

# BEST PRACTICES IN:

## Newer Topical Retinoid Therapies for the Treatment of Acne

**A**cne is the most common skin disorder in the US, affecting approximately 40 to 50 million people.<sup>1</sup> Each year, as many as 6 million acne-related office visits are made to physicians who treat the disorder.<sup>2</sup> Although acne is rarely associated with severe morbidity, mortality, or disability, it can lead to physical scarring that can affect an individual's psychological and emotional well-being.

### Current Thinking Around Acne Therapy

According to the American Academy of Dermatology's (AAD) "Guidelines of care for acne vulgaris management," published in 2007, topical retinoids should be used as first-line therapy in all but the most severe cases of acne, which require more aggressive treatment.<sup>3</sup> Other effective topical therapies for acne cited by the AAD include benzoyl peroxide and combinations with erythromycin or clindamycin. Topical antibiotics have also been used to treat acne for many years, however, the use of these agents as monotherapy can be associated with the development of bacterial resistance.<sup>3</sup>

### Topical Retinoids: The Cornerstone of Therapy

Most cases of acne can benefit from treatment with topical retinoids, which are considered a cornerstone of therapy for both pediatric and adult acne.<sup>3,4</sup> Currently, three topical retinoids/retinoid analogs—adapalene, tazarotene, and tretinoin—are approved for use in the US.

While the exact mechanism of action of topical retinoids in the treatment of acne has not been established, it is thought that retinoids improve acne by increasing the turnover of follicular epithelial cells, thus normalizing follicular keratinization and inhibiting the development of the precursor acne lesion, the microcomedo. Retinoids also help to resolve mature comedones. Preclinical data suggest that retinoids and retinoid analogs may also have anti-inflammatory effects. Clinical data confirm that retinoids and retinoid analogs significantly reduce inflammatory lesions.<sup>5,6,7</sup> (Figure) In addition, the application of a topical retinoid may enhance the penetration of other medications, such as topical antibiotics and benzoyl peroxide.<sup>8</sup>

**Figure. Topical Retinoids Reduce Facial Lesions**



Facial lesions before and after 12 weeks of treatment with adapalene gel 0.3%.

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### Evolution of Topical Retinoids

Tretinoin was the first topical retinoid to be approved for use in the US in 1971. It was initially formulated in a penetrating hydroalcoholic vehicle containing a high concentration of active ingredient, but caused many patients to develop skin irritation. Subsequently, tretinoin cream and gel vehicles in a variety of concentrations became available and improved the irritation side effects, although it remained a problem for some patients. Newer topical delivery systems—the microsphere and the polyolprepolymer-2 vehicle—have since been developed to deliver the active tretinoin while minimizing irritation.<sup>9,10</sup>

Another means of reducing the irritation potential of



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topical retinoids has been the development of next-generation retinoids that bind selectively to retinoic acid receptors. Adapalene—a receptor-selective retinoid analog—is effective at treating both comedonal and inflammatory acne, shows low irritation potential, and has not been shown to cause sensitization or phototoxicity.<sup>9,11</sup> In 1996, adapalene 0.1% gel was first approved to treat acne and a cream form followed in 2000. Tazarotene, another next-generation topical retinoid, was approved in 2001 for treating acne and psoriasis. Tazarotene normalizes keratinocyte differentiation and reverses keratinocyte proliferation. It is efficacious as monotherapy and is commonly used in combination with a topical antibacterial in patients with acne vulgaris.<sup>12</sup>

The most recent retinoid analog product to be approved to treat acne is adapalene 0.3% gel, which received approval in 2007. A phase III, randomized, multicenter, double-blinded clinical trial that compared the safety and efficacy of adapalene 0.3% gel with adapalene 0.1% gel, and with vehicle, found that the median lesion count reduction was better for the adapalene 0.3% gel than for the adapalene 0.1% and vehicle gels.<sup>13</sup> At week 12, Generalized Estimating Equation (GEE) analysis showed a statistically significant difference between the adapalene 0.3% and 0.1% groups in the percent reduction in total lesion counts ( $P=0.020$ ) and inflammatory lesion counts ( $P=0.015$ ). The pivotal phase II trial of adapalene 0.3% gel demonstrated that for more challenging acne (higher lesion counts with more inflammatory lesions), adapalene gel 0.3% was superior to adapalene gel 0.1% and vehicle gel in reducing total inflammatory and noninflammatory lesions by week 12.<sup>7</sup>

### Tolerability of Topical Retinoids

Studies have investigated the cumulative irritancy potential of different topical retinoid molecules in a number of formulations. Adapalene 0.1% cream and gel formulations, as well as solution, have been shown to have significantly less irritation potential than various formulations of tretinoin and tazarotene.<sup>14,15</sup>

In clinical studies, the most typical adverse events associated with the use of retinoids include erythema, dry skin, pruritus, irritation, and stinging/burning. Similar to other retinoids, adverse events associated with use of adapalene gel 0.3% are primarily local cutaneous irritation. However, results from clinical studies comparing adapalene gel 0.3% to adapalene gel 0.1% confirm that adapalene gel 0.3% retains a similar safety profile to the less-concentrated adapalene formulation.<sup>13</sup>

More recently, Dosik and Arsonnaud conducted a 3-week study that compared the local cutaneous tolerability

of adapalene 0.3% gel once daily with tazarotene 0.05% cream (Note: tazarotene 0.05% cream is not indicated for the topical treatment of acne vulgaris) once daily.<sup>16</sup> Study participants were instructed to apply adapalene 0.3% gel to one half of the face and tazarotene 0.5% cream to the other half of the face. Investigator-assessed overall tolerability was in favor of adapalene at days 19 and 22, and subject-assessed tolerability was in favor of adapalene at day 5 ( $P=0.043$  for all). Otherwise, the two drugs were comparable with respect to local cutaneous tolerability.

As with all retinoid products, patients should be instructed to avoid harsh, drying cleansers, to apply daily sunscreen, and to protect their face from the cold and wind. Noncomedogenic moisturizers should be used to help reduce dryness and irritation.

### Summary

Topical retinoids have long been a mainstay of acne therapy with demonstrated efficacy against both inflammatory and noninflammatory lesions. Formulations in variable concentrations are helpful for tailoring regimens for individual skin types. The most recently approved topical retinoid formulation, adapalene 0.3% gel, has been demonstrated to be an effective treatment option for acne while maintaining a favorable tolerability profile.

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