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

Robert Skidmore, MD; Rodney Kovach, MD; Clay Walker, PhD; John Thomas, PhD; Mark Bradshaw, PhD; James Leyden, MD; Christopher Powala, BS; Robert Ashley, MA

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 nodules 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 noninflammatory 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.

Arch Dermatol. 2003;139:459-464

Tetracyclines are indicated for use as adjunctive therapy in patients with severe acne; doxycycline and minocycline are the most commonly prescribed. Doxycycline treatment at doses of 100 to 200 mg/d has been shown to reduce the number and severity of inflammatory lesions. However, these antimicrobial doses are often associated with the emergence of resistant bacteria and adverse effects such as gram-negative folliculitis, vaginal candidiasis, gastrointestinal upset, and dose-related phototoxic effects. Pioneering work in the 1980s with minocycline and other chemically modified tetracyclines led to the discovery that these compounds could inhibit matrix metalloproteinases (MMPs) and down-regulate connective tissue destruction in inflammatory diseases independent of their antimicrobial activity. 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.

See also page 467

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. Adverse effects and the emergence of tetracycline-resistant organisms were not observed in the early studies, and these initial investigations led to long-
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 ≤90%); 3, fair improvement (≥75% but ≤80%); 4, covered about 50% of the face; 5, fairly severe acne (>70% but ≤80% coverage); 6, moderately severe acne (>80% but ≤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-

![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.](https://jamanetwork.com/)

---

**METHODS**

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) 1β, and tumor necrosis factor α (TNF-α). 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 ≤90%); 3, fairly clear skin (>70% but ≤80%); 4, covered about 50% of the face: 5, fairly severe acne (>70% but ≤80% coverage); 6, moderately severe acne (>80% but ≤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-
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

In the doxycycline group, 21 patients (53%) had moderate acne, 19 patients (47%) had severe acne, and 9 patients (21%) had very severe acne. In the placebo group, 25 patients (59%) had moderate acne, 13 patients (31%) had severe acne, and 3 patients (7%) had very severe acne. These differences were not statistically significant (P = 0.23). The mean age was 23 years, with a range from 18 to 37 years. Forty patients completed the 6 months of 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).

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

<table>
<thead>
<tr>
<th>Target Microorganisms</th>
<th>Medium</th>
<th>Incubation Conditions</th>
<th>Confirmatory Tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total anaerobic organisms</td>
<td>Trypticase soy blood agar</td>
<td>Anaerobic, 37°C, 5-7 d</td>
<td>None</td>
</tr>
<tr>
<td>Total facultative organisms</td>
<td>Trypticase soy blood agar</td>
<td>Anaerobic, 37°C, 5-7 d</td>
<td>None</td>
</tr>
<tr>
<td>Total doxycycline-resistant organisms (anaerobic)</td>
<td>Trypticase soy blood agar</td>
<td>Anaerobic, 37°C, 5-7 d</td>
<td>None</td>
</tr>
<tr>
<td>Total doxycycline-resistant organisms (facultative)</td>
<td>Trypticase soy blood agar</td>
<td>Anaerobic, 37°C, 5-7 d</td>
<td>None</td>
</tr>
<tr>
<td>Propionibacterium acnes</td>
<td>Trypticase soy blood agar</td>
<td>Anaerobic, 37°C, 5-7 d</td>
<td>None</td>
</tr>
<tr>
<td>Enterics</td>
<td>MacConkey agar</td>
<td>Aerobic, 37°C, 5-7 d</td>
<td>None</td>
</tr>
<tr>
<td>Staphylococcus species</td>
<td>Mannitol salt agar</td>
<td>Aerobic, 37°C, 5-7 d</td>
<td>None</td>
</tr>
<tr>
<td>Streptococcus species</td>
<td>Mitis-Salivarius agar</td>
<td>Aerobic, 37°C, 5-7 d</td>
<td>None</td>
</tr>
<tr>
<td>Gram-positive rods</td>
<td>Trypticase soy blood agar</td>
<td>Anaerobic, 37°C, 5-7 d</td>
<td>None</td>
</tr>
</tbody>
</table>

### 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 events in each body system were compared between study groups using 2-tailed Fisher exact tests. Clinical laboratory data were analyzed using χ² 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.
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 (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.

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. 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.

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
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, 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 doxycycline and other antimicrobials.

![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.](https://jamanetwork.com/)

©2003 American Medical Association. All rights reserved.

Downloaded From: https://jamanetwork.com/ by a Non-Human Traffic (NHT) User on 08/14/2019
This study was presented in part by Dr Skidmore as a poster, titled “Effects of Subantimicrobial-Dose Doxycycline Hyclate in the Treatment of Moderate Acne,” at the summer meeting of the American Academy of Dermatology, New York, NY, August 1-4, 2002.

Corresponding author and reprints: Robert Skidmore, MD, Division of Dermatology, Department of Medicine, 1601 SW Archer Rd, UF-VA Educational Building, No. 125, Gainesville, FL 32608 (e-mail: skidmra@medicine.ufl.edu).

REFERENCES