

Effects of Subantimicrobial-Dose Doxycycline in the Treatment of Moderate Acne

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Objective: To determine if treatment with subantimicrobial-dose (SD) doxycycline hyclate (20-mg tablets taken twice daily) improved clinical outcome, had any detectable effect on skin flora, led to overgrowth or colonization of skin by opportunistic pathogens, or resulted in an increase in antibiotic resistance by the surface skin microflora in patients with moderate acne compared with placebo.

Design: Multicenter, double-blind, randomized, placebo-controlled, parallel-group trial.

Setting: Two university-based clinics.

Subjects: Adults (N=51) with moderate facial acne.

Interventions: Patients were randomized to receive SD doxycycline (Periostat; CollaGenex Pharmaceuticals Inc, Newtown, Pa) or placebo twice daily for 6 months.

Main Efficacy Outcomes: Primary: changes from baseline in numbers of inflammatory, noninflammatory, and total lesions. Secondary: changes from baseline of individual counts of papules, pustules, and nod-

ules and global assessments of clinical improvement by patient and physician.

Results: Forty patients completed 6 months of treatment. At 6 months, the SD doxycycline group had a significantly greater percent reduction in the number of comedones ($P<.01$), inflammatory and noninflammatory lesions combined ($P<.01$), and total inflammatory lesions ($P<.05$) than did the placebo group. They also had significantly greater improvement according to the clinician's global assessment ($P=.03$). There were no significant differences in microbial counts between groups and no evidence of change in antibiotic susceptibility or colonization by potential pathogens. The treatment was well tolerated.

Conclusions: Twice-daily SD doxycycline treatment significantly reduced the number of inflammatory and non-inflammatory lesions in patients with moderate facial acne, was well tolerated, had no detectable antimicrobial effect on the skin flora, and did not result in any increase in the number or severity of resistant organisms.

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TETRACYCLINES ARE indicated for use as adjunctive therapy in patients with severe acne; doxycycline and minocycline are the most commonly prescribed.^{1,2} Doxycycline treatment at doses of 100 to 200 mg/d has been shown to reduce the number and severity of inflammatory lesions.^{1,2} However, these antimicrobial doses are often associated with the emergence of resistant bacteria^{3,4} and adverse effects such as gram-negative folliculitis, vaginal candidiasis, gastrointestinal upset, and dose-related phototoxic effects,^{1-3,5} sequelae that adversely influence the use of these doses in the treatment of acne.³

Pioneering work in the 1980s with minocycline⁶ and other chemically modified tetracyclines⁷ led to the discovery that these compounds could inhibit matrix me-

talloproteinases (MMPs) and down-regulate connective tissue destruction in inflammatory diseases independent of their antimicrobial activity.⁸ More recent work has confirmed this therapeutic potential in studies of subantimicrobial-dose (SD) doxycycline (20 mg) administered twice daily for 2 weeks to 18 months in the treatment of chronic adult periodontitis.⁸⁻¹¹

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Doxycycline was chosen for these studies over the other tetracyclines because it is well absorbed, has a favorable safety profile, and is a more potent inhibitor of the collagenases associated with inflammation.⁸ Adverse effects and the emergence of tetracycline-resistant organisms were not observed in the early studies,^{9,10} and these initial investigations led to long-

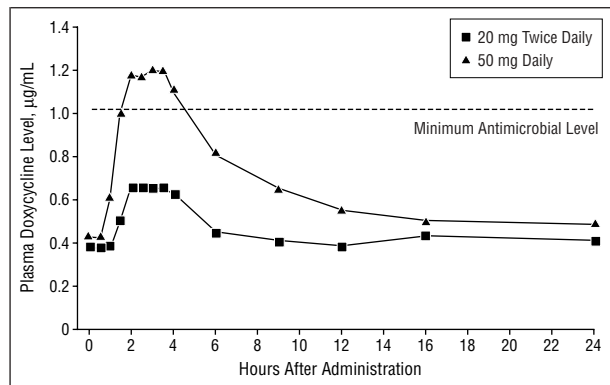


Figure 1. Steady-state doxycycline plasma concentrations. Administration of 20 mg of doxycycline hyclate twice daily to healthy adults resulted in concentrations well below the minimum antimicrobial level.

term, randomized, placebo-controlled, multicenter, double-blind clinical trials, which led to the approval, in 1998, of twice-daily SD doxycycline administration (Perio-stat; CollaGenex Pharmaceuticals Inc, Newtown, Pa) as an adjunct in the treatment of chronic adult periodontitis.¹¹ The postulated mechanism of action of SD doxycycline is down-regulation of the inflammatory host response characteristic of adult periodontitis through inhibition of multiple proteinases and cytokines, including MMP-8, MMP-13, MMP-9, interleukin (IL) 1 β , and tumor necrosis factor α (TNF- α).⁸

We chose the twice-daily SD doxycycline hyclate because it provided the maximum dose that achieved plasma concentrations consistently well below those required for an antimicrobial effect,¹² resulting in mean maximum and average steady-state plasma concentrations of 0.79 $\mu\text{g/mL}$ and 0.48 $\mu\text{g/mL}$, respectively, after 1.5 hours (**Figure 1**),¹¹ thereby avoiding the emergence of resistant organisms, yet retaining efficacy in treating periodontitis. This postulate has been confirmed in extensive studies of the oral, gastrointestinal, genitourinary, and skin microflora treated with SD doxycycline administered twice daily for 6 to 18 months; findings in these studies showed no reductions in the microflora, no development of resistant organisms, and no cross-resistance to 6 commercially available antimicrobial agents.^{11,13}

It is believed that elevated host collagenolytic activity, induced by infection of the periodontal pocket with various periopathogenic bacteria, is responsible for the rapid destruction of host connective tissue and bone that leads to the clinical signs and symptoms of periodontitis.^{14,15} Similarly, in inflammatory acne, the resident organism *Propionibacterium acnes* proliferates in an abnormal environment (the microcomedo) and causes inflammation by metabolizing sebum, recruiting infiltrating neutrophils, and inducing the production of a variety of proinflammatory cytokines.

It has been postulated that the effect of doxycycline and other tetracyclines on acne may be due not only to an antimicrobial effect but also to the drug's ability to inhibit *P. acnes*-derived lipase (thus reducing free fatty acid levels in the follicle)^{16,17} and down-regulate IL-1 β and TNF- α (which potentiate the inflammatory pathway and lead to further recruitment of cellular components, such as polymorphonuclear leukocyte-derived col-

lagenase and MMP-8).^{8,18} However, it is not known whether these anti-inflammatory properties of tetracyclines are sufficient by themselves to manage the clinical signs and symptoms of acne. Therefore, we conducted a placebo-controlled clinical trial to evaluate the effectiveness of twice-daily SD doxycycline treatment in acne. This trial represents the first acne treatment study in which the anti-inflammatory effects of a tetracycline have been studied independent of its antimicrobial effect.

METHODS

The present study is a multicenter, double-blind, randomized, placebo-controlled, parallel-group trial conducted at the University of Florida in Gainesville and the West Virginia University School of Medicine in Morgantown. Patients qualified for the study if they were 18 years or older and had moderate facial acne, defined by the total count of noninflammatory lesions (6-200 comedones) and inflammatory lesions (10-75 papules and pustules and ≤ 5 nodules).

No topical acne treatments or systemic antibiotics were permitted during the 6 weeks preceding the trial period. During the study, use of penicillin, other tetracycline antibiotics, or any acne treatment was not permitted, nor was use of sulfa drugs, erythromycin, cephalosporins, quinolones, or nonsteroidal anti-inflammatory drugs for more than 14 days. Patients who had isotretinoin treatment must have discontinued use 6 months prior to the start of the study. Patients were not permitted to use a hormonal method of contraception 6 months before the start or during the course of the study.

Medical history and patient and physician assessments of severity of acne were taken, numbers and types of acne lesions were noted, and microbiological samples, vital signs, and standard clinical laboratory test results were evaluated for each patient at the baseline visit. Patients were randomized to receive either a tablet containing 20 mg of doxycycline hyclate or a matching placebo tablet and were instructed to take 1 tablet in the morning and 1 in the evening.

Patients returned to the clinic for evaluation 2, 4, and 6 months after the baseline visit. At each of these visits, numbers and types of lesions were evaluated, and patient and physician assessments were recorded. Vital signs and adverse events were also evaluated at each visit, and drug compliance was reviewed. Clinical laboratory and microbiological samples were obtained at the 6-month visit. Telephone calls were made to each patient at 1-month intervals between visits to assess drug compliance and the patient's general well-being.

EFFICACY AND SAFETY EVALUATIONS

The primary efficacy parameters were percent change from baseline in the counts of inflammatory lesions (papules, pustules, and nodules), noninflammatory lesions (open and closed comedones), and total lesions (inflammatory plus noninflammatory). The secondary efficacy parameters were the change from baseline of individual counts of papules, pustules, and nodules; clinician global assessment score; and patient self-assessment score. The assessment scale used by physician and patient alike at baseline was as follows: 1, clear or almost clear skin ($>90\%$); 2, moderately clear skin ($>80\%$ but $\leq 90\%$); 3, fairly clear skin ($>70\%$ but $\leq 80\%$); 4, acne covered about 50% of the face; 5, fairly severe acne ($>70\%$ but $\leq 80\%$ coverage); 6, moderately severe acne ($>80\%$ but $\leq 90\%$ coverage); 7, severe acne, with almost total coverage ($>90\%$). At the follow-up visits, the following assessment scale was used: 1, clear (100%); 2, almost clear (90% to $<100\%$); 3, marked improvement (75% to $<90\%$); 4, moderate improvement (50% to $<75\%$); 5, fair improve-

Table 1. Target Microorganisms, Media, Incubation Conditions, and Confirmatory Tests for the Recovery and Enumeration of Microorganisms From the Surface of the Skin

Target Microorganisms	Medium	Incubation Conditions	Confirmatory Tests
Total anaerobic organisms	Trypticase soy blood agar	Anaerobic, 37°C, 5-7 d	None
Total facultative organisms	Trypticase soy blood agar	10% carbon dioxide, 37°C, 3-5 d	None
Total doxycycline-resistant organisms (anaerobic)	Trypticase soy blood agar/doxycycline	Anaerobic, 37°C, 5-7 d	None
Total doxycycline-resistant organisms (facultative)	Trypticase soy blood agar/doxycycline	10% carbon dioxide, 37°C, 3-5 d	None
<i>Propionibacterium acnes</i>	Trypticase soy blood agar	Anaerobic, 37°C, 5-7 d	Colonial and cellular morphology
Enterics	MacConkey agar	Aerobic, 37°C, 2-3 d	Colonial and cellular morphology
<i>Staphylococcus</i> species	Mannitol salt agar	Aerobic, 37°C, 2-3 d	Colonial and cellular morphology
<i>Streptococcus</i> species	Mitis-Salivarius agar	Aerobic, 37°C, 2-3 d	Colonial and cellular morphology, hemolysis
Gram-positive rods	Trypticase soy blood agar	Anaerobic, 37°C, 5-7 d, and 10% carbon dioxide, 37°C, 3-5 d	Colonial and cellular morphology, gram stain

ment (25% to <50%); 6, no change; 7, worse. Safety was assessed by comparing adverse events recorded during the course of the study and comparing clinical laboratory values at baseline and at the end of the study.

MICROBIOLOGICAL EVALUATIONS AND SAMPLE COLLECTION

The microbiological objectives of the study were to determine whether twice-daily SD doxycycline therapy (1) had any detectable antimicrobial effect on the normal skin flora; (2) led to overgrowth or colonization of the skin by opportunistic pathogens; or (3) resulted in an increase in antibiotic resistance in the predominant skin microflora. Microbial samples of the surface of the skin were collected from a 2-cm² area in the center of the brow at baseline and after 6 months of treatment. The sample was collected by placing a 2-cm² template over the glabella and gently rubbing a sterile cotton swab over the area. The swab was placed in a tube containing 1.0 mL of pre-reduced, anaerobically sterilized Ringer solution and immediately transported to the laboratory for processing.

SAMPLE PROCESSING

The sample was plated on nonselective media to determine the total number of anaerobic and facultative bacteria. The microbial media used are listed in **Table 1**, along with incubation conditions and confirmatory tests for the target microorganisms. Total anaerobic counts and total facultative counts were determined from the plate dilutions that gave rise to 30 to 300 colony-forming units. For all other media, colony counts were taken from plates with 30 to 300 colony-forming units. If there were fewer than 30 colonies on the most diluted plate, the actual number of colonies was counted.

The sample was also plated on the same nonselective medium containing 4 µg/mL of doxycycline for the isolation of doxycycline-resistant bacteria. The number of anaerobic bacteria and the number of facultative bacteria resistant to at least 4 µg of doxycycline were determined and expressed as a percentage of the total for each organism. These isolates were identified by genus and species if possible and then tested for susceptibility to 6 antibiotics (doxycycline, minocycline, tetracycline, erythromycin, clindamycin, and vancomycin) by agar dilution. The results were reported as the minimal inhibitory concentration (MIC) required to inhibit visible growth on the agar medium. An MIC to inhibit 50% of the colony's growth and one to inhibit 90% were calculated for all bacterial organisms for each group at each sample period.

STATISTICAL ANALYSIS

Individual changes from baseline lesion counts were found to be nonnormally distributed; therefore, nonparametric analyses of variance were performed on rank-transformed changes from baseline counts. The ranked percent change from baseline count was also analyzed for the 3 primary lesion parameters: total inflammatory lesions, total comedones (noninflammatory), and total lesions (inflammatory plus noninflammatory). This was considered the preferred analysis for these parameters because it adjusted for the high individual variation observed at baseline.

Clinical global assessment and patient self-assessment scores, which were based on ordinal scales, were analyzed nonparametrically. The proportions of patients who experienced one or more adverse event in each body system were compared between study groups using 2-tailed Fisher exact tests. Clinical laboratory data were analyzed using χ^2 statistics applied to shift tables.

Microbiological data were analyzed using the unpaired *t* test. If the data did not follow a normal distribution, the nonparametric Mann-Whitney test was used to avoid the bias of outliers. Differences within groups were evaluated using a paired *t* test or a rank sum test.

RESULTS

PATIENTS

A total of 51 adults with moderate facial acne were enrolled in the study; 26 were randomly assigned to receive 20 mg of doxycycline hyclate twice daily and 25 to receive placebo. Patients were approximately equally divided between the sexes, with 25 men and 26 women; however, men accounted for 68% (n=17) of the placebo group and 31% (n=8) of the doxycycline group. Most of the patients (35/51; 69%) were white, with the remaining patients of Asian, African, and Hispanic ancestry. The mean age was 23 years, with a range from 18 to 37 years. Forty patients completed the 6 months of treatment, 21 in the doxycycline group and 19 in the placebo group. Of the 11 patients who discontinued treatment, 5 were lost to follow-up, 4 used concomitant medications prohibited by the protocol, and 2 had adverse events (1 bleeding ulcer and 1 recurring yeast infection).

Table 2. Summary Lesion Counts at 6 Months*

Parameter	Doxycycline Group (n = 21)	Placebo Group (n = 19)	P Value†
Total Inflammatory Lesions			
Baseline	31.38 (4.32)	27.37 (4.54)	
Month 6	15.67 (2.75)	19.11 (2.89)	
Change from baseline	-15.71 (3.87)	-8.26 (4.07)	.04
Change from baseline, %	-50.1	-30.2	
Total Comedones			
Baseline	54.95 (7.69)	51.00 (8.08)	
Month 6	25.48 (4.37)	45.58 (4.59)	
Change from baseline	-29.48 (7.46)	-5.42 (7.84)	<.01
Change from baseline, %	-53.6	-10.6	
Total Lesions			
Baseline	86.33 (10.54)	78.37 (11.08)	
Month 6	41.14 (5.86)	64.68 (6.16)	
Change from baseline	-45.19 (9.93)	-13.68 (10.44)	<.01
Change from baseline, %	-52.3	-17.5	

*Unless otherwise indicated, data are mean (SE) number of lesions.
†P value from ranked percentage change from baseline.

EFFICACY

There were no significant differences between the 2 study groups in any efficacy parameter at baseline. The mean change (reduction) in total inflammatory lesions from baseline to the end of treatment (6 months) was 50% in the doxycycline group and 30% in the placebo group ($P=.04$) (**Table 2; Figure 2**). There was a consistent reduction in lesion count in the doxycycline group over the course of the study, with clinically relevant mean reductions of 24% and 36% at 2 and 4 months, respectively, compared with an inconsistent clinical response in the placebo group, which had a mean increase of 9% at 2 months and a reduction of 29% at 4 months.

The mean reduction in the number of comedones from baseline to the end of treatment was 54% in the doxycycline group compared with 11% in the placebo group ($P<.01$). There were clinically relevant mean reductions of 25% and 32% in the doxycycline group at 2 and 4 months, respectively, compared with a mean increase of 2% at 2 months and a mean reduction of 24% at 4 months in the placebo group.

In the number of all lesions combined, the mean reduction from baseline to the end of treatment was 52% in the doxycycline group and 18% in the placebo group ($P<.01$). There were clinically significant mean reductions of 25% and 33% in the doxycycline group at 2 and 4 months, respectively, compared with a mean increase of 4% at 2 months and a mean reduction of 26% at 4 months in the placebo group.

At baseline, the clinician's global assessment and patient self-assessment scores for both study groups showed that acne covered approximately 50% of the face on average. The clinician's global assessment scores improved in both groups over time, with mean scores in the doxycycline group of 5.5, 5.0, and 4.4 at 2, 4, and 6 months, respectively, compared with 5.8, 5.4, and 5.1 in the placebo group. A score of 4 indicated moderate improvement (50% to <75%) and 5 indicated fair improvement

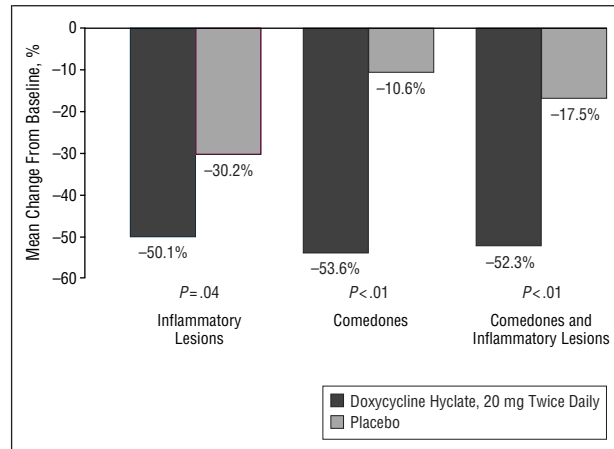


Figure 2. Mean percent decrease from baseline to 6 months in the total number of comedones, inflammatory lesions, and all lesions combined.

(25% to <50%). At 6 months, the scores in the doxycycline group were significantly better than in the placebo group ($P=.03$). The pattern of improvement was similar with the patient self-assessments, with mean scores in the doxycycline group of 5.4, 4.9, and 4.8 at 2, 4, and 6 months, respectively, compared with 5.5, 5.1, and 5.3 in the placebo group. The differences in these scores between the study groups were not statistically significant but consistently trended toward improvement in the treatment group.

MICROBIOLOGICAL FINDINGS

There were no statistically significant differences between or within the groups from baseline to 6 months in microbial colony counts, indicating that there was no change in the composition of the normal skin flora (**Figure 3**). Antibiotic susceptibility testing showed no differences between or within the study groups in the MICs obtained for doxycycline. There were no strong correlations between resistance to doxycycline and resistance to any of the 5 other antibiotics tested. The strongest correlation was between erythromycin and clindamycin resistance ($r=0.5$ to <0.70). This was expected because most bacteria that are resistant to clindamycin are also resistant to erythromycin. Moderate correlations ($r=0.5$) were detected between doxycycline and both tetracycline and minocycline in some instances. Again, this was expected because many bacteria with resistance to one tetracycline are frequently resistant to the others and also because of the carriage of tetracycline-resistant genes coding for ribosomal protection.¹⁹ There were no differences between the correlation coefficients for cross-resistance in the doxycycline 6-month samples and either the placebo 6-month samples or the doxycycline baseline samples.

SAFETY

Doxycycline and placebo were equally well tolerated. Treatment-emergent adverse events were reported for 12 patients (46%) in the doxycycline group and 8 patients (32%) in the placebo group. The most frequently reported adverse events were influenza in 3 patients in the

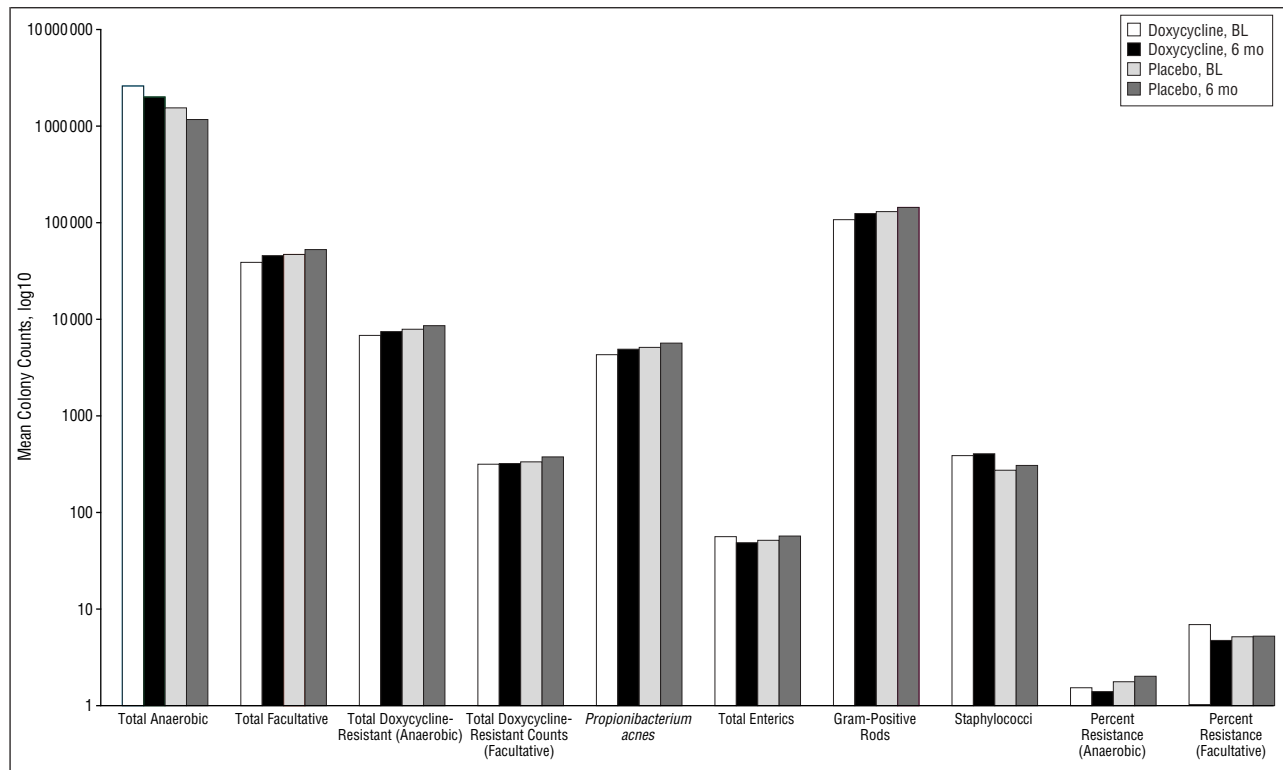


Figure 3. Mean number of target organisms at baseline (BL) and after 6 months of treatment with placebo or 20 mg of doxycycline hyclate twice daily.

doxycycline group, headache in 3 patients in the placebo group, and rash in 2 patients in the doxycycline group. No other adverse event was reported for more than 1 patient in either treatment group. Most of the adverse events were mild or moderate. Prior to the data being unblinded, events considered possibly related to the study medication were heartburn and vaginal yeast infection in the doxycycline group and headache, heartburn, and stomach upset in the placebo group.

Two patients, both in the doxycycline group, dropped out of the study because of adverse events. One patient experienced 2 episodes of gastrointestinal bleeding and was diagnosed with a gastric ulcer during the study; these events were not considered to be related to the doxycycline administration. Another patient, who had a history of recurrent vaginitis, reported an episode of vaginitis during treatment. Although independent confirmation of yeast vaginitis was not obtained, the vaginitis was considered related to treatment because of the temporal relationship to administration of the study drug.

There were no notable changes in vital signs, which were assessed at each study visit. Laboratory evaluations after 6 months of treatment showed clinically significant changes for 3 patients: low hemoglobin and hematocrit values and a low red blood cell count in 1 woman treated with doxycycline; and elevated liver function findings (alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase) in 2 patients given placebo.

COMMENT

Early studies demonstrating the effectiveness of treatment with SD doxycycline (Periostat) administered twice

daily as an adjunct in the treatment of chronic adult periodontitis paved the way for further research on this dosing regimen for acne.²⁰ This regimen is now well accepted and consistent with recommendations from the Food and Drug Administration and the Centers for Disease Control and Prevention that subtherapeutic antimicrobial doses, such as 50 mg of doxycycline administered once daily, should be avoided because they increase the likelihood that resistant microorganisms will emerge. The pharmacokinetic profile of SD doxycycline administered twice daily shows that plasma concentrations remain well below antimicrobial levels. In addition, long-term doxycycline therapy at this dosage resulted in fewer adverse events such as gastrointestinal upset, vaginitis, and phototoxic effects than have been reported with higher doxycycline doses.

The present study shows that SD doxycycline administered twice daily for 6 months in patients with moderate inflammatory acne resulted in a greater than 50% reduction in the number of total lesions (inflammatory plus noninflammatory) and a similar reduction in the number of comedones and inflammatory lesions measured independently. Treatment with SD doxycycline twice daily had no effect on *P. acnes* or other microflora of the skin, and there was no change in the composition of the normal skin flora. The treatment did not result in the emergence of organisms resistant to doxycycline or cross-resistance to commercially available antimicrobial agents, including vancomycin. There was no increase in the proportion of flora resistant to doxycycline, nor was there an increase in MIC values for bacteria resistant to 4 µg/mL of doxycycline. There was no evidence of development of cross-resistance between doxy-

cycline and related or unrelated antibiotics. Although the present study only evaluated the microflora of the skin, previous studies of the microflora of the oral cavity and the gastrointestinal and genitourinary tracts using twice-daily administrations of 20 mg of doxycycline and matching placebo over 6 to 18 months demonstrated no differences between groups in the quantity and types of flora recovered at any time point, no evidence for the development of tetracycline-resistant organisms, and no evidence of the development of cross-resistance to 6 commercially available antimicrobial agents.^{11,13}

In studies of periodontitis, SD doxycycline administered twice daily has been shown to significantly inhibit polymorphonuclear leukocyte-derived collagenase (MMP-8) and the generation of inflammatory cytokines, thereby preventing the tissue destruction induced by the inflammatory response to the periodontal infection. Similarly, doxycycline's effect on inflammatory acne lesions may be due to its inhibition of IL-6, IL-1 β , and TNF- α , inflammatory cytokines up-regulated in response to *P. acnes*. In turn, this inhibits the inflammatory pathway that leads to further recruitment of cellular components, such as neutrophils and their proteolytic enzymes, for example, MMP-8.^{21,22} Furthermore, by down-regulating *P. acnes* lipase, doxycycline can reduce the virulence of this organism, reducing the levels of free fatty acids that act as a potent chemokine for neutrophil recruitment.¹⁷

The observation in the present study that SD doxycycline administered twice daily reduced comedone counts by greater than 50% was not anticipated. Comedonal acne is believed to result from the up-regulation of keratinocyte proliferation and sloughing, which results in the blockage of the sebaceous gland by keratin and cellular debris. It is postulated that these changes are mediated through the up-regulation of IL-1, and it is possible that this activity is also suppressed by SD doxycycline administered twice daily.²³

In conclusion, this is the first placebo-controlled trial of SD doxycycline treatment administered twice daily for acne and the first to show that the nonantimicrobial properties of doxycycline are effective and sufficient in controlling and improving the clinical signs and symptoms of acne without any effect on the skin flora. Twice-daily treatment with SD doxycycline for adults with moderate facial acne for 6 months significantly reduced the number of acne lesions, was well tolerated, had no detectable antimicrobial effect on the cultivable skin flora, and did not result in the emergence of resistant organisms.

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