The treatment paradigm in acne has changed very little in recent years, and yet there still seems to be confusion about the utility of certain agents. Ahead, I will examine common claims regarding agents such as retinoids and benzoyl peroxide and attempt to separate fact versus the fiction in acne care.

THE UTILITY OF RETINOIDS

The traditional dogma when it comes to retinoids is that they are excellent “comedone busters” but are not as effective for inflammatory lesions, or papules and pustules. But a survey of published data and clinical trials suggest that retinoids may actually have a much broader use and can be used effectively for all types of acne lesions.

In clinical trials, comedonal (or “non-inflammatory”) lesions are evaluated separately from inflammatory lesions. Open comedones (blackheads) and closed comedones (whiteheads) are considered noninflammatory lesions.1 There are also various types of inflammatory acne lesions.1-4 For example, cysts are deep lesions containing substantial amounts of fluid that are severely inflamed and can be extremely painful. These lesions contain substantial amounts of fluid.1 Pustules are round, pus-filled lesions resulting from rupture of the follicular sac,1 whereas papules are smaller, slightly raised lesions approximately 5mm or less in diameter.1 As a result of inflammatory acne, hyperpigmentation (discoloration of the skin) and scarring can result.1,5,6

Topical retinoids such as adapalene, tretinoin, and tazarotene have comedolytic and anti-inflammatory effects, but no direct impact on P. acnes. Therefore, the combination of topical retinoid and topical antimicrobial is warranted is often utilized for moderate to severe acne.

Topical retinoids offer the potential to enhance follicular penetration when used with topical antibiotics.7 The activity of the combination clears more lesions more rapidly than antimicrobial therapy alone. Topical retinoids also contribute to the maintenance of remissions.

Retinoids also have anti-inflammatory properties. They down regulate toll like receptor 2, P. acnes induct pro-inflammatory cytokines, TNF-alpha and IL-1B, through TLR-2.8,9 Retinoids are also known to inhibit AP-1 (activator protein transcription factor), which is activated by inflammatory cytokines.10

Topical tretinoin. Topical tretinoin has been the cornerstone of acne treatment for more than 30 years.11 The origi-
nal tretinoin formulations caused pustular flaring and skin irritation, including erythema, desquamation, burning, and pruritus shortly after application.11-13 To overcome these problems, tretinoin was reformulated in a porous microsphere copolymer. The microsphere particles are localized in the follicle, where they release tretinoin in a slow, controlled manner.13,14 concentrations of tretinoin on the skin are reduced, thereby reducing inflammation.13

Efficacy results have shown that topical tretinoin can indeed be effective for acne vulgaris. In one study, tretinoin (Atralin Gel 0.05%) (Medicis/Valeant) was found to be superior to the vehicle gel for inflammatory, noninflammatory, and total lesions.15 Moreover, the difference between Atralin Gel 0.05% and vehicle gel was statistically significant for inflammatory lesions, noninflammatory lesions and total lesion count.15

Adapalene. Adapalene is a newer topical retinoid. A recent meta-analysis of five well-controlled studies involving more than 900 patients found the efficacy of adapalene 0.1% gel (Differin, Galderma) to be comparable to that of tretinoin 0.025% gel (Retin-A, Valeant).16 Other clinical trials found that adapalene 0.3% gel was superior to adapalene 0.1% gel in the treatment of moderate to moderately severe acne, while retaining comparable safety and tolerability.17-18 Studies in patients without acne found that adapalene 0.1% gel was less irritating than tretinoin, tretinoin 0.04% microsphere gel, and tazarotene 0.05% (Tazorac, Allergan) and 0.1% gel.19-22 In a recent split-face comparison, subjects with healthy skin applied 0.3% adapalene gel to one side of the face and tazarotene 0.0.5% cream to the other side once daily after cleansing for a total of three weeks; tolerability ratings of erythema, scaling, dryness, and stinging/burning for both products were similar; however, subject responses to a six-question survey regarding cosmetic acceptability favored adapalene, and 70 percent of patients reported that adapalene gel was easier to spread than the tazarotene cream.23

In a 12-month study, the median percent reductions in inflammatory, non-inflammatory, and total lesions in patients using adapalene 0.3% gel were 61.9 percent, 54.5 percent, and 56.6 percent, respectively.24 Tazarotene. In a 12-week, randomized, comparative trial, once-daily application of tazarotene 0.1% gel microsphere was associated with a significantly greater rate of treatment success, defined as ≥50 percent global improvement, than tretinoin 0.1% microsphere gel (67 percent vs 49 percent, P=0.03) and significantly greater reductions in disease severity (36 percent vs 26 percent, P=0.02).25 Preliminary results in the first 87 participants in a 15-week, multicenter, double-blind, randomized trial in patients with moderately severe acne suggest that tazarotene 0.1% gel applied every other day on alternate evenings is as effective as adapalene 0.1% gel applied every evening. Both achieved comparable reductions in overall disease severity, and numbers of inflammatory and noninflammatory lesions.26 The local tolerability of tazarotene 0.1% gel was comparable to that of 0.1% tretinoin 0.1% microsphere gel and adapalene 0.1% gel.25,26 A meta-analysis of data from six randomized comparative trials in which patients used tazarotene 0.1% gel or cream once daily for 12 weeks showed that overall, tolerability was better with use of the cream rather than the gel.27

Another study found that patients receiving tazarotene foam 0.1% (Fabior, Stiefel/GSK) were clear/almost clear with 2-grade improvement, as well as lesion reduction at week 12.28

**BENZOYL PEROXIDE:**

YOUR GRANDFATHER’S ACNE TREATMENT?

Benzoyl peroxide (BPO) has been a standby treatment for acne for so many years that a perception seems to have taken hold that it is outdated. The reality, however, is that BPO has a central role in acne treatment. In fact, it plays multiple roles, given the range of formulations available.

BPO is bactericidal against *P. acnes* that also has mild comedolytic action.11 It may be used alone or in combination
with topical antibiotics to increase the effectiveness of topical antibiotics and reduce the development of resistance. BPO is also used in combination with topical retinoids. Local side effects can occur, however, the use of lower concentration formulations may result in less irritation.

BPO is available in various potencies, including 2.5%, 5%, and 10%. However, when it comes to the reduction of inflammatory lesions, twice-daily application of 2.5% may be all that’s required. In one study comparing treatment with all three potencies, the 2.5% BPO gel reduced the anaerobic population by 97 percent after twice-daily treatments for one week and by 99 percent after two weeks.

BPO has also been shown to be effective when combined with clindamycin phosphate. One study found statistically significant efficacy of clindamycin phosphate 1.2%-BPO 2.5% gel (Acanya, Medics/Valeant) over active ingredients and vehicle for inflammatory lesions, noninflammatory lesions, and total lesions. It has also demonstrated efficacy over clindamycin monotherapy by a significant margin.

Although this combination has shown to be effective, antibiotic resistance has become an increasingly important topic to dermatologists. For example, the rapid increase in the number of patients with community-acquired MRSA skin and soft tissue infections (SSTIs) has been well documented. Dermatologists use a variety of antibiotics for patients with SSTIs, but resistance to antibiotics has been linked to wide-availability and over-prescribing of the drugs.

While the lay press has sensationalized the issue with reports of “flesh-eating bacteria,” antibiotic resistance is such a problem today that efforts have turned from treating to preventing infections. Thus, prudent antibiotic stewardship is an important element of dermatology practice.

Another common BPO combination is adapalene 0.1%-BPO 2.5% gel (Epiduo, Galderma). In one study, total P. acnes CFUs were reduced by 88.3 percent at two weeks and 96.9 percent at four weeks in patients receiving adapalene 0.1%-BPO 2.5% gel. All reductions in bacterial CFUs were statistically significant from baseline (P<.001).

BPO washes have also shown some efficacy, particularly in the reduction of P acnes counts. A poster presented during the 2007 Hawaii Dermatology Seminar assessed the effect of BPO 6% cleanser on P. acnes counts and antibiotic-resistant strains. In the study, patients used BPO 6% cleanser daily for three weeks under supervised conditions. All 30 patients had high-level erythromycin-resistant organisms and low- to high-level resistance to tetracycline, doxycycline, and mino-

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IN VITRO PERCUTANEOUS ABSORPTION OF BENZOYL PEROXIDE

An in vitro human skin percutaneous absorption study was conducted and compared Clindamycin-BPO 2.5% gel with two commercial clindamycin-BPO formulations containing 5% BPO (Benzaclin and Duac). Using metabolically active human abdominal skin obtained following elective surgery and dermatomed prior to use, the percutaneous absorption of BPO was studied over 24 hours following a single application of test product (5 mg/cm²) to skin mounted in Blonough flow-through diffusion cells maintained at a constant temperature of 32°C. These cells have a nominal diffusion area of 0.64 cm². Fresh receptor solution (phosphate buffered saline, pH 7.4, containing 0.1% sodium azide and 4% bovine serum albumin) was continuously pumped under the tissue at a flow rate of 1.5 mL/hr and collected in 6-hour intervals. After 24 hours, BPO and benzoic acid levels in the receptor solution samples were determined by reversed phase HPLC with UV and mass spectroscopic detection (HPLC/UV/MS/MS). Receptor fluid was diluted 1:1 using acetonitrile. The resulting solution was centrifuged and the supernatant analyzed by HPLC/UV/MS/MS.

The rapid conversion of BPO to benzoic acid in the skin was observed. BPO was not detected in the receptor phase. Quantifiable levels of benzoic acid were detected in the 6-hour and 12-hour collections of the receptor phase. These results are consistent with the literature where it has been reported that topically applied BPO is rapidly metabolized to benzoic acid by the skin. Results from this in vitro percutaneous absorption study also support the hypothesis that benzoic acid readily passes from the epidermis and dermis into the receptor fluid phase. The penetration of BPO into the skin and subsequent metabolism appears to be relatively fast, being essentially complete within 12 hours of application.

BPO skin penetration, measured as benzoic acid, from Clindamycin-BPO 2.5% Gel was compared to the clindamycin-BPO 5% marketed products. This slide depicts the cumulative benzoic acid levels in the receptor phase plotted against time in hours. The absorption of BPO in human skin, measured as benzoic acid, from clindamycin phosphate 1.2%-BPO 2.5% gel was comparable in vitro to that of the commercial clindamycin-BPO 5% gels. However, the exact clinical significance of this data is unknown.

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1. Bucks D et al, J Drugs Dermatol 2009,8(7); 634-38
cyclocine. Results showed that the total *P. acnes* and resistant strains of erythromycin, tetracycline, doxycycline, and minocycline were reduced after one week of treatment; this pattern continued over three weeks.  

BPO cleansers, however, may not be as effective as we originally thought for acne on the trunk. One study which compared a BPO 8% cleanser with a 5.3% foam for 20-second contact and found that the cleanser did not reduce the *P. acnes* counts.  

Short contact BPO was evaluated in another study in which patients were treated once daily with BPO (9.8%) foam for two weeks, applied under supervision at the study center on weekdays and unsupervised at home over the weekends. The BPO (9.8%) foam was applied to non-moistened skin, massaged into the skin for 20 seconds, and left for two minutes before being rinsed off with water and wiped with a cloth. Results showed that BP 9.8% foam reduced *P. acnes* on the back when applied as a two-minute short contact therapy.

**EDUCATION: THE MOST IMPORTANT THERAPEUTIC TOOL**

Patients are constantly bombarded with messages that acne can clear overnight. In reality, though, it can take weeks and months to get acne under control. The available evidence suggests that the therapeutics tools available (including various retinoid and BPO formulations) are indeed effective, but it is important to impress upon patients that many regimens can take several months to achieve peak efficacy.

But arguably the most important aspect of boosting overall adherence is patient education. It's important to explain to the patient why a particular regimen was chosen; this emphasizes individualized benefits and encourages adherence. Patients should also be told that partial clinical improvement should be evident within four to six weeks of initiating or changing an acne regimen.  

I often tell my patients that treating acne is like treating weeds in a garden. Even if many lesions may clear, the body doesn’t stop making acne. Therefore, it is important to treat the entire area of acne prone skin. This often takes several weeks or months of treatment. The better patients understand that, the more likely it is that they will take medications as directed and see the best outcomes.

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**PRACTICAL POINTER**

Traditional thinking regarding the use of retinoids and benzoyl peroxides tends to undersell their utility. In fact, both play a central role in the treatment of acne. But in order to optimize these effective agents, patients must understand why a particular regimen was chosen and that many regimens can take several months to achieve peak efficacy.

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17. Dosik JS, Topiar, 0.1% gel and compared with tazarotene microsphere 0.04% and 0.1% gel. Cutis. 2005;75:238-243.


22. Gollnick H, Cunliffe W, Berson D, et al. Comparative tolerance of adapalene 0.1% 0.2% 0.1% cream and adapalene gel. Cutis. 2005;75:238-243.


36. Leyden J, et al. Topiar, 0.1% gel and compared with tazarotene microsphere 0.04% and 0.1% gel. Cutis. 2005;75:238-243.

37. Leyden J, et al. Topiar, 0.1% gel and compared with tazarotene microsphere 0.04% and 0.1% gel. Cutis. 2005;75:238-243.