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DERMATOLOGY FORUM REPORT™

The 2006 Process of Care™ for Acne Vulgaris: Emerging Concepts in Acne—Redefining Minocycline Therapy for Moderate-to-Severe Acne Vulgaris

CME CERTIFIED MONOGRAPH

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This CME-certified monograph is intended for dermatologists and primary care physicians.

Upon completing this activity, you should be able to:

1. Discuss the role of Toll-like receptors in the pathogenesis of acne vulgaris.
2. Identify and contrast available treatment options for moderate-to-severe acne vulgaris.
3. Discuss the safety and efficacy weight-based dosing of minocycline for moderate-to-severe acne vulgaris.
4. Discuss the clinical rationale for using combination therapies for treating moderate-to-severe acne vulgaris.

Instructions

The learner should read the learning objectives and review the activity in its entirety. After reviewing the material, the learner should complete the Activity Self-assessment Test consisting of a series of multiple-choice questions.

Upon successfully completing this activity as designed and achieving a passing score of 70% or higher on the Activity Self-assessment Test, participants will receive a continuing education credit letter awarding the appropriate credit and the Activity Self-assessment Test answers four to six weeks after the receipt of the registration and evaluation materials.

Estimated time to complete this activity as designed is 1.0 hours.

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The 2006 Process of Care™ for Acne Vulgaris: Emerging Concepts in Acne—Redefining Minocycline Therapy for Moderate-to-Severe Acne Vulgaris

Expert Commentary

Lawrence F. Eichenfield, MD, Professor, Pediatrics and Medicine (Dermatology), University of California, San Diego School of Medicine; Director, Pediatric and Adolescent Dermatology, Children's Hospital; San Diego, California

Acne affects between 40 and 50 million individuals in the United States.¹ Although acne is typically associated with adolescence, affecting 79% to 95% of 16- to 18-year-old adolescents,²⁻⁴ acne may also affect younger children and adults. In 10- to 12-year-old children, acne affects from 28% to 61% of individuals.²⁻⁴ In adults older than 25 years, 54% of women and 40% of men exhibit some degree of facial acne, with symptoms persisting into middle age.⁵

There is a variety of safe and effective therapeutic options to treat pediatric, adolescent, and adult patients with acne vulgaris. Indeed, the past several decades have seen a proliferation of topical and systemic therapies developed for the treatment of acne vulgaris. Traditional topical and systemic agents for acne vulgaris include benzoyl peroxide, topical retinoids (tretinoin, adapalene, tazarotene), topical antibiotic agents (erythromycin, clindamycin), systemic oral antibiotic agents (erythromycin, tetracycline, doxycycline, minocycline), hormonal therapy (oral contraceptives, spironolactone), and oral isotretinoin. As the severity of acne vulgaris may range from mild to severe, systemic oral antibiotic therapy is typically indicated for moderate-to-severe inflammatory acne,^{6,7} or for acne considered emotionally burdensome for the patient for psychological or social reasons.⁶

Physicians have used erythromycin, tetracycline, doxycycline, and minocycline to treat acne vulgaris for decades. However, none of these agents have been systematically evaluated in clinical trials registered with the Food and Drug Administration (FDA) in which safety and efficacy are established and FDA approval obtained.

Erythromycin therapy may be associated with intolerable gastrointestinal side effects including nausea, vomiting, diarrhea, abdominal pain, and anorexia.⁶ Erythromycin is extensively metabolized by cytochrome P450 CYP3A and also inhibits CYP3A4; therefore, drug interactions may occur when erythromycin is concomitantly administered with medications such as HMG CoA reductase inhibitors (eg, lovastatin,

atorvastatin, simvastatin), azole antifungal agents (eg, ketoconazole), or antiepileptic agents (eg, carbamazepine) known to be metabolized by CYP3A4.⁸ Moreover, *Propionibacterium acnes* (*P. acnes*) sensitivity to erythromycin and related agents has decreased greatly over the past 20 years to the point where clinical resistance can occur. Tetracycline must be administered on an empty stomach as the presence of food or dairy products may hinder its absorption. Consequently, tetracycline may be associated with minor gastrointestinal side effects including nausea, vomiting, and diarrhea.

Doxycycline and minocycline are absorbed well, and minocycline is less likely than erythromycin and tetracycline to produce gastrointestinal side effects.⁹ Compared with doxycycline and tetracycline, minocycline has been associated with the greatest log reduction of *P. acnes*, most rapid onset of effect, and greatest residual reduction in *P. acnes*.¹⁰ Moreover, minocycline exhibits the lowest prevalence of *P. acnes* resistance compared with doxycycline, erythromycin, and tetracycline.¹¹ Resistance of *P. acnes* to oral antibiotics has been correlated with acne treatment failure.¹²⁻¹⁴ However, doxycycline may be limited by dose-related phototoxicity in some patients,¹⁵ and minocycline may be associated with vestibular adverse events,¹⁶ tissue pigmentation,¹⁶ and rarely, lupus-like syndrome.¹⁷ Vestibular adverse events are an important reason for treatment discontinuation.^{18,19}

The recent approval of minocycline extended-release tablets (Solodyn) by the FDA for the treatment of inflammatory lesions of non-nodular moderate-to-severe acne vulgaris represents the first oral systemic antibiotic approved for the first-line treatment of acne.²⁰ Minocycline extended-release tablets provide efficacy in treating moderate-to-severe acne vulgaris, while potentially minimizing the vestibular adverse effects that have been associated with minocycline administration.²¹ When dosed on a 1 mg/kg weight-basis, minocycline extended-release tablets provide the lowest established effective dose of minocycline for treating moderate-to-severe acne vulgaris. In addition, minocycline extended-release tablets are administered once daily, thus offering the potential to enhance patient compliance.

As newer, safer, and more effective therapeutic options for acne vulgaris become available, particularly in the setting of moderate-to-severe acne, a thorough understanding of acne

pathogenesis and the impact of new agents on its course is likely to improve short- and long-term outcomes in patients with moderate-to-severe acne vulgaris. With the recent introduction of minocycline extended-release tablets and data showing the utility of weight-based dosing of minocycline, the role of minocycline in treating acne may be redefined.

Toward that end, a panel of nationally recognized thought leaders in this setting (the Panelists, hereafter) convened to discuss new and emerging concepts in the treatment of moderate-to-severe acne vulgaris. *The 2006 Process of Care™ for Acne Vulgaris* is a synopsis of their analyses and discussions of key issues in the management of acne vulgaris. I hope the information in this monograph proves beneficial in managing your patients with moderate-to-severe acne vulgaris. For your additional benefit, CME credits accompany this monograph.

New Concepts in the Pathogenesis of Acne

Toll-like Receptors

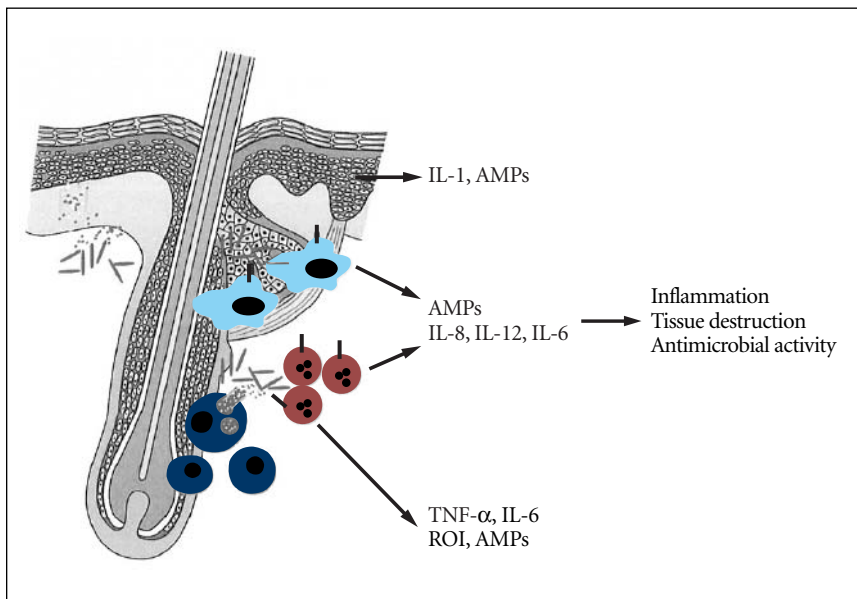
Acne is a disorder of the pilosebaceous unit resulting from multiple factors including abnormal desquamation of follicular epithelial cells, sebum production, hormones, *P. acnes*, and host-immune response.²² Through these multifactorial and complex mechanisms, acne lesions begin as subclinical micro-comedones that evolve into comedones and inflammatory lesions characterized by papules, pustules, nodules, and cysts. Although it is well-accepted that *P. acnes*, a gram-positive anaerobic bacterium that colonizes sebaceous follicles, is involved in the etiology of acne, its precise role in the pathogenesis of acne remains unclear. *P. acnes* has been shown to secrete extracellular factors such as lipases, producing fatty

acids that may contribute to the formation of comedones, promoting follicle wall rupture, and leading to inflammation. Furthermore, viable *P. acnes* in stationary growth phases has been shown to stimulate interleukin (IL)-1 α production from keratinocyte monolayers, suggesting that *P. acnes* may promote hyperkeratinization, the earliest step in the formation of acne lesions.²³

The innate immune response to *P. acnes* has been implicated as a factor in the pathogenesis of acne. The innate immune response is comprised of physical barriers (eg, skin, mucosa) and rapid cellular responses provided by dendritic cells, monocytes, natural killer cells, granulocytes, and epithelial cells. Toll-like receptors (TLRs) are pattern recognition receptors, transmembrane proteins capable of mediating responses to pathogen-associated molecular patterns. Because TLRs are a critical component in the innate immune response to pathogens, the expression of TLRs at sites of host-pathogen interaction, such as the skin, is critical for host defense. The demonstration of TLR2 expression within acne lesions²² suggests that inflammation, activated by *P. acnes* through TLR2, may be an important factor in the pathogenesis of acne. Moreover, activation of TLR2 by *P. acnes* induces IL-12 and IL-8;²⁴ IL-8 is a known neutrophil chemoattractant, and thus contributes to the formation of inflammatory lesions.

TLR activation also promotes the release of antimicrobial peptides (AMPs), which may play a role in the pathogenesis of acne. As illustrated in Figure 1, *P. acnes* triggers production and release of cytokines and AMPs from keratinocytes, monocytes, neutrophils, and T cells present in the perifollicular region where *P. acnes* resides. These substances inflame the surrounding skin, resulting in both tissue and microbe destruction.

Figure 1. Innate Immune Response in Acne.



IL = interleukin; AMP = antimicrobial peptides; TNF = tumor necrosis factor; ROI = reactive oxygen intermediates.

“One of the questions we face as investigators is how bacteria mediate not only the inflammatory process, but also the development of comedones. Certainly, there is emerging evidence for the role of Toll-like receptors in that regard,” stated Lawrence F. Eichenfield, MD, Professor, Pediatrics and Medicine (Dermatology), University of California, San Diego School of Medicine; Director, Pediatric and Adolescent Dermatology, Children’s Hospital; San Diego, California. “Furthermore, Toll-like receptors may facilitate the role of interleukin and the development of comedones,” added Dr. Eichenfield.

“There are independent pieces of evidence,” interjected James J. Leyden, MD, Professor of Dermatology, University of

Pennsylvania, Philadelphia, Pennsylvania. “Terrence Kealey demonstrated that interleukin-1 alpha caused hypercornification of the infundibulum similar to that seen in comedones,^[25] and Cunliffe’s group showed that *P. acnes* can interact with epithelial cell and cause release of interleukin-1.^[26] Then Ben Vowels, Ken McGinley, and I showed that the cell wall peptidoglycan of *P. acnes* interacts with macrophages causing the release of various cytokines including interleukin-1, interleukin-8, and TNF-alpha.^[27] Subsequently, Toll-like receptors were identified as the mechanism for the peptidoglycan interaction. *P. acnes* interaction with Toll-like receptors is thus a very important piece of the complex pathophysiology of acne,” added Dr. Leyden.

“Understanding the mechanisms of inflammatory pathways involved in acne underscores the benefit of antibiotics with both antibacterial and anti-inflammatory properties,” stated James Q. Del Rosso, DO, FAOCD, Clinical Associate Professor, Department of Dermatology, University of Nevada School of Medicine, Las Vegas, Nevada. “But much work remains to be done because many questions concerning the inflammatory process, particularly with respect to acne, remain unanswered,” commented Dr. Del Rosso.

Concepts of Oral Antibiotic Therapy for Acne

Need for Systemic Antibiotic Therapy

The decision to initiate systemic antibiotic therapy for acne is usually based on the extent and severity of inflammatory lesions. Moderate-to-severe acne, acne resistant to topical therapy alone, or acne covering extensive body surface may be best treated with systemic antibiotics.^{6,28} Systemic antibiotics used to treat acne have both antimicrobial and anti-inflammatory properties. Systemic antibiotics reduce *P. acnes* within sebaceous follicles, thereby inhibiting production of bacterial-induced inflammatory cytokines.²⁹ More specifically, tetracycline and erythromycin suppress leukocyte chemotaxis³⁰ and bacterial lipase activity,³¹ whereas minocycline and doxycycline inhibit cytokines and matrix metalloproteinases thought to contribute to inflammation and tissue breakdown.³²

Selection of Oral Antibiotic Therapy

The Panelists acknowledged that macrolide antibiotics (eg, erythromycin) are no longer the preferred treatment options for moderate-to-severe acne due to decreased sensitivity of *P. acnes*. According to the Panelists, the systemic antibiotics most widely used to treat acne are the tetracyclines—tetracycline, doxycycline, and minocycline. Although some physicians

regard these agents as essentially interchangeable, the Panelists agreed that there are substantive differences between the different tetracycline antibiotics, specifically doxycycline and minocycline, in terms of tissue distribution and lipophilic characteristics, which result in better delivery to the target tissue.

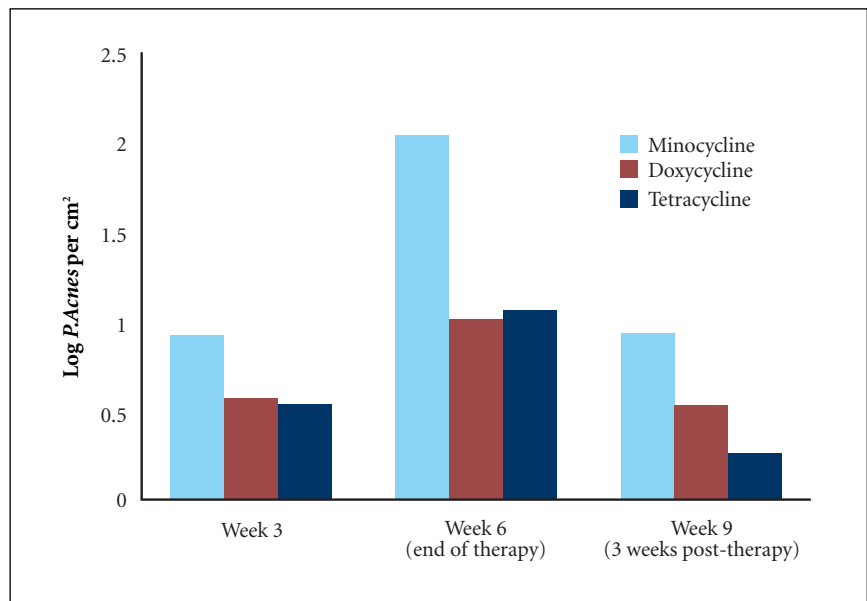
“We established differences between these agents several years ago. Unfortunately, I believe some clinicians have lost sight of the fact that, at least in terms of a microbiological effect, there is a significant difference between tetracycline, doxycycline, and minocycline,” stated Dr. Leyden.

In a 9-week, parallel comparison trial, 60 subjects with acne were divided into 3 treatment groups and randomized to minocycline 200 mg daily, doxycycline 200 mg daily, or tetracycline 1000 mg daily for 6 weeks, followed by a 3-week follow-up period.¹⁰ Subjects were required to have minimum *P. acnes* levels of 10,000 colony-forming units per cm² at baseline. Quantitative bacteriologic cultures were obtained at baseline, after 3 and 6 weeks of treatment, and at 9 weeks (3 weeks post-treatment).

Minocycline produced highly significant reductions in *P. acnes* after 3, 6, and 9 weeks compared with baseline (all $P \leq .01$) (Figure 2). Doxycycline and tetracycline produced significant reductions in *P. acnes* ($P \leq .01$) after 3 and 6 weeks. At 9 weeks, doxycycline produced significant reductions in *P. acnes* ($P = .05$), but tetracycline produced insignificant reductions in *P. acnes*.

At 3 weeks, differences between minocycline, doxycycline, and tetracycline had not yet reached statistical significance. At 6 weeks, the 2-log net reduction in *P. acnes* produced by minocycline was significantly greater ($P \leq .01$) than the 1-log

Figure 2. Net Reduction in *P. Acnes*—Combined Data (Forehead and Cheeks).



reduction produced by either doxycycline or tetracycline. Because the minimum inhibitory concentrations (MICs) are comparable, the results at 3 and 6 weeks suggest that minocycline achieves a higher concentration in sebaceous follicles than other tetracyclines. This conclusion is further substantiated by the slower return to baseline pre-antibiotic levels of *P. acnes* in those treated with minocycline.

Minocycline produced the highest degree of residual activity. The residual reduction in *P. acnes* with minocycline was not only significantly higher versus baseline ($P \leq .01$), but it was equal to that after 3 weeks of minocycline therapy. Doxycycline produced a modest residual effect much lower than minocycline; tetracycline produced little to no residual effect. At 9 weeks, *P. acnes* levels in subjects treated with tetracycline had returned to baseline.

“Our premise was that both minocycline and doxycycline were more lipophilic than tetracycline,” stated Dr. Leyden. “However, minocycline is more lipid soluble than doxycycline. Moreover, the greater lipophilicity of minocycline is supported by the greater octanol/water partition coefficient of minocycline [1.48] versus doxycycline [0.92] and tetracycline [0.52] at the near physiologic pH of 6.6. The *in vivo* difference with respect to a faster, greater reduction in *P. acnes* and a slower return to pre-treatment levels suggests that there is more minocycline in the sebaceous follicle than with doxycycline, and more with doxycycline than with tetracycline. Unfortunately, we do not have a way to measure the drug concentration in sebaceous glands directly, but the data suggest that minocycline accumulates in the follicle because of its lipophilicity. Certainly, the level of drug in the follicle is more important than the serum concentration,” explained Dr. Leyden.

Although the study results demonstrated that the antimicrobial effects against *P. acnes* are greater with minocycline than with doxycycline or tetracycline, the clinical relevance of such findings on efficacy have not been investigated under controlled and sufficiently powered comparative clinical trials.

Dr. Del Rosso interjected, “Let me pose this question. What happens with ‘dead’ *P. acnes*? Is there a continued stimulation of inflammation?”

“If you are asking if dead *P. acnes* remains inflammatory—the answer is yes,” responded Guy F. Webster, MD, PhD, Clinical Professor, Department of Dermatology, Thomas Jefferson University, Philadelphia, Pennsylvania. “When you inject dead *P. acnes* into the skin, it remains as a lingering inflammatory stimulus for weeks and weeks and weeks^[33],” added Dr. Webster.

“That is why I asked the question,” stated Dr. Del Rosso. “And this speaks to the importance of several issues. First, it is common for erythema to persist for several weeks at sites of

resolved inflammatory lesions, suggesting persistent inflammation. Secondly, you must consider the importance of the residual antimicrobial effect. Once *P. acnes* is killed, there is still an inflammatory component that you must consider and take into account when first selecting antibiotic therapy. Last, but not least, the duration of antibiotic therapy is significant because acne is a chronic inflammatory disorder, not an infection,” noted Dr. Del Rosso.

“I believe everyone here would agree that when you are initiating systemic antibiotic therapy, the duration of initial therapy usually ranges from 3 to 6 months,” commented Dr. Eichenfield.

According to the Global Alliance to Improve Outcomes in Acne,³⁴ the duration of oral antibiotics should be minimized to reduce the potential for the emergence of antibiotic resistance with *P. acnes*, as well as with other commensal or pathogenic organisms such as staphylococci or streptococci. The Global Alliance recommends that the minimum duration of therapy with oral antibiotics be 6 to 8 weeks with a maximum of 12 to 18 weeks. However, if the patient cannot tolerate other therapies and a therapeutic benefit is evident, antibiotic therapy may be continued indefinitely. In such patients, the Global Alliance also recommends adding benzoyl peroxide to suppress emergence of resistant strains of *P. acnes*. The Panelists stated that although limited exposure is often desirable, duration of therapy is dictated by the disease severity, the patient response to therapy, and the course of acne after discontinuation of oral antibiotic therapy is attempted.

Differences in Tolerability

“In terms of tolerability, how do doxycycline and minocycline differ?” asked Dr. Eichenfield.

“Erosive esophagitis is certainly an issue with doxycycline^[35],” responded Dirk M. Elston, MD, Director, Department of Dermatology, Geisinger Medical Center, Danville, Pennsylvania.

“Yes, erosive esophagitis is an issue, but I believe the far more common side effect seen with doxycycline is the peculiar gnawing nausea that accompanies its administration,” added Dr. Leyden.

“Perhaps of most concern to practicing dermatologists is the photosensitivity that has been associated with tetracyclines,” commented Dr. Eichenfield. “As someone who treats patients in the Sunbelt, photosensitivity is particularly important. Many of our patients are outside a great deal and photosensitivity is clearly an issue. In addition, many of these patients are on concomitant retinoid agents, so we are concerned about the impact,” added Dr. Eichenfield.

“Photosensitivity is significantly associated with doxycycline^[36],” noted Dr. Elston. “Minocycline is less commonly associated with photosensitivity,” added Dr. Elston.

Long-term minocycline use has rarely been associated with the development of lupus-like symptoms in some acne patients, especially in female patients with long-term use (>12 months).¹⁷ The Panelists, however, felt that these events were relatively uncommon and should not be exaggerated to create undue concerns about using minocycline to treat acne.

“I believe the term ‘lupus-like syndrome’ may be misleading to some dermatologists. It is important to recognize that most patients do not present with cutaneous signs of lupus,” stated Dr. Del Rosso.

“I am tempted to agree,” responded Dr. Leyden. “But we have to clarify what is actually in the literature. There was an important paper that examined the hazard ratio/relative risk factor of different tetracyclines and their association with lupus-like syndrome.¹⁷ The real question is whether those lupus-like syndromes were really drug-induced hepatitis associated with a positive antinuclear antibody (ANA) or whether those patients had other serologic markers that would be consistent with a drug-induced lupus erythematosus,” stated Dr. Leyden.

“Because there is a big difference,” interjected Dr. Webster.

“One of the original publications on this topic¹⁷ stated that although acne itself is often seen in association with autoimmune liver disease, the patient cases analyzed suggest a drug reaction from minocycline,” added Alan R. Shalita, MD, Professor and Chairman, Department of Dermatology, Downstate Medical Center, State University of New York (SUNY), Brooklyn, New York.

“The lupus-like syndrome is a very rare phenomenon found in a very small subset of patients who receive long-term treatment,” advised Dr. Eichenfield. “And it’s a phenomenon of a set of findings that may include arthralgia, hepatitis, and a positive ANA. It is distinct from systemic lupus erythematosus because it resolves upon drug discontinuation,” added Dr. Eichenfield.

“I do not routinely check ANA status before initiating treatment with minocycline,” noted Diane S. Berson, MD, Assistant Professor of Dermatology and Assistant Attending Dermatologist, New York-Presbyterian Hospital, New York, New York.

Some Panelists questioned whether the lupus-like syndrome was indeed drug-induced systemic lupus erythematosus or perhaps serum sickness.

“Serum sickness-like drug reaction associated with minocycline is extremely rare,” advised Dr. Del Rosso. “It is far more common with one particular cephalosporin antibiotic—cefactor,” added Dr. Del Rosso.

The sentiment of the Panelists was captured in their agreement that an ANA-negative status is not required for safe initiation of minocycline therapy and that ANA testing is not a prerequisite to therapy.

Minocycline Extended-release—Potential Enhanced Tolerability of Minocycline

“Certainly, minocycline has been a safe and effective treatment for moderate-to-severe acne. And there is a new extended-release formulation of minocycline that many of you here have been involved with as clinical investigators. I believe this formulation may not only reduce the incidence of vestibular effects associated with minocycline administration, but may redefine the role of minocycline in treating moderate-to-severe acne—weight-based dosing. Dr. Shalita, could you set the stage for us?” asked Dr. Eichenfield.

“If you go back in the literature, you will find no scientific study to demonstrate what the correct dose is for tetracycline, doxycycline, or minocycline in treating acne,” advised Dr. Shalita. “The doses were arbitrarily decided and based on anti-infective doses—a loading dose followed by either 1000 mg daily of tetracycline, 200 mg daily of doxycycline, or 200 mg daily of minocycline. Now, for the first time, we actually have a dose-response clinical study that indicates the ideal dose for treating acne with minocycline is no more than 1 mg per kilogram. And that dose has been demonstrated in more than one thousand patients—so, this is real,” indicated Dr. Shalita.

“This dosage allows penetration into the sebaceous follicle due to its [minocycline] lipophilic property, without the need for higher systemic doses that are potentially associated with vestibular side effects,” advised Dr. Berson.

The development of minocycline extended-release tablets was based on 2 hypotheses: first, that the efficacy of minocycline in treating acne vulgaris was not related to its serum concentrations; and second, that the high peak serum concentrations of minocycline were responsible for the acute vestibular adverse events. The highly lipophilic property of minocycline is well-suited for penetration into lipid-rich tissues such as the pilosebaceous unit,¹⁰ where sebum serves as a growth medium for *P. acnes* within the follicles. The extent of systemic minocycline bioavailability in acne is less important than the lipophilic property of the molecule, as accumulation of greater minocycline levels in the pilosebaceous unit provides a clinically effective level of *P. acnes* reduction documented with minocycline use.³⁸ The pharmacokinetic delivery of minocycline extended-release tablets avoids the more rapid increase in serum levels observed with immediate-release minocycline³⁸ that may influence the potential for vestibular adverse events (eg, dizziness, vertigo). Minocycline extended-release tablets were designed to address the clinical conundrum of finding an effective dose for treating moderate-to-severe acne

vulgaris based on patient weight while minimizing potential adverse events.

“So this extended-release formulation is distinct from all other formulations of minocycline,” stated Dr. Eichenfield. “It was evaluated at 1 mg per kilogram using 3 doses—45 mg, 90 mg, and 135 mg—in efficacy studies up to 12 weeks and long-term safety studies up to 2 years,” added Dr. Eichenfield.

“Because antibiotics used to treat acne have been approved as adjunctive therapy by the FDA, the minocycline extended-release formulation is the first antibiotic approved by the FDA specifically as first-line therapy for acne,” stated Dr. Leyden. “Although we have always known the efficacy of minocycline in treating acne, this development really began when we examined whether we could improve on the issue of vestibular adverse events,” added Dr. Leyden.

“One study, which evaluated the dissolution rates of various formulations of minocycline, demonstrated a difference in the incidence of vertigo. And the difference was attributed to a slower release of minocycline,” advised Dr. Shalita.

“I summarized this data recently in an article published in *Cutis*^[38],” commented Dr. Del Rosso.

The results of that study demonstrated that the greater frequency of vestibular adverse events with generic minocycline formulations (compared with a brand formulation of minocycline [Dynacin]) appeared to be explained by differences in dissolution rate, drug release, and rate of rise in serum level of minocycline.³⁸ Specifically, the generic formulation of minocycline exhibited a 100% release in less than 15 minutes, which attributed to the rapid rise in the serum level of minocycline (Figure 3). Based on these observations, investigators hypothesized that an extended-release formulation of minocycline may potentially reduce the incidence of vestibular adverse events.

Dissolution studies for minocycline extended-release tablets indicate the following pharmacokinetic parameters:

- Release in 1 hour: >30% to ≤53%
- Release in 2 hours: >53% to ≤84%
- Release in 4 hours: >85%
- Delayed T_{max} : 3.5 hours compared with 2.25 hours for immediate-release minocycline
- Reduced C_{max} : 72% of immediate-release minocycline
- Reduced area-under-the-curve: ~80% of immediate-release minocycline

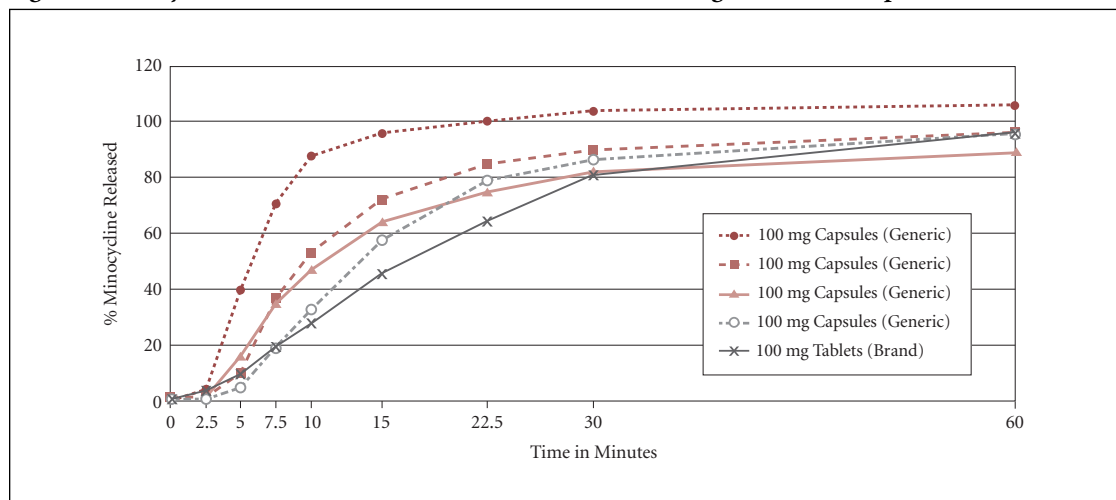
“Given the pharmacokinetic data, it is important for clinicians to know that minocycline extended-release tablets are *not* bioequivalent to any other formulation of minocycline,” asserted Dr. Eichenfield.

“This is very important as the bioavailability of the minocycline extended-release formulation differs from all other minocycline products that are immediate-release formulations,” stated Dr. Del Rosso. “Therefore, pharmacists have no option to legitimately substitute for the extended-release formulation and should not do so, as other minocycline products—both brand and generic—are not bioequivalent,” reiterated Dr. Del Rosso.

“And, as Dr. Shalita indicated, we have been traditionally dosing minocycline at 200 mg daily,” stated Dr. Leyden. “Now we have an extended-release formulation, with lower peak concentrations, and data indicating that 1 mg per kilogram is an effective dose for treating acne. And not higher, because 2 mg and 3 mg per kilogram were also evaluated but showed no additional therapeutic effect—only a higher incidence of vestibular side effects,” advised Dr. Leyden.

“Because minocycline extended-release tablets are dosed once daily, this may ensure better compliance,” noted Dr. Berson. “Oftentimes, patients, especially adolescents, only take their medication once a day, even when prescribed twice a day,” added Dr. Berson.

Figure 3. Minocycline HCL USP in Vitro Dissolution Studies: 100 mg Tablets and Capsules.



During the phase 2 dose-response studies, higher dose regimens (2 mg/kg, 3 mg/kg) offered no additional therapeutic benefit, but were associated with an increased risk of vestibular adverse events (Table 1, Table 2).

The results of the phase 2 studies demonstrated that the 1 mg/kg dose was the lowest effective dose for treating acne, which led to further evaluation in phase 3 trials.

Efficacy and Safety

The efficacy and safety of once-daily minocycline extended-release tablets were evaluated in 2 multicenter, randomized, double-blind, placebo-controlled, 12-week phase 3 studies.²⁰ A total of 924 subjects (age ≥12 years) with non-nodular moderate-to-severe inflammatory acne vulgaris were randomized to 1 mg/kg minocycline extended-release tablets or placebo for 12 weeks. The primary efficacy end points included the mean percent change in inflammatory lesion counts from baseline to 12 weeks and the percentage of subjects with an Evaluator’s Global Severity Assessment (EGSA) of “clear” or “almost clear” (dichotomized as “success” or “failure”, according to FDA requirements) at 12 weeks. Safety assessments were based on the incidence of adverse events and clinical laboratory parameters (complete blood counts, serum chemistries). Patients were evaluated at 4, 8, and 12 weeks.

At the end of 12 weeks, subjects treated with minocycline extended-release tablets demonstrated significantly greater reduction in the number of inflammatory lesion counts from baseline compared with placebo (Table 3). In addition, subjects treated with minocycline extended-release tablets significantly improved in the overall appearance in their acne as judged by the EGSA (Table 3). Although all subjects had an EGSA of moderate, severe, or very severe at baseline, the majority of subjects treated with minocycline extended-release tablets were graded as “mild,” “almost clear,” or “clear” (56.8% minocycline vs 42.0% placebo for Study 1; 52.4%

Table 1. Inflammatory Lesion Counts: Mean Baseline and % Reduction at Day 84.

	Minocycline Extended-release (1 mg/kg)	Minocycline Extended-release (2 mg/kg)	Minocycline Extended-release (3 mg/kg)	Placebo
Baseline	38.8	47.0	39.1	40.3
% Reduction at Day 84	56.8	49.3	46.6	39.4

Table 2. Subjects (%) with Acute Vestibular Adverse Events* (Days 1–5).

	Minocycline Extended-release (1 mg/kg)	Minocycline Extended-release (2 mg/kg)	Minocycline Extended-release (3 mg/kg)	Placebo
Subjects, n (%)	6 (10.2%)	14 (23.7%)	17 (28.3%)	9 (16.4%)

* Acute vestibular adverse events defined as dizziness, nausea, tinnitus, vertigo, or vomiting in the first 5 days of treatment.

minocycline vs 40.2% placebo for Study 2) by the end of the 12-week period.

Minocycline extended-release tablets were well-tolerated with overall treatment-emergent adverse events comparable to placebo (Table 4). The majority of adverse events were mild in severity. Adverse events possibly related to vestibular function (dizziness, nausea, tinnitus, vertigo, and vomiting) were comparable between minocycline extended-release tablets and placebo, with the exception of dizziness, which was reported in 8.8% of subjects treated with minocycline extended-release tablets compared with 4.7% of subjects treated with placebo. An analysis of treatment-emergent adverse events by age group revealed no significant differences between pediatric subjects (12 to 17 years) and adult subjects (≥18 years). No clinically significant treatment-dependent effects on clinical laboratory parameters associated with liver or thyroid function were observed.

Adverse events led to treatment discontinuation in 20 subjects (3.0%) treated with minocycline extended-release tablets compared with 6 subjects (1.6%) treated with placebo. The most common reasons for treatment discontinuation due to adverse events were pruritus, urticaria, rash, and fatigue.

Table 3. Efficacy Results at 12 Weeks for Minocycline Extended-release Tablets and Placebo.

	Study 1			Study 2		
	Minocycline Extended-release (1 mg/kg) (N = 300)	Placebo (N = 151)	P-value	Minocycline Extended-release (1 mg/kg) (N = 315)	Placebo (N = 158)	P-value
Mean % Improvement in Inflammatory Lesions	43.1%	31.7%	.001	45.8%	30.8%	<.001
% of Subjects “Clear” or “Almost Clear” on EGSA	17.3%	7.9%	.006*	15.9%	9.5%	.018*

* P-value determined from Day 84 data only from Cochran-Mantel-Haenszel test. EGSA = Evaluator’s Global Severity Assessment.

Table 4. Selected Treatment-emergent Adverse Events in at Least 2% of Clinical Trial Subjects.

	Minocycline Extended-release (1 mg/kg) (n = 674)	Placebo (n = 364)
At least one treatment-emergent adverse event	56.2%	54.1%
Headache	22.6%	22.8%
Nausea	9.5%	11.3%
Fatigue	9.2%	6.6%
Dizziness	8.8%	4.7%
Diarrhea	5.2%	5.8%
Gastrointestinal pain	5.0%	6.9%
Pruritus	4.6%	4.4%
Malaise	3.9%	2.5%
Abdominal pain, upper	3.3%	3.8%
Mood alteration	2.5%	2.5%
Vomiting	2.1%	2.5%
Somnolence	1.9%	0.8%
Tinnitus	1.5%	1.4%
Vertigo	1.2%	0.8%

Table 5 illustrates the recommended dosing for minocycline extended-release tablets.

“The reduction in maximum concentration avoids the spike in minocycline concentration that we believe is responsible for the vestibular side effects,” advised Dr. Leyden.

“In addition, with once-daily dosing and available topical treatment options, minocycline extended-release tablets will be an easier drug to prescribe for treating acne,” commented Dr. Berson.

“And there is data to indicate that this formulation of minocycline is not affected by the presence or absence of food, correct?” questioned Dr. Eichenfield.

Table 5. Recommended Dosing of Minocycline Extended-release Tablets.

Patient’s Weight (lbs)	Patient’s Weight (kg)	Tablet Strength (mg)	Actual Dose (mg/kg)
99–131	45–59	45	1.00–0.76
132–199	60–90	90	1.50–1.00
200–300	90–136	135	1.48–0.99

“That is correct,” responded Dr. Leyden. “The critical point with this formulation is that we are minimizing exposure to minocycline, thus reducing vestibular side effects but retaining its efficacy for treating acne at lower doses,” added Dr. Leyden.

“These studies lead me to surmise that we have been historically overdosing minocycline in our patients with acne.”

—Lawrence F. Eichenfield, MD

“That’s a fair statement.”

— James J. Leyden, MD

“Because the pigmentation associated with minocycline administration is dose-related,^[16] should we not observe a reduced incidence in pigmentation?” inquired Dr. Webster.

“Yes. In the phase 3 studies, no changes in pigmentation were observed in patients receiving minocycline extended-release tablets. The bottom line is that the lower dose [1 mg/kg] is better tolerated and as equally effective as the higher doses [2 mg/kg, 3 mg/kg],” responded Dr. Leyden.

“That is totally counterintuitive to dermatologists. Another important consideration is the impact of this formulation on oral contraceptives,” commented Dr. Eichenfield.

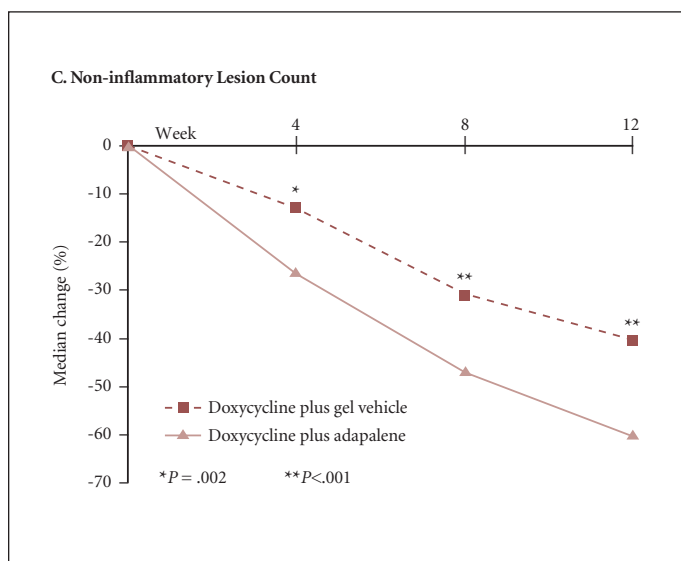
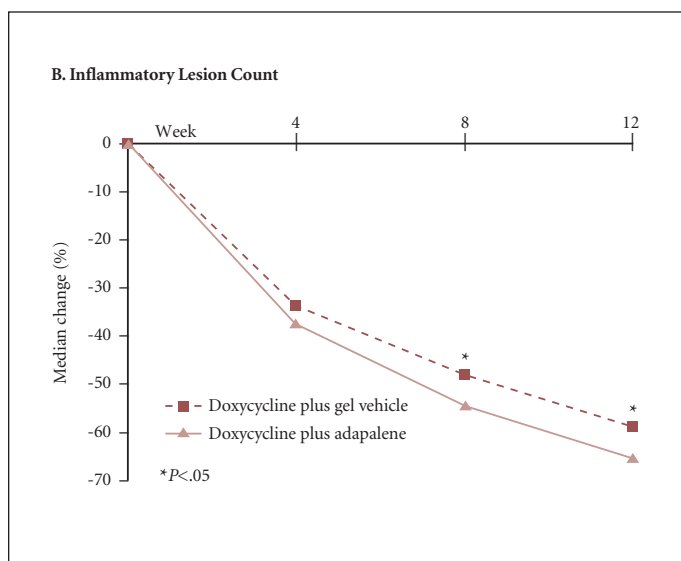
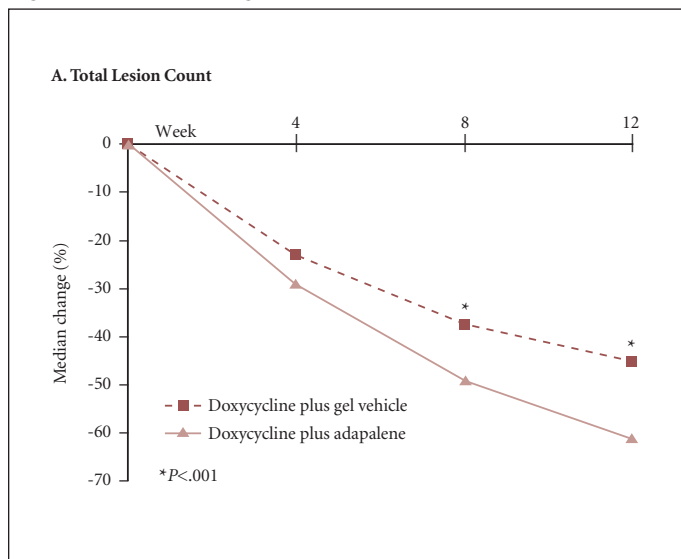
A double-blind, randomized, switch-over study was conducted to evaluate the effect of minocycline extended-release tablets (1 mg/kg) on low-dose estrogen contraception and hormone levels over one menstrual cycle.²⁰ No evidence of drug-related effects on plasma concentrations of estradiol, follicle stimulating hormone (FSH), luteinizing hormone (LH), or progestinic hormones was found. In addition, no treatment-related changes in estradiol plasma concentrations, breakthrough bleeding, or contraceptive failure were observed.

“I believe this is the first controlled study of minocycline that showed no effect on hormone levels—doxycycline has the same finding,” interjected Dr. Shalita.

“This finding is encouraging because many women who take oral contraceptives have inflammatory acne for which an oral antibiotic is indicated,” advised Dr. Berson.

In concluding their discussion on minocycline extended-release tablets, the Panelists acknowledged that future comparative clinical trials are

Figure 4. Median Change in Lesion Counts.³⁹



needed to assess fully its potential benefits vis-à-vis other minocycline formulations. In addition, the Panelists noted that long-term safety studies are currently underway and represent the first long-term evaluation of ANA production in patients receiving minocycline. Preliminary results will be published in the near future.

Maintenance Therapy

“Maintenance therapy for acne is an area that hasn’t been explored extensively,” offered Dr. Eichenfield.

“No, it really hasn’t,” concurred Dr. Leyden. “But, two studies come to mind. One study evaluated the combination of adapalene gel 0.1% and doxycycline^[39], and the other study evaluated tazarotene and minocycline as monotherapy and in combination^[40],” stated Dr. Leyden.

In a multicenter, vehicle-controlled, parallel group, 12-week study, patients with acne were randomized to doxycycline 100 mg plus adapalene gel 0.1% (n = 238) or doxycycline 100 mg plus gel vehicle (n = 229).³⁹ At Week 12, the combination of doxycycline and adapalene was significantly superior to doxycycline alone for change from baseline in total ($P<.001$), inflammatory ($P<.05$), and non-inflammatory lesions ($P<.001$) (Figure 4). Both treatments were well-tolerated and no serious adverse events were reported.

In a multicenter study composed of a 12-week, open-label treatment phase followed by a 12-week, double-blind, parallel-group maintenance phase, tazarotene and minocycline therapy was evaluated in 189 patients with moderately-severe to severe acne vulgaris.⁴⁰ During the initial phase, patients applied tazarotene gel 0.1% once daily and received minocycline 100 mg twice daily. Patients who achieved a 75% global improvement in their acne were entered into the maintenance phase and randomized to tazarotene gel 0.1% plus placebo, vehicle gel placebo plus minocycline 100 mg twice daily, or tazarotene gel 0.1% plus minocycline 100 mg twice daily.

All 3 maintenance regimens were effective in sustaining improvement in acne achieved during initial treatment with tazarotene plus minocycline. No statistically significant differences among the 3 maintenance regimens were detected at any point for mean overall disease severity score, percentage of patients maintaining a 50% or greater or a 75% or greater global improvement, or mean percentage change from baseline in non-inflammatory or inflammatory lesion counts. Although no statistical differences were observed, the data suggested that efficacy against inflammatory acne was slightly greater with minocycline monotherapy or tazarotene plus minocycline than with tazarotene alone. All regimens were well-tolerated.

The investigators concluded that initial treatment with tazarotene plus minocycline was effective in improving moderately-severe to severe acne, but noted that maintenance therapy with topical retinoid monotherapy may prevent potential problems such as the development of *P. acnes* resistance.

The Panelists agreed that for extended periods of treatment the use of benzoyl peroxide in conjunction with oral antibiotic therapy might help minimize the development of resistance. Topical retinoids should also be considered components of maintenance therapy, the Panelists noted.

Conclusion

The past several decades have seen a proliferation of topical and systemic therapies developed for the treatment of acne vulgaris. Traditional topical and systemic agents for acne vulgaris include benzoyl peroxide, topical retinoids, topical antibiotic agents, systemic oral antibiotic agents, hormonal therapy, and oral isotretinoin. As the severity of acne vulgaris

may range from mild to severe, systemic oral antibiotic therapy is typically indicated for moderate-to-severe inflammatory acne.

Physicians have used erythromycin, tetracycline, doxycycline, and minocycline to treat acne vulgaris for decades. However, the recent approval of minocycline extended-release tablets offers new insights into treating moderate-to-severe acne vulgaris. Unlike immediate-release formulations, minocycline extended-release tablets utilize a novel pharmacokinetic delivery that, when dosed on a 1 mg/kg weight-basis, provides the lowest established effective dose of minocycline for treating moderate-to-severe acne vulgaris, while minimizing potential adverse events. In addition, minocycline extended-release tablets are administered once daily, thus offering the potential to enhance patient compliance.

As newer, safer, and more effective therapeutic options for acne vulgaris become available, a thorough understanding of these agents will enhance long-term outcomes in patients with acne vulgaris.

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The 2006 Process of Care™ for Acne Vulgaris: Emerging Concepts in Acne—Redefining Minocycline Therapy for Moderate-to-Severe Acne Vulgaris

Activity Self-assessment Test

1. What percentage of 16- to 18-year-old adolescents does acne affect?
 - A. 49% to 65%
 - B. 59% to 75%
 - C. 69% to 85%
 - D. 79% to 95%
2. Traditional topical agents for treating acne include:
 - A. Benzoyl peroxide
 - B. Adapalene
 - C. Tazarotene
 - D. Erythromycin
 - E. All of the above
3. Which of the following agents has the lowest prevalence of *P. acnes* resistance?
 - A. Erythromycin
 - B. Minocycline
 - C. Doxycycline
 - D. Tetracycline
4. What is the FDA-approved dosing for minocycline extended-release tablets in treating moderate-to-severe acne vulgaris?
 - A. 1 mg/kg
 - B. 2 mg/kg
 - C. 3 mg/kg
 - D. All are approved doses
5. Acne is a disorder of the pilosebaceous unit resulting from:
 - A. Abnormal hyperkeratinization
 - B. Sebum production
 - C. *P. acnes*
 - D. Host-immune response
 - E. All of the above
6. Minocycline accumulates in the pilosebaceous unit due to its:
 - A. High serum concentration
 - B. High lipophilicity
 - C. Rapid onset of action
7. According to the Panelists, an appropriate duration of therapy for systemic antibiotics in treating acne is:
 - A. 6 to 8 weeks
 - B. 12 to 18 weeks
 - C. Dictated by the disease severity and the patient response
8. In the study comparing generic and brand formulations of minocycline, the greater frequency of vestibular adverse events was attributed to:
 - A. Differences in dissolution rates
 - B. Differences in drug release
 - C. Rate of rise in serum minocycline levels
 - D. All of the above
9. True or False. The reduction in vestibular adverse events seen with minocycline extended-release tablets is most likely due to avoiding the spike in minocycline concentration seen with immediate-release minocycline.
 - A. True
 - B. False
10. The combination of adapalene and doxycycline was significantly superior to doxycycline alone in reducing:
 - A. Total lesions
 - B. Inflammatory lesions
 - C. Non-inflammatory lesions
 - D. All of the above



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| 2. A B C D E | 4. A B C D | 6. A B C | 8. A B C D | 10. A B C D |
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PROGRAM OBJECTIVES:

Having completed this activity, I am better able to:

	Strongly Agree			Strongly Disagree	
Discuss the role of Toll-like receptors in the pathogenesis of acne vulgaris.	5	4	3	2	1
Identify and contrast available treatment options for moderate-to-severe acne vulgaris.	5	4	3	2	1
Discuss the safety and efficacy weight-based dosing of minocycline for moderate-to-severe acne vulgaris.	5	4	3	2	1
Discuss the clinical rationale for using combination therapies for treating moderate-to-severe acne vulgaris.	5	4	3	2	1

OVERALL EVALUATION:

	Strongly Agree			Strongly Disagree	
The information presented increased my awareness/understanding of the subject.	5	4	3	2	1
The information presented will influence how I practice.	5	4	3	2	1
The information presented will help me improve patient care.	5	4	3	2	1
The program was educationally sound and scientifically balanced.	5	4	3	2	1
Overall, the program met my expectations.	5	4	3	2	1
I would recommend this program to my colleagues.	5	4	3	2	1

The program was free of commercial bias or influence. Yes No (Please provide additional information below.)

If you anticipate changing one or more aspects of your practice as a result of your participation in this activity, please provide a brief description of how you plan to do so.

Please provide any additional comments pertaining to this activity (positives/negatives) and suggestions for improvement.

Please list any topics that you would like to be addressed in future educational activities.

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