

## August 2007: VOLUME 1, NUMBER 3

### *Recent Developments in Acne Treatment: Retinoids and Antibiotics*

#### In This Issue...

[EDITOR'S NOTE: The July 2007 issue and podcast of our sister publication, eInfections Review, discusses erythema migrans in the context of tick-borne diseases. Interested readers are invited to access these accredited programs by [visiting this page](#).]

While antibiotic therapy for moderate to severe acne is a time-honored and clinically proven treatment, until recently proper dosage has never been determined via a rigorous, controlled investigation. Retinoids, previously thought to be effective only in comedonal acne, have recently been shown to be effective in inflammatory acne in a variety of combination therapies. Research continues to support the efficacy of benzoyl peroxide, even when used as a cleanser, to minimize or eliminate the emergence of less sensitive Propionibacterium acnes strains.

In this issue we review investigations into these key areas of acne treatment: the proper dosing of minocycline; antibiotic and retinoid maintenance efficacy; antibiotic resistance; and the concomitant use of benzoyl peroxide.

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**Alan R. Shalita, MD**, has disclosed that he has received grants for clinical research and educational activities from, has served as an advisor, consultant and speaker to, and has served as an investigator for Allergan, Collagenex, Dow Pharma, DUSA and QLT. He serves as a consultant to Bradley/Doak, Galderma, Medicis and Steifel Warner-Chilcott. He is a stockholder of Allergan and Medicis.

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## LEARNING OBJECTIVES

**At the conclusion of this activity, participants should be able to:**

- Explain how the antibiotic treatment of acne can be calculated as dose per body weight
- Describe how retinoids may be used in conjunction with both topical and systemic antibiotics, and may then be used as monotherapy for maintenance
- Discuss how bacterial resistance in acne treatment can be minimized by the concomitant use of benzoyl peroxide

## COMMENTARY

The articles reviewed here present different perspectives on the use of antibiotics in the treatment of acne. One increasing concern among physicians is that the appropriate dosing of antibiotics for acne has never been calculated properly, and has thus been rather arbitrary. The study by Stewart et al demonstrates, for the first time, that for extended-release minocycline, a dose of 1 mg per kg is appropriate for large numbers of patients with inflammatory acne.

Antibiotics, however, have rarely been used as monotherapy for acne. Although investigating different antibiotics and different retinoids, the two 2006 studies reviewed here clearly conclude that retinoids, when used in conjunction with antibiotics, are highly effective as initial treatment. Further, they may be used safely and efficaciously as maintenance therapy for a considerable period of time. In addition, as reported by Schlessinger et al, a combination of a topical retinoid (tretinoin) with a topical antibiotic (clindamycin) is more effective than either agent used alone. This evidence strongly suggests that most patients with immoderate to severe inflammatory acne will benefit from a combination of a topical retinoid and either systemic or topical antibiotics. When less sensitive strains of *P. acnes* are of concern, then, as demonstrated by Leyden et al, a benzoyl peroxide product may

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be added.

Taken together, the data presented here can help us safely develop improved treatment regimens for the majority of our patients presenting with moderate to severe acne.

## PROPER DOSING FOR MINOCYCLINE IN ACNE TREATMENT

Stewart DM, Torok HM, Weiss JS, Plott RT, for the Solodyn Phase 2 Study Group. **Dose-ranging efficacy of new once-daily extended-release minocycline for acne vulgaris.** *Cutis.* 2006;78(4suppl):11-20.



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As part of the Phase 2 trials for a new extended-release (ER) minocycline hydrochloride formulation, the authors conducted a multi-center, 12-week, randomized, double-blinded, placebo-controlled, dose-ranging study in 233 subjects with moderate to severe facial acne vulgaris. The objective was to determine the lowest effective once-daily oral dose with the safest adverse effect profile.

Subjects were randomly assigned to treatment with daily dosages of ER-minocycline (1-, 2-, or 3-mg/kg tablets), or daily placebo tablets, for 12 weeks. At the end of the trial, the investigators found the number of inflammatory lesions decreased approximately 50% from baseline levels in all dose groups. However, no dose-dependent effect was observed, with the percentage decrease in the number of inflammatory lesions in the 1-mg/kg treatment group equal to or greater than the higher doses. Further, comparing the percentage decrease in inflammatory lesions between the 1 mg/kg and placebo groups, the authors reported a statistically significant difference ( $P=.015$ ). Of special importance, the investigators found that acute vestibular adverse events (AVAEs) **did** appear to be dose proportional, with the higher dose regimens associated with a higher incidence of AVAEs as well as central nervous system side effects.

These data clearly demonstrate that optimum results with this newer, once daily formulation of minocycline can be achieved with the lowest effective dose (1 mg/kg), and that there is no advantage to higher doses. Higher doses are not more effective and are associated with significantly greater side effects. Further, it is likely that once-daily dosing may improve patient convenience and thereby improve compliance.



Leyden, J, Thiboutot DM, Shalita, AR, et al. **Comparison of tazarotene and minocycline maintenance therapies in acne vulgaris: A multicenter, double-blind, randomized, parallel-group study.** *Arch Dermatol.* 2006;142:605-612.

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Thiboutot, DM, Shalita, AR, Yamauchi, PS, et al. **Adapalene gel, 0.1%, as maintenance therapy for acne vulgaris: a randomized, controlled, investigator-blind follow-up of a recent combination study.** *Arch Dermatol.* 2006;142:597-602

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These two 2006 studies were designed to assess the efficacy of maintenance therapy with a retinoid alone following combined antibiotic-retinoid treatment of acne. Leyden et al enrolled 189 patients from ambulatory research and referral centers who presented with moderately severe to severe acne vulgaris. The study was designed to evaluate the efficacy of 3 maintenance regimens (topical tazarotene, oral minocycline hydrochloride, or both) in sustaining improvement in acne. An open-label treatment phase was followed by double-blind, randomized, parallel-group maintenance phase. All patients were treated with 0.1% tazarotene gel (each evening) and a 100-mg capsule (twice daily) of minocycline hydrochloride for up to 12 weeks. Patients with 75% or greater global improvement at week 12 were then randomly assigned to an additional 12 weeks of maintenance therapy in 3 arms: tazarotene gel plus placebo capsules, vehicle gel plus minocycline capsules, or tazarotene gel plus minocycline capsules. One hundred-ten patients entered the maintenance phase, with 90 completing the study and 2 discontinuing because of adverse events. At 12 weeks of maintenance therapy, the mean reductions from baseline in noninflammatory and inflammatory lesion count were as follows:

	LESION REDUCTION	
	Non-Inflammatory	Inflammatory
Tazarotene alone	60%	54%
Minocycline alone	52%	66%
Tazarotene + Minocycline	64%	66%

At week 24, more than 80% of patients in each group had maintained a 50% or greater global improvement from baseline, and more than 50% had maintained a 75% or greater global improvement. While maintenance with combination tazarotene and minocycline therapy showed a trend for greater efficacy, there was no statistical significance versus tazarotene alone.

Similarly, Thiboutot et al sought to assess the maintenance effect of adapalene gel 0.1% in subjects successfully treated in a previous 12-week study of an adapalene-doxycycline 100 mg combination therapy. Two hundred fifty-three subjects with severe acne vulgaris from the initial study, who showed at least moderate (50%) improvement from baseline, were randomized to receive adapalene gel 0.1% or gel

vehicle once daily for 16 weeks. The study's main outcome measures included a maintenance rate of at least 50% improvement in lesion counts from the previous therapy (total, inflammatory, and noninflammatory), global severity assessment, cutaneous tolerability, and adverse events.

The researchers report that adapalene maintenance therapy resulted in significantly larger maintenance rates (75% vs 54%;  $P < .001$ ) and significantly lower lesion counts (total [ $P = .005$ ], inflammatory [ $P = .01$ ], and noninflammatory [ $P = .02$ ]) compared with gel vehicle. Adapalene was safe and well tolerated in this study.

In both investigations, maintenance treatment for 12 weeks with a retinoid alone produced very good to excellent results. In light of the increasing concern about the development of decreased sensitivity by *P. acnes* to antibiotics, the ability to maintain clinical improvement with a topical retinoid alone (either tazarotene or adapalene) may obviate the need for long-term antibiotic treatment in moderate to severe inflammatory acne.

## TOPICAL RETINOID-ANTIBIOTIC COMBINATION IN ACNE TREATMENT

Schlessinger J, Menter A, Gold M, et al for the ZIANA Study Group. **Clinical safety and efficacy studies of a novel formulation combining 1.2% clindamycin phosphate and 0.025% tretinoin for the treatment of acne vulgaris.** *J Drugs Dermatol.* 2007;6(6):607-615.



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This 2007 article reports on studies comparing the efficacy and safety of a solution of clindamycin phosphate 1.2% combined with partially solubilized and crystalline tretinoin 0.025% suspended in an aqueous-based, alcohol-free gel formulation (CLIN/RA gel) versus the individual ingredients alone in subjects with moderate inflammatory acne. This novel topical agent is approved by the FDA for the treatment of acne vulgaris in patients 12 years of age or older.

The authors describe 2 randomized, vehicle-controlled trials involving more than 4,500 subjects, and report that treatment with the combination significantly reduced lesion counts and improved patients' overall appearance to a greater extent than the individual components. Further, the combination was extremely well tolerated, with 1% or less of the subjects discontinuing due to adverse events.

These data confirm the prior observations made with a different formulation of the same 2 ingredients and suggest that topical therapy alone may be useful in many patients with moderate inflammatory acne, thus obviating the need for systemic antibiotics. One area where additional research is needed concerns maintenance therapy: could maintenance with the retinoid alone maintain the results observed after combined retinoid-systemic antibiotic therapy? As with all antibiotic use in acne, the concern regarding the development of less sensitive strains of *P. acnes* remains, raising the question: could these less sensitive strains be minimized by the concomitant use of benzoyl peroxide?

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Leyden J, Levy S. **The development of antibiotic resistance in Propionibacterium acnes.** *Cutis.* 2001;67(2 Suppl):21-24.



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Leyden and Levy report on 2 separate studies comparing the ability of a combination topical gel consisting of 5% benzoyl peroxide and 1% clindamycin versus clindamycin alone in reducing facial *Propionibacterium acnes* counts and decreasing the development of resistant organisms.

The first study compared the combination gel with 3 topical formulations of 1% clindamycin phosphate (gel, lotion, and solution) in 80 subjects. After a single week of treatment, the investigators reported a 99.7% reduction from baseline in facial *P. acnes* with the combination gel, a significantly greater reduction ( $P < .001$ ) than the 30%, 56%, or 62% reductions obtained with the clindamycin gel, lotion, or solution, respectively. After 2 weeks of treatment, the reduction from baseline *P. acnes* counts with the combination gel increased to 99.9% again, significantly greater ( $P < .001$ ) than the reduction achieved with 1% clindamycin alone, regardless of the formulation.

The second study compared the combination gel with 1% clindamycin gel in 79 patients with mild to moderate acne. The authors report that after 4 weeks of treatment, consistent with the previous study, the combination gel was more effective than clindamycin alone in reducing the total *P. acnes* count. However, by week 12, samples from patients using clindamycin alone showed an increase in the number of resistant bacteria, while counts of resistant bacteria remained stable or declined in those using the combination gel.

The results clearly indicate that the topical gel combination of benzoyl peroxide and clindamycin is much more effective in reducing *P. acnes* than the antibiotic alone. Moreover, clindamycin alone produced resistant strains that did not occur when benzoyl peroxide was combined with the antibiotic. This investigation confirms previous studies using the combination of benzoyl peroxide and erythromycin in a topical formulation,<sup>1</sup> where both *P. acnes* and staphylococci were reduced in the benzoyl peroxide arm. One reason why the combination provides such greater efficacy may be that, while the antibiotics used in acne treatment are bacteriostatic, benzoyl peroxide is bactericidal, therefore, increased resistance to these antibiotics may be reduced or eliminated by the concomitant use of benzoyl peroxide cleanser.<sup>2,3</sup>

## References

1. Shalita, AR, Chalker, DK, Ellis, CN, Parish, LC, Smith, JG. A multicenter, double-blind, controlled study of the combination of erythromycin/benzoyl peroxide, erythromycin alone, and benzoyl peroxide alone in the treatment of acne vulgaris. *Cutis.* 1992, 49:6A.
2. Harkaway, K.S., McGinley, K.J., Foglia, A.N., Lee, W.L., Fried, F., Shalita, A.R. and Leyden, J. J. [Antibiotic resistance patterns in coagulase-negative staphylococci after treatment with topical erythromycin, benzoyl peroxide and combination therapy.](#) *Brit. J. Derm* 126(6):586-90, 1992 June.
3. Leyden, JJ. Personal Communication, July 2007.

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