

A SUPPLEMENT TO

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ELSEVIER



# Treating Acne: Advances in Retinoid Therapy

New Topical Acne Treatment  
Judit Nyirady, MD

Topical Retinoids: Acne & Beyond  
Hilary E. Baldwin, MD

**SDEF** Skin Disease  
Education  
Foundation

*Produced in affiliation with the 27th Annual Hawaii Dermatology Seminar*

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#### ACCREDITATION

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#### TARGET AUDIENCE

This activity has been developed for dermatologists and other health care professionals involved in the treatment of acne vulgaris and other dermatological conditions.

#### LEARNING OBJECTIVES

By reading and studying this supplement, participants should be able to:

- Discuss clinical studies involving low-dose tretinoin gel in patients with acne vulgaris.
- Distinguish risk (irritation potential)-benefit (anti-acne efficacy) relationships among commercially available topical retinoid formulations.
- Describe the therapeutic advantages of nonirritating topical retinoids in a variety of clinical conditions.

#### EDUCATIONAL NEEDS

Retinoids have long been the mainstay of acne therapy. A wide variety of topical formulations is available, each providing a different therapeutic index but generally aiming to maximize efficacy while minimizing cutaneous irritation. A new low-dose (0.04%) tretinoin microsphere gel has been introduced that offers significant anti-acne efficacy without substantial skin irritation. To optimize patient treatment plans, dermatologists must appreciate the range of available treatment options as well as the substantial therapeutic benefit of a nonirritating retinoid in a variety of dermatological conditions.

#### FACULTY DISCLOSURE

Faculty/authors must disclose any significant financial interest or relationship with proprietary entities that may have a direct relationship to the subject matter. They must also disclose any discussion of investigational or unlabeled uses of products.

**Dr. Baldwin** has received clinical grants from OrthoNeutrogena. She discusses the investigational/off-label use of tretinoin microsphere gel and imiquimod. **Dr. Nyirady** is clinical director, dermatology, Johnson & Johnson Consumer and Personal Products Worldwide.

# New Topical Acne Treatment

Judit Nyirady, MD

Retinoid therapy has been the mainstay of topical acne therapy for the past 30 years. Its anti-acne efficacy is attributed to modification of abnormal follicular keratinization.<sup>1-3</sup> Tretinoin not only promotes detachment and shedding of corneocytes but also normalizes keratinocyte proliferation and differentiation. Through these actions, tretinoin extrudes comedone contents and prevents new microcomedo formation.<sup>4,5</sup> Tretinoin continues to be a first-line treatment for inflammatory and

retinoin microsphere gel. The first study evaluated two strengths (0.04% and 0.06%)<sup>6</sup> of tretinoin microsphere gel. The second study further assessed the safety and efficacy of the 0.04% tretinoin microsphere gel formulation.<sup>7</sup> In both studies, subjects 11 to 49 years old with acne vulgaris applied study medication nightly to the face for 12 weeks.

The primary efficacy variable was percent change from baseline in total facial acne lesions. Secondary efficacy variables included percent change from baseline in inflammatory and noninflammatory lesions as well as investigator global assessment of clinical response. In addition to monitoring adverse events, erythema, peeling, dryness, burning/stinging, and itching were each graded on a four-point irritation scale every 2 weeks.

All 561 subjects enrolled in the two studies were included in the safety analysis: 225 received 0.04% tretinoin microsphere gel; 226 received 0.06% tretinoin microsphere gel; and 226 received placebo. Efficacy results focused on the 432 subjects in the intent-to-treat population: 219 received 0.04% tretinoin microsphere gel and 213 received placebo. Nineteen subjects participated in both studies, and were represented only once in the efficacy analysis.

**“Considered collectively, the findings of three clinical studies with this new low-dose tretinoin microsphere formulation demonstrated significant anti-acne efficacy without substantial skin irritation.”**

Based on data from both studies, 12 weeks of treatment with 0.04% tretinoin microsphere gel reduced total facial acne lesions 37.8%, noninflammatory lesions 33.7%, and inflammatory lesions 43.3% (Figure 1). This improvement progressed steadily throughout the study but was statistically significant ( $P < 0.00125$ ) by week 2 for inflammatory lesions and by week 4 for total and non-inflammatory lesions, when compared with the placebo group.

Even at the peak period of cutaneous irritation (2 weeks), 0.04% tretinoin microsphere gel produced generally mild reactions. Based on the four-point irritation scale (none, mild, moderate, severe), the majority of subjects experienced either no cutaneous reactions or only mild cutaneous symptoms that subsided with time (Figure 2 on page 4). During the 12-week study period, two subjects treated with 0.04% tretinoin microsphere gel (1%) experienced severe

**TABLE.**  
*Tretinoin Formulations*

Type	Concentration (%)
microsphere gel	0.1 + 0.04
cream	0.025 + 0.05 + 0.1
gel	0.01 + 0.025
liquid	0.05

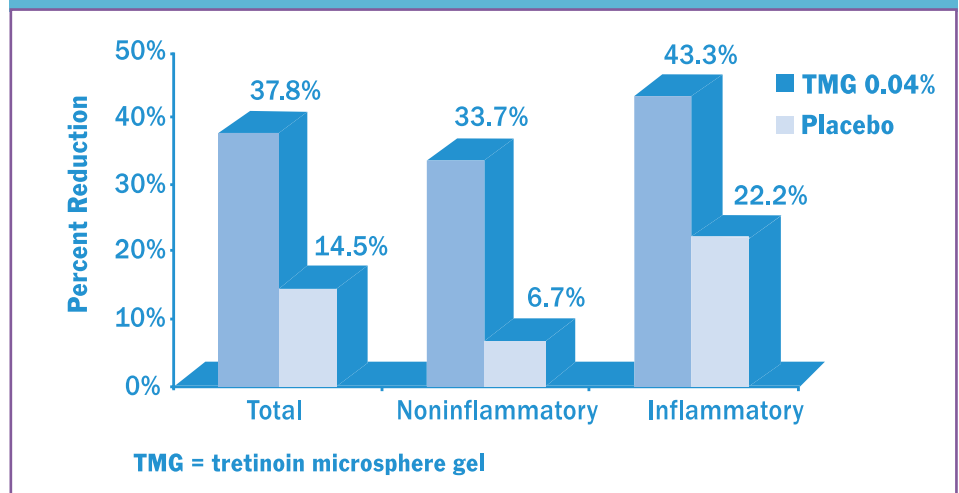
noninflammatory acne. Numerous formulations and concentrations of tretinoin are available to satisfy the needs of physicians and patients (Table).

## Effective and Well Tolerated

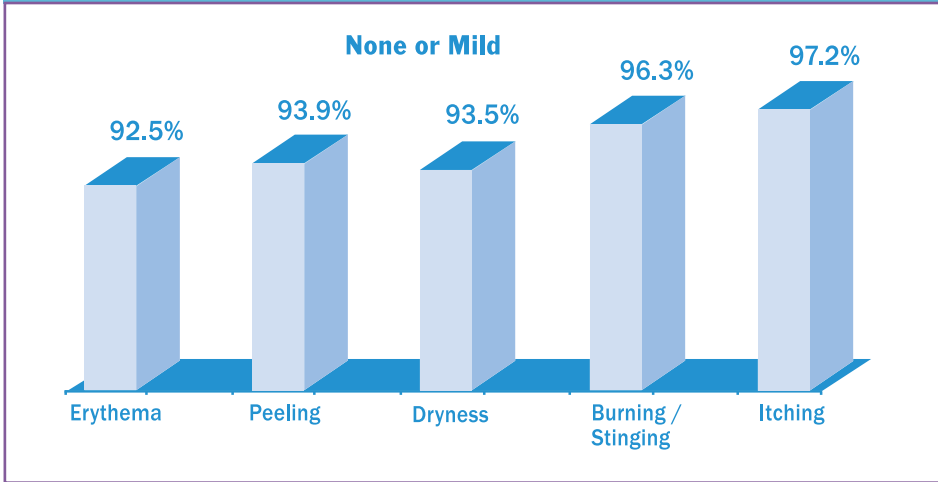
A new tretinoin product is now available that provides effective topical therapy for acne, even for subjects with especially sensitive or dry skin. It is a tretinoin microsphere gel with lower concentration (0.04%) than previously available. Considered collectively, the findings of three clinical studies with this new low-dose tretinoin microsphere gel formulation demonstrated significant anti-acne efficacy without substantial skin irritation. Since each patient represents a unique set of therapeutic needs, this new low-dose tretinoin microsphere gel improves treatment flexibility, thus facilitating individualized therapeutic plans.

Two multicenter, randomized, double-blind, and placebo-controlled studies, enrolling 561 subjects, were conducted to assess efficacy and tolerability of 0.04%

**FIGURE 1.** *Combined Analysis: Percent Reduction in Lesion Count at Week 12*



**FIGURE 2. Cutaneous Irritation at Week 2**



irritation, and another three subjects (1.3%) discontinued treatment due to irritation. By week 12, the vast majority of subjects experienced no or only mild skin irritation. More specifically, no or mild erythema, peeling, dryness, burning/stinging, and itching were reported in 96%, 95.9%, 98%, 100%, and 99.5% of subjects, respectively.

This new formulation, a microsphere gel containing 0.04% tretinoin, is effective and very well tolerated by subjects with acne vulgaris. Notably, it effectively reduces both noninflammatory and inflammatory facial acne without producing substantial cutaneous irritation.

### Cutaneous Irritation Potential

In a single-center, randomized, investigator-blinded study, the cutaneous irritation potential of 0.04% tretinoin microsphere gel and 0.1% adapalene gel were compared. Each of 56 healthy volunteers was administered 0.2 mg of the two gels three times weekly for a 3-week period. Gels were applied to the upper back for 24 hours under semi-occlusive patches.

Application sites were assessed 24 hours after application and graded on a scale for erythema that ranged from 0 (no visible reaction) to 4 (intense erythema, induration, and bullae). The cumulative irritation score for each of the two topical agents was determined by calculating the sum of all scores for all subjects in each treatment group. In addition, the

number of days subjects experienced each grade of erythema was calculated.

Since 56 subjects completed the study, the highest possible cumulative irritation score for either group was 2,016 (56 subjects x 9 applications x maximum erythema score of 4). The cumulative irritation scores for low-dose tretinoin microsphere gel and adapalene gel were 5.5 and 24, respectively. The percent of subject days at each erythema score (**Figure 3**) confirms that both gels produced virtually no irritation. Nearly all subjects (98%) in each treatment group exhibited grade 0 scores throughout the study. However, tretinoin microsphere gel generated a lower cumulative irritation score than did adapalene gel.

## Conclusions

Tretinoin microsphere gel (0.04%) improves noninflammatory and inflammatory acne without inducing substantial cutaneous irritation. The efficacy and excellent tolerability of this new tretinoin gel optimizes clinical outcome by meeting individual needs.

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**FIGURE 3. Percent of Subject Days at Each Ratings Score**

	Rating					
	0	1	2	3	4	5
<b>TMG 0.4%</b>	98.2%	1.4%	0.4%	0%	0%	0%
<b>Adapalene Gel 0.1%</b>	97.8%	0.4%	0.8%	0%	0.2%	0.8%

Percent of subject days is computed as the sum of the number of days (applications) at each rating, expressed as a percent of the total number of subjects (56) times the number of days (9). For example, for the '0' rating, the percent is  $100 \times ((48 \text{ subjects} \times 9 \text{ days}) + (7 \text{ subjects} \times 8 \text{ days}) + (1 \text{ subject} \times 7 \text{ days})) / (56 \text{ subjects} \times 9 \text{ days}) = 98.2\%$

TMG = tretinoin microsphere gel

# Topical Retinoids: Acne and Beyond

Hilary E. Baldwin, MD

Low-dose (0.04%) tretinoin microsphere gel is approved for topical treatment of acne vulgaris. When a new retinoid becomes available, it is prudent to consider its suitability for conditions commonly treated with older retinoids. Therefore, this presentation discusses the use of low-dose tretinoin microsphere gel for keratosis pilaris, verrucae vulgaris and planus, molluscum contagiosum, and postinflammatory hyperpigmentation as well as for acne vulgaris.

It should be noted that this presentation is based on personal clinical experience with specific patient populations and may not be applicable to others. Patients referred to my practice may be among those most severely afflicted or experiencing treatment resistance. Furthermore, my practice is located in the northeast, where harsh winters can exacerbate skin problems and thereby influence choice of treatment.

## Comparison of Topical Retinoids

Based on my clinical experience, adapalene cream and gel are less effective than other topical retinoids (Table). Adapalene cream, however, may be helpful in very young patients with early comedonal acne. A retinoid gel often is more effective than its corresponding cream, as in the cases of adapalene and tazarotene. Tazarotene creams (0.05% and 0.1%) and 0.1% tretinoin gel both are more effective than adapalene (cream or

gel). The most effective topical retinoids in my practice are the tazarotene gels. Although gels tend to be more effective than creams, creams can be less irritating. For example, adapalene and tazarotene creams are certainly less irritating than their gel counterparts. The tazarotene gels are more irritating than adapalene gel; therefore, some patients in the northeast (most of my patients) cannot use them during the winter months due to skin dryness.

The new low-dose (0.04%) tretinoin microsphere gel is slightly more effective than tazarotene 0.05% cream and slightly less effective than tazarotene 0.1% cream or tretinoin 0.1% gel. In terms of irritancy, the low-dose tretinoin gel is virtually minimally irritating.

## Acne Vulgaris

Low-dose retinoids are first-line therapy in mild to moderate acne, especially in acne that is primarily comedonal. Tretinoin microsphere gel, however, also is effective for inflammatory acne. Low-dose tretinoin microsphere gel has replaced adapalene cream for my youngest patients, who are 9 to 12 years old.

In this age group it is usually the parent, not the child, who is motivated to seek treatment. Thus, it is particularly important that skin irritation does not discourage the child and jeopardize compliance. In addition, patients should be shown the appropriate amount of cream or gel to use since the size-of-a-pea instruction can be misleading.

Carefully customizing treatment for these young patients with very sensitive skin is crucial, and using low-dose tretinoin microsphere gel adds a degree of flexibility. It is only slightly more irritating than adapalene cream, the least irritating topical retinoid. However, low-dose

**“Carefully customizing treatment for these young patients with very sensitive skin is crucial, and using low-dose tretinoin microsphere gel adds a degree of flexibility.”**

tretinoin microsphere gel is slightly more effective than low-dose (0.05%) tazarotene cream. Accordingly, therapy may be initiated with adapalene cream, followed by low-dose tretinoin microsphere gel, and eventually by 0.1% tretinoin gel or 0.1% tazarotene cream.

Low-dose tretinoin microsphere gel also provides an option for patients who respond well to 0.1% tretinoin gel until winter weather triggers skin dryness. Since 0.1% tretinoin gel has been effective for these patients, switching to another medication may disrupt acne management. Low-dose (0.04%) tretinoin microsphere gel, a slightly milder form of the successful therapy, is an effective solution.

Another group of patients with acne who benefit from low-dose tretinoin microsphere gel are those who find most retinoids too drying. This is particularly a problem for African American females since postinflammatory changes can result from even the slightest irritation. Given this particular sensitivity, low-dose tretinoin microsphere gel helps to contain irritation without forgoing effective retinoid treatment.

## Keratosis Pilaris

Keratosis pilaris is a difficult condition to treat because of a high degree of treatment failure. Nevertheless, improvement in skin texture is achievable<sup>1</sup> and is especially satisfying to those patients bothered more by how keratosis pilaris feels than by how it appears. An effective treatment

**TABLE. Topical Retinoids: Efficacy and Irritancy\***

Effective		Irritating
ADAcrm	least	ADAcrm
ADAgel	↓	TMG4
TAZcrm5		TMG1; TAZcrm5
TMG4		ADAgel
TAZcrm1; TMG1		TAZcrm1
TAZgel5		TAZgel5
TAZgel1		most

ADA=adapalene; crm=cream; TAZ=tazarotene; TMG=tretinoin microsphere gel; 1=0.1%; 4=0.04%; 5=0.05%

\* Based on author's experience

protocol is 12% lactic acid cream after bathing, followed by a topical retinoid before bed. Since the upper arm area is not especially sebaceous, the wrong topical retinoid can cause serious irritation (particularly when treated concomitantly with lactic acid). Tretinoin 0.05% cream is my preferred retinoid because of its soothing emollient nature; alcohol-based gels are simply too irritating. Nonetheless, low-dose (0.04%) tretinoin microsphere gel is also effective for this particular condition.

### Verrucae Vulgaris and Planus

A well publicized study has shown that an effective treatment strategy for verrucae, particularly flat warts, is occlusion with duct tape.<sup>2</sup> When used under occlusion, however, most topical retinoids are simply too irritating for the surrounding skin. Previously, adapalene gel was the most successful treatment for treating my patients with verrucae; however, now the most effective treatment is low-dose tretinoin microsphere gel because it is less irritating under occlusion. An effective treatment plan involves low-dose tretinoin microsphere gel in the morning and imiquimod, a topical immune response modifier, also occluded, in the evening; this combination works better than either agent alone.

### Molluscum Contagiosum

Topical retinoids have been used for many years as monotherapy for mollusca<sup>3,4</sup> but they are not always effective. They are used because they are keratolytic and, theoretically, unroof the top of the molluscum. Topical retinoids irritate the skin, however, and induce patients to scratch, thus unroofing the molluscum much in the way a dermatologist would, using a curette.

As polytherapy, however, retinoids combined with imiquimod, an immune response modifier, can be effective.<sup>5-8</sup> Similar to the treatment of verrucae, adapalene gel or low-dose tretinoin microsphere gel, occluded by duct tape, is

applied mornings and accompanied by evening applications of imiquimod, also under occlusion. Caution must be used when utilizing this combination in children or in adults with venereal molluscum. Children with atopic dermatitis and adults with genital mollusca may find the combination too irritating. There have been two or three children among my patients whose atopic dermatitis was under complete control but who nonetheless developed blistering when imiquimod was introduced. The mollusca did disappear; however, marked postinflammatory changes also occurred. A similar reaction can occur among patients with genital mollusca. For these two patient populations, low-dose (0.04%) tretinoin microsphere gel alone may be more acceptable.

### Postinflammatory Hyperpigmentation

Because topical retinoids are keratolytic and alter melanosomes, they have the ability to lighten skin.<sup>9</sup> Nevertheless, when used as monotherapy, their efficacy against postinflammatory pigmentation is limited. On the other hand, when combined with hydroquinone, a depigmenting agent, tretinoin is very effective. Two new combination products, one containing mequinol and tretinoin and one containing tretinoin, hydroquinone, and a corticosteroid, have proved helpful for patients with postinflammatory hyperpigmentation.<sup>10</sup> A less costly alternative with slightly less efficacy is low-dose tretinoin microsphere gel combined with hydroquinone.<sup>10</sup> I have found this combination to be less irritating than stronger retinoids and thus less likely to promote accidental postinflammatory hyperpigmentation from irritation.

### Conclusions

Low-dose (0.04%) tretinoin microsphere gel is a retinoid that is effective in treating acne while being less irritating than most other topical retinoids. I recommend it especially for children

whose skin is easily irritated, and for African Americans, whose skin is prone to postinflammatory hyperpigmentation. Other patients with sensitive skin include those who are easily hyperpigmented or who require treatment of the genital area. Finally, low-dose tretinoin microsphere gel can be effective for patients who do not tolerate skin dryness under any circumstances.

Furthermore, low-dose tretinoin microsphere gel used as monotherapy or as combination therapy is an option for other dermatologic conditions such as verrucae and mollusca. Because it is less irritating than other topical retinoids, low-dose (0.04%) tretinoin microsphere gel lends itself to occlusion therapy, thus permitting effective combination therapy for verrucae and mollusca. The non-irritating nature of low-dose tretinoin microsphere gel also reduces the risk of hyperpigmentation, thus enabling retinoid treatment of postinflammatory hyperpigmentation.

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## INSTRUCTIONS:

For each question or incomplete statement, one answer or completion is correct. Four out of five correct responses are required for credit. Circle the most appropriate response.

### 1. Topical tretinoin anti-acne efficacy is due to all but:

- (a) modification of abnormal follicular keratinization
- (b) promotion detachment and shedding of corneocytes
- (c) normalization of keratinocyte proliferation and differentiation
- (d) reduction in melanocytes and elastic fibers

### 2. Nonirritating formulations of topical retinoids are least critical for:

- (a) patients with oily complexions
- (b) occlusion therapy
- (c) African American women
- (d) young patients with acne

### 3. The most effective treatment of verrucae, particularly flat warts, is:

- (a) 12% lactic acid cream after bathing, followed by topical retinoid before bed
- (b) tazarotene gel plus imiquimod, both under occlusion
- (c) nonirritating topical retinoid plus imiquimod, both under occlusion
- (d) a combination of hydroquinone and tretinoin gel

### 4. Postinflammatory hyperpigmentation responds well to:

- (a) adapalene gel plus 0.1% tazarotene gel
- (b) low-dose tretinoin gel plus hydroquinone
- (c) imiquimod plus low-dose tretinoin
- (d) adapalene plus 12% lactic acid

### 5. Because of its nonirritating nature, low-dose tretinoin gel:

- (a) effectively cures keratosis pilaris
- (b) enables effective treatment of verrucae and mollusca
- (c) is not ideal for patients with particularly sensitive skin
- (d) may induce postinflammatory hyperpigmentation

## EVALUATION FORM

We would appreciate your answering the following questions in order to help us plan for other activities of this type.

### 1. How would you rate the clarity of the presentation of the material? (Please check.)

	Excellent	Good	Fair	Poor
Text	_____	_____	_____	_____
Images	_____	_____	_____	_____
Post-Test	_____	_____	_____	_____

### 2. How would you rate the clinical relevance of the material?

\_\_\_\_\_

### 3. How would you rate this material, compared with similar independent study presentations in print format?

\_\_\_\_\_

### 4. Was this a fair and balanced presentation? Please comment on the scientific rigor, fairness, and balance of the material.

### 5. Do you believe such materials, supported by education grants from industry, are appropriate and useful?

Please rate from 0 (not appropriate/useful) to 10 (very appropriate/useful). \_\_\_\_\_

### 6. What topics would you find useful for future programs?

\_\_\_\_\_

\_\_\_\_\_

### 7. Other comments:

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