

Review article

## A Review of Adapalene in the Treatment of Acne Vulgaris

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### Abstract

Topical retinoids help address the early lesions of acne vulgaris. Consensus guidelines advocate the use of topical retinoids as the primary treatment for most forms of acne vulgaris. However, all topical retinoid preparations may be irritating, and this may contribute to underutilization in clinical practices. Topical adapalene fosters topical retinoid treatment of acne with less irritation. Adapalene is a more stable molecule than tretinoin. Adapalene can be used without concern for photo-deactivation. Because of its chemical stability, adapalene can be used in combination with benzoyl peroxide products. The availability of a stable topical retinoid associated with little irritation may facilitate meeting acne treatment consensus guidelines. © 2008 Society for Adolescent Medicine. All rights reserved.

### Keywords:

Topical retinoids; Tretinoin; Comedolytic; Anti-inflammatory; Pediatricians

The pathophysiology of acne involves four key mechanisms of action: abnormal proliferation and differentiation of keratinocytes, increased sebum production, hyperproliferation of *Propionibacterium acnes*, and an inflammatory response initiated by bacterial antigens and cytokines. Topical retinoids target the abnormal proliferation and differentiation of keratinocytes and also have anti-inflammatory effects. In addition, topical retinoids enhance penetration of other agents, such as topical antibiotics, resulting in synergistic effects [1–3].

Retinoids used for acne therapy include tretinoin, tazarotene, adapalene, and isotretinoin (systemic). Topical retinoids are comedolytic and are successful at inhibiting the formation of micro-comedones, the precursor to all acne lesions. The first-generation retinoids (retinol, tretinoin, and isotretinoin) are irritating, and may limit compliance. Ada-

palene is a third generation retinoid with minimal side effects. Adapalene has become widely used because of its comparable efficacy and favorable tolerability profile when compared with other topical retinoids [2,3].

### Adapalene for Treatment of Acne Vulgaris

#### Indications and use

Adapalene is available in two formulations: gel (.1%, .3%) and cream (.1%). After washing with a gentle cleanser, a thin layer should be applied once daily in the evening to the entire face and any other affected area approved by the physician [4]. Special care should be taken to avoid the eyes, lips, mucous membranes, and other sensitive areas [4]. As retinoids may increase photosensitivity, patients should be instructed to minimize sun exposure and to apply a noncomedogenic sunscreen every morning. The safety and efficacy in children <12 years of age have not been determined [5]. Adapalene is pregnancy category C and should be used with caution in pregnant women.

#### Description and clinical pharmacology

Adapalene's chemical structure is more stable to light and oxidation compared with tretinoin. In an *in vitro*

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study of adapalene and tretinoin, 95% of tretinoin was degraded within 24 hours in the presence of sunlight and benzoyl peroxide, whereas adapalene had essentially no degradation under these conditions, even at 72 hours [3,6]. Unlike generic tretinoin gel, adapalene is formulated in an aqueous gel, which may account for some of the improved tolerability. However, adapalene is also better tolerated than other formulations of tretinoin (cream and microsphere gel) [7].

A proposed mechanism for adapalene's greater tolerability is its selective binding affinity. Unlike tretinoin, adapalene does not bind to the cytosolic retinoic acid binding proteins but instead selectively binds to the nuclear retinoic acid receptor (RAR) subtypes  $\beta$  and  $\gamma$  [3,8]. This selective binding affinity may play a role in adapalene's greater inhibition of keratinocyte differentiation than tretinoin, which was demonstrated in a study using keratinocyte transglutaminase expression as a marker [3]. This inhibition of keratinocyte differentiation and proliferation is responsible for adapalene's comedolytic effect. In an *in vivo* study, adapalene's ability to reduce comedone formation was demonstrated by a 50–60% reduction in comedone counts compared with vehicle [9].

Another important factor in acne pathogenesis is the inflammation that occurs after microcomedone formation. Adapalene inhibits the inflammatory response to microcomedone formation and bacterial antigens [1,2]. Adapalene's anti-inflammatory effects result from inhibition of neutrophil chemotaxis and the lipoxygenase pathway, both of which are associated with cutaneous inflammatory reactions [2,8]. Adapalene is more effective at inhibiting neutrophil lipoxygenase than is tretinoin [2,8]. Adapalene also has other unique anti-inflammatory mechanisms that may contribute to its efficacy [8].

## Clinical Studies of Adapalene

### Clinical efficacy

Adapalene is an effective acne treatment. A multicenter, randomized, investigator-blinded study with 297 enrolled patients compared the efficacy of adapalene .1% solution to that of tretinoin .025% gel in a once-daily dosage regimen for 12 weeks. Both agents provided significant mean improvements in inflammatory lesions (47% and 50%, respectively), and noninflammatory lesions (57% and 54%) [10]. In another multicenter, randomized, investigator-blinded study, 105 patients with mild to moderate acne vulgaris were treated with adapalene .1% gel versus tretinoin .025% gel for 3 months. Adapalene gel was found to be more efficacious than tretinoin gel after 1 week of treatment, with respect to a decrease in inflammatory lesions (32% and 17%, respectively,  $p = .001$ ) and total lesion counts (28% and 22%,  $p = .042$ ); however there was no statistically significant difference at week 12 [11].

Another 12-week study compared adapalene .1% gel to tretinoin .1% microsphere. At week 4, a greater reduction in non-inflammatory lesions was observed for the tretinoin .1% microsphere; however the tretinoin group also had a greater incidence of skin irritation. Both products had similar efficacies (33% vs. 35% mean total lesion reduction) by week 12 [12].

A new formulation of adapalene in a .3% gel is now available and is even more effective than its .1% predecessor. Compared with adapalene .1% gel, adapalene .3% gel showed greater median percent reduction in total lesion (56% vs. 48%;  $p = .020$ ) and inflammatory lesion counts (63% vs. 58%;  $p = .015$ ) [13]. Both concentration performed significantly better than gel vehicle ( $p < .001$ ). Currently, there are no head-to-head efficacy comparisons of adapalene .3% gel to tretinoin gel, cream, or microsphere.

The value of adapalene for maintenance therapy was established in a multicenter, randomized, investigator-blinded study with a total of 253 subjects. The subjects were successfully treated (at least 50% improvement from baseline) in a previous 12-week study, and were randomized to receive adapalene .1% gel or gel vehicle once daily for 16 weeks. Adapalene maintenance therapy resulted in higher rates of maintaining at least 50% improvement (75% vs. 54%;  $p < .001$ ) and significantly lower lesion counts compared with gel vehicle [14].

Because of the chemical stability of adapalene, it is well suited for use in combination with other topicals such as benzoyl peroxide or antibiotics. The effectiveness of adapalene in combination therapy for the treatment of mild to severe acne vulgaris was determined in several studies. In a multicenter, randomized, investigator-blinded study with a total of 249 subjects, the efficacy and tolerability of the combination of adapalene .1% gel and topical clindamycin .1% lotion was compared with topical clindamycin .1% lotion and gel vehicle for the treatment of mild to moderate acne. The subjects applied adapalene or vehicle gel once daily in the evening, and topical clindamycin twice daily for 12 weeks. The combination of adapalene and topical clindamycin was more effective than topical clindamycin alone in reducing the total lesions (46.7% vs. 25.5%,  $p < .001$ ), inflammatory lesions (55.0% vs. 44.2%,  $p = .004$ ), and non-inflammatory lesions (42.5% vs. 16.3%,  $p < .001$ ) [15]. In another multicenter, randomized, investigator-blinded study, 467 patients with severe acne were randomized to receive either the combination of adapalene .1% gel and oral doxycycline or gel vehicle and oral doxycycline for a duration of 12 weeks. Compared with oral doxycycline alone, the combination of adapalene and oral doxycycline resulted in a larger reduction in median percent change of total lesions (61% vs. 45%,  $p < .001$ ), inflammatory lesions (65% vs. 59%,  $p = .02$ ), and non-inflammatory lesions (60% vs. 41%,  $p < .001$ ) [16].

### Safety and tolerability

In two controlled, randomized, investigator-blinded, intraindividual comparison studies, the tolerance of adapalene .1% gel was compared with six different tretinoin formulations (tretinoin .025%, .05%, and .1% cream; tretinoin .01% and .025% gel; and tretinoin .1% gel microsphere) and control (petrolatum). In these studies, adapalene, tretinoin formulations, and petrolatum were applied to the back daily followed by occlusion 5 days per week for 3 weeks to evaluate the cumulative irritation potential. The evaluation of irritancy was based on an eight-point scale accounting for dryness, erythema, papular or papulovesicular responses, edema, and erosions or crusting. Adapalene was significantly better tolerated than all formulations of tretinoin (including tretinoin microsphere), and was not statistically different from the control, petrolatum gel (no *p* value reported) [7].

In one multicenter, randomized, investigator-blinded study, 105 patients with mild to moderate acne vulgaris were treated with adapalene .1% gel versus tretinoin .025% gel for 3 months to compare the onset of action, tolerability, and impact on quality of life. Adapalene was significantly better tolerated ( $p < .05$ ) than tretinoin when evaluated on a four-point scale for dryness, erythema, immediate and persistent burning, and pruritus. Using the DLQI, there was a statistically significant improvement in quality of life for both treatment groups ( $p < .05$ ). At weeks 1 and 12, there were improvements in quality of life in favor of adapalene for items related to problems with close contacts, skin symptoms, and social interactions [11].

The effectiveness and safety of adapalene gel .1% when used with other acne treatments was evaluated in a prospective, open-label, multicenter, observational, phase 4 study. Adverse events and tolerability of adapalene gel .1% were evaluated in 1864 subjects. Subjects naïve to acne treatment ( $n = 1396$ ) received initial combination therapy with adapalene gel, whereas subjects already on nonretinoid therapy ( $n = 468$ ) added adapalene to their existing regimen. The overall rates of moderate to severe cutaneous irritation at

week 12 measured on a four-point scale of erythema, peeling/scaling, dryness, and stinging/burning were low, ranging between 1.5% and 3.2% [17].

### Discussion

The development of topical retinoids has proved to be essential in the management of acne. As such, our review of adapalene is important from a therapeutic perspective because topical retinoids are underutilized in practice [16]. The most compelling predictor of the use or nonuse of topical retinoids was physician specialty, with nondermatologists significantly less likely to use topical retinoids than dermatologists (39.4% vs. 23%) [18]. More recent data suggest that there is an even broader disparity in use of topical retinoids between dermatologists and pediatricians. (46.4% vs. 15.2%) [19].

Physicians may be reluctant to prescribe topical retinoids because of the irritating side effects of the earlier retinoids, resulting in poor adherence to treatments and complaints about the treatment regimen. Acne treatment regimens may also be complicated by the need to use some retinoids at different times than benzoyl peroxide or sun exposure. Adapalene, however, can be used in conjunction with benzoyl peroxide and sun exposure, with less risk of irritation.

In 2003, an international committee of physicians and researchers developed the most recent set of guidelines for acne management [20]. These largely evidence-based recommendations advocate targeting as many processes in the pathogenesis of acne vulgaris as possible. The consensus guidelines state that a topical retinoid should be used as the primary treatment for mild to moderate acne (including inflammatory acne), secondary to its anti-inflammatory properties and its inhibition of the formation of the microcomedone, the precursor to all acne lesions. Therefore topical retinoids target two key mechanisms in the pathogenesis of acne. To target three pathogenic factors, it is recommended that antimicrobial agents be used in combination with topical retinoids when inflammatory lesions

Table 1  
Acne treatment algorithm

Treatment	Mild		Moderate		Severe
	Comedonal	Papular/pustular	Papular/pustular	Nodular	Nodular
First-line	Topical retinoid	Topical retinoid + BPO	Oral antibiotic + topical retinoid + BPO <sup>a</sup>		Oral antibiotic + topical retinoid + BPO/AB <sup>a</sup>
Second-line	Salicylic acid	Topical retinoid + salicylic acid or BPO/AB	Oral antibiotic + topical retinoid + BPO/AB <sup>a</sup>	Oral antibiotic + topical retinoid + BPO/AB <sup>a</sup> or Oral isotretinoin <sup>b</sup>	Oral isotretinoin <sup>a</sup>
Maintenance	Topical retinoid ± BPO or BPO/AB				

BPO = benzoyl peroxide; AB = topical antibiotic.

Adapted from Gollnick et al. [20].

<sup>a</sup> For female patients, hormonal therapy (oral contraceptives) may be added.

<sup>b</sup> For refractory cases only.

are present. Oral antibiotics are the drug of choice for moderate to severe acne, but should be used in combination with topical retinoids, and should be discontinued as soon as possible (within 8–12 weeks) to prevent development of bacterial resistance. Finally, topical retinoids are critical for maintenance therapy because of their effect on the microcomedone (Table 1) [20].

Several topical retinoid preparations are available that can be used in monotherapy and combination regimens that meet acne treatment consensus guidelines. From an economic view, the two leading topical retinoids, adapalene gel and tretinoin microsphere, are comparable in price (~150 per 45 g) [21]. Similar to the microsphere formulation of tretinoin, the chemical stability of adapalene facilitates its use in combination regimens with topical benzoyl peroxide products. Although adapalene has similar, and often slightly better, efficacy than other topical retinoids, it is the lack of side effects that places adapalene clinically above the rest.

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