seven days in both groups, with SC hydration maintained in the sodium chloride group. A second study demonstrated that TEWL increased immediately after diamond microdermabrasion, which remained significantly increased at 24 hours and returned to baseline by Day 2.[36]

TEWL was assessed in patients with AV (n=8) treated on two occasions, two weeks apart, with photodynamic therapy using methylaminolevulinic acid and red light (MAL-PDT) at baseline, 4, 8, and 12 weeks following the second treatment.[37] These outcomes were compared to TEWL measurements obtained from untreated acne subjects (n=8). No significant differences in TEWL were noted between the treated and untreated groups or at any time point compared to baseline. These investigators concluded that MAL-PDT using red light did not adversely alter SC permeability barrier function as measured by TEWL.

Summary

Although data are somewhat limited, AV does appear to be associated with some inherent epidermal barrier impairments, with consideration given to characteristics of both the follicular SC and the surface SC. Although follicular keratinocytes in acne lesions exhibit increased filaggrin expression, the relevance of this in acne pathogenesis is not entirely clear. Acne-prone facial skin in individuals with AV is associated overall with higher magnitudes of sebum production and larger sebaceous glands as compared to facial skin of individuals without AV.

In addition, there are some data suggesting that SC permeability barrier impairment occurs inherently in facial skin of patients with AV, the magnitude of impairment correlates with severity of AV, and decreased levels of free sphingosine and total ceramides suggest some deficiency of the intercellular lipid membrane.

In addition, certain medications used to treat AV can cause alterations in SC integrity and function, either via the active ingredient, the vehicle, or both, which can result in signs and symptoms of cutaneous irritation. . Providing specific skin care recommendations, including product selection and proper use, is an important part of the management of AV and may adjunctively augment the efficacy of topical medications in reducing acne lesions. More research is needed in this very important and clinically relevant area related to AV and its management.

References

1. Heughebaert C, Shalita A. Comedogenesis. In: Shalita AR, Del Rosso JQ, Webster GF, eds. *Acne Vulgaris.* New York: Informa

Healthcare; 2011:28–42.
2. Kurokawa I, Mayer-da-Silva A, Gollnick H, et al. Monoclonal antibody labeling for cytokeratins and filaggrin in the human pilosebaceous unit of normal, seborrhoeic and acne skin. *J Invest Dermatol.* 1988:91:566–571.
3. Jarrousse V, Castex-Rizzi N, Khammari A, et al. Modulation of integrins and filaggrin expression by *Propionibacterium acnes* extracts on keratinocytes. *Arch Dermatol Res.* 2007;299:441–447.
4. Common JE, Brown SJ, Haines RL, et al. Filaggrin null mutations are not a protective factor for acne vulgaris. *J Invest Dermatol.* 2011;131(6):1378–1380.
5. Sergeant A, Campbell LE, Hull PR, et al. Heterozygous null alleles in filaggrin contribute to clinical dry skin in young adults and the elderly. *J Invest Dermatol.* 2009;129:1042–1045.
6. Plewig G, Kligman AM. Sebaceous glands. In: Plewig G, Kligman AM, eds. *Acne and Rosacea*, 3rd ed. Berlin, Germany: Springer-Verlag; 2000:70.
7. Jeremy AHT, Holland DB, Roberts SG, et al. Inflammatory events are involved in acne lesion initiation. *J Invest Dermatol.* 2003;121:20–27.
8. Holland DB, Jeremy AHT. The role of inflammation in the pathogenesis of acne and acne scarring. *Semin Cutan Med Surg.* 2005;24:79–83.
9. Kim J, Ochoa M-T, Krutzik SR, et al. Activation of toll-like receptor 2 in acne triggers inflammatory cytokine responses. *J Immunol.* 2002;169:1535–1541.
10. Norris J, Cunliffe WJ. A histological and immunocytochemical study of early acne lesions. *Br J Dermatol.* 1988;118:651–659.
11. Layton AM, C, Cunliffe W, Ingham E. Immunohistochemical investigation of evolving inflammation in lesions of acne vulgaris. *Exp Dermatol.* 1998;7:191–197.
12. Del Rosso JQ, Levin J. The clinical relevance of maintaining the functional integrity of the stratum corneum in both healthy and disease-affected skin. *J Clin Aesthet Dermatol.* 2011;4(9):22–42.
13. Yamamoto A, Takenouchi K, Ito M. Impaired water barrier function in acne vulgaris. *Arch Dermatol Res.* 1995;287(2):214–218.
14. Krishna S, Kim C, Kim J. Innate immunity in the pathogenesis of acne vulgaris. In: Shalita AR, Del Rosso JQ, Webster GF, eds. *Acne Vulgaris.* London: Informa Healthcare; 2011:12–27.
15. Webster GF, Kim J. Immunology of acne. In: Gaspari AA, Tyring SK, eds. *Clinical and Basic Immunodermatology.* London: Springer-Verlag; 2008:217–222.
16. Nelson A, Thiboutot DM. Sebum. In: Shalita AR, Del Rosso JQ, Webster GF, eds. *Acne Vulgaris.* London: Informa Healthcare; 2011:3–11.
17. Pappas A. Epidermal surface lipids. *Dermatoendocrinol.* 2009;1(2):72–76.
18. Pappas A, Johnsen S, Liu JC, et al. Sebum analysis of individuals with and without acne. *Dermatoendocrinol.* 2009;1(3):157–161.
19. Downing D, Stewart M, Wertz P, Strauss J. Essential fatty acids and acne. *J Am Acad Dermatol.* 1986;14:221–225.
20. Schmuth M, Elias PM, Williams ML. Pathogenesis of barrier abnormalities in disorders of conification. In: Elias PM, Feingold KR, eds. *Skin Barrier.* New York: Taylor & Francis; 2006:469–510.
21. Draelos ZD, Ertel KD, Berge CE. Tretinoin facilitating facial retinization through barrier improvement. *Cutis.* 2006;78:275–281.
22. Weber SU, Thiele JJ, Han N, et al. Topical tocotrienol supplementation inhibits lipid peroxidation but fails to mitigate increased transepidermal water loss after benzoyl peroxide treatment of human skin. *Free Radic Biol Med.* 2003;34:170–176.
23. Herane MI, Fuenzalida H, Zegpi E, et al. Specific gel-cream as adjuvant to oral isotretinoin improved hydration and prevented TEWL increase—a double-blind, randomized, placebo-controlled study. *J Cosmet Dermatol.* 2009;8(3):181–185.
24. Stucker M, Hoffman M, Altmeyer P. Instrumental evaluation of retinoid-induced skin irritation. *Skin Res Technol.* 2002;8:133–140.
25. Tagami H, Tadaki T, Obata, M, et al. Functional assessment of the stratum corneum under the influence of oral aromatic retinoid (etretinate) in guinea-pigs and humans. Comparison with topical retinoic acid treatment. *Br J Dermatol.* 1992;127:470–475.
26. Gollnick H, Cunliffe W, Berson D, et al. Management of acne: a report from the Global Alliance to improve outcomes in acne. *J Am Acad Dermatol.* 2003;49(Suppl 1):S1–S38.
27. Del Rosso JQ. Topical antibiotics. In: Shalita AR, Del Rosso JQ, Webster GF, eds. *Acne Vulgaris.* London: Informa Healthcare; 2011:95–104.
28. Tanghetti EA, Popp KF. A current review of topical benzoyl peroxide: new perspectives on formuation and utilization. *Dermatol Clin.* 2009;27:17–24.
29. Hui A, Shalita A. Topical retinoids. In: Shalita AR, Del Rosso JQ, Webster GF, eds. *Acne Vulgaris.* London: Informa Healthcare; 2011:86–94.
30. Wolf JE Jr. Potential anti-inflammatory effects of topical retinoids and retinoid analogues. *Adv Ther.* 2002;19(3):109–118.
31. Elias PM. Epidermal effects of

retinoids: supramolecular observations and clinical implications. *J Am Acad Dermatol.* 1986;15(4 Pt 2):797–809.
32. Tagami H. Location-related differences in structure and function of the stratum corneum with special emphasis on facial skin. *International Journal of Cosmetic Science.* 2008;30:413–434.
33. Tanghetti EA. Cleanser and moisturizer use with tazarotene 0.1% cream for acne vulgaris. Poster presented at Fall Clinical Dermatology. Las Vegas, Nevada; October 2010.
34. Feldman SR, Chen DM. How patients experience and manage dryness and irritation from acne treatment. *J Drugs Dermatol.* 2011;10(6):605–608.
35. Ragan P, Grimes P. Skin barrier changes induced by aluminum oxide and sodium chloride microdermabrasion. *Dermatol Surg.* 2002;28:390–393.
36. Hei Sung Kim HS, Sook Hee Lim SH, Ji Youn Song JY, et al. Skin barrier function recovery after diamond microdermabrasion. *J Dermatol.* 2009;36:529–533.
37. Faurschou A, Wiegell SR, Wulf HC. Transepidermal water loss after photodynamic therapy, UVB radiation and topical corticosteroid is independent of inflammation. *Skin Res Technol.* 2007;13:202–206.

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