Two randomized phase III clinical trials evaluating anti-inflammatory dose doxycycline (40-mg doxycycline, USP capsules) administered once daily for treatment of rosacea

James Q. Del Rosso, DO,[a] Guy F. Webster, MD, PhD,[b] Mark Jackson, MD,[c] Marta Rendon, MD,[d] Phoebe Rich, MD,[e] Helen Torok, MD,[f] and Mark Bradshaw, PhD[g]

Las Vegas, Nevada; Philadelphia, Pennsylvania; Louisville, Kentucky; Miami, Florida; Portland, Oregon; and Medina, Ohio

Background: Doxycycline monotherapy at antimicrobial doses has been shown to be effective for the treatment of rosacea.

Objective: To evaluate the efficacy and safety of once-daily anti-inflammatory dose doxycycline for the treatment of rosacea.

Methods: In two phase III, parallel-group, multicenter, randomized, double-blind, placebo-controlled studies (studies 301 and 302), patients received 40-mg of controlled-release doxycycline (n = 269) or placebo (n = 268) for 16 weeks. The primary efficacy end point was the mean change from baseline in facial inflammatory lesion count.

Results: The mean lesion count at baseline was approximately 20 in each study arm. At week 16, the mean change from baseline in lesion count in the active-treatment groups was −11.8 in study 301 and −9.5 in study 302 compared with −5.9 and −4.3, respectively, in the placebo groups (*P* < .001 for both comparisons). Anti-inflammatory dose doxycycline was well tolerated; the most common adverse events were nasopharyngitis (4.8%), diarrhea (4.4%), and headache (4.4%).

Limitations: In both studies, the reduction of inflammatory lesion counts did not plateau within the 16-week time frame in either treatment group. Rosacea is often treated for a period of months or years.

The duration of the studies did not allow for assessment of safety beyond 16 weeks or whether the progressive improvement seen with active treatment would continue beyond 16 weeks. Neither study assessed the effect of treatment in patients with only erythematotelangiectatic (subtype 1) rosacea.

Conclusion: Once-daily anti-inflammatory dose doxycycline appears to be effective and safe for the treatment of rosacea. (J Am Acad Dermatol 2007;56:791-802.)

Rosacea is a common chronic facial dermatosis characterized by intermittent periods of exacerbation and remission.[1,2] Epidemiologic data suggest there is a genetic predisposition for this disease, with several intrinsic and extrinsic factors potentially correlating with the phenotypic expression of rosacea.[2-7] Clinical subtypes and grading of rosacea have been defined in the literature.[8,9]

Although there is no curative therapy for rosacea, recommended treatment strategies used to control its signs and symptoms include a combination of proper skin care, avoidance of recognized trigger factors, photoprotection, topical agents, oral therapy, and light-based physical modalities, such as intense-pulsed light.[1,2,10-13] The most widely used systemic agents for the treatment of rosacea are oral tetracycline derivatives, including tetracycline, doxycycline, and minocycline.

The use of oral tetracyclines for rosacea is based primarily on widespread clinical experience and a limited collection of placebo-controlled, comparative clinical trials.[2,10,12,13] The dosing ranges of tetracycline (250-1000 mg/d) and doxycycline (100-200 mg/d) used to treat rosacea produce selection pressure against sensitive commensal flora, transient flora, and selected bacterial pathogens.[12,14,15] Based on single-dose pharmacokinetics, conventional formulations of doxycycline that are not controlled-release and administered at a dose of 40 mg or higher achieve serum levels that may produce selection pressure against susceptible bacterial strains based on minimum inhibitory concentration evaluations.[14,15] As the pathogenesis of rosacea appears to be multifactorial and is not definitively associated with eradication or reduction of a bacterial pathogen, it is scientifically plausible to use tetracycline agents as therapy for rosacea in a manner that does not exert antibiotic activity, avoids development of drug-resistant microbes, and exploits only their anti-inflammatory activities.

The following details the results of two phase III, parallel-group, multicenter, randomized, double-blind, placebo-controlled trials (studies 301 and 302) that evaluate the efficacy and safety of 40-mg doxycycline monohydrate in a formulation with 30-mg immediate-release and 10-mg delayed-release

Abbreviations used:

AE:	adverse event
ANOVA:	analysis of variance
CEA:	Clinician's Erythema Assessment (scale)
CMH:	Cochran-Mantel-Haenszel (test)
IGA:	Investigator's Global Assessment (scale)
ITT:	intent to treat

beads, once daily (anti-inflammatory dose doxycycline) versus placebo once daily for the treatment of adults with rosacea. The studies were collectively inclusive of 269 patients who received anti-inflammatory dose doxycycline and 268 patients who received placebo. Both studies included patients with a marked number of total inflammatory lesions (10-40 papules and pustules and <2 nodules), moderate-to-severe erythema, and presence of telangiectasia.

METHODS
Overall design of the studies

Two 16-week, phase III, parallel-group, multicenter (14 sites for each study), randomized, double-blind, placebo-controlled studies (study 301 and study 302) were conducted in parallel (Fig 1). Study protocols for both studies were virtually identical with the exception of a posttherapy assessment in study 302 that evaluated the persistence of efficacy and safety profile 4 weeks after discontinuation of study medication. Both studies enrolled a similar number of patients (n = 251 in study 301 and n = 286 in study 302) and were conducted between June 2004 and April 2005 in the United States and Puerto Rico.

Study populations

Patients were eligible for enrollment if they were healthy adults, at least 18 years of age with moderate-to-severe rosacea, which was defined as the presence of 10 to 40 papules and pustules and 2 or fewer nodules. At study entry, patients scored higher than 2 on the Investigator's Global Assessment (IGA) scale, a subjective 5-point measure of overall disease severity. IGA scores range from 0 to 4: 0 = no signs

	Study 301	Study 302
Assessed for eligibility	365	371
Total excluded	114	85
Not meeting exclusion criteria	92	68
Refused to participate	22	17

Randomized

Allocated to Anti-inflammatory Dose Doxycycline

	Study 301	Study 302
Received intervention	127	142

Allocated to Placebo

	Study 301	Study 302
Received intervention	124	144

Follow-Up

Total Discontinuations	26	27
Adverse event	10	9
Illness not drug-related	1	1
Uncooperative	5	2
Lost to follow-up	4	5
Protocol violation	2	4
Treatment failure	2	1
Other*	2	5

Follow-Up

Total Discontinuations	21	26
Adverse event	4	7
Illness not drug-related	1	0
Uncooperative	4	1
Lost to follow-up	2	5
Protocol violation	2	5
Treatment failure	2	4
Other*	6	4

16-Week Analysis

Analyzed	127	142

16-Week Analysis

Analyzed	124	144

Post-therapy Assessment in Study 302 †

Analyzed	84

Post-therapy Assessment in Study 302 †

Analyzed	76

*Other reasons for withdrawal included personal reasons and administrative reasons.
†The post-therapy assessment was not conducted in study 301.

Fig 1. Flow diagram.

or symptoms present (clear); 1 = 1 to 2 small, noninflammatory papules (near clear); 2 = 3 to 10 papules/pustules (mild); 3 = 11 to 19 papules/pustules (moderate); and 4 = 20 or more papules/pustules and nodules (severe). Patients were also required to have telangiectasia and moderate to severe erythema as determined with the use of the Clinician's Erythema Assessment (CEA) scale. Scores on the CEA scale range from 0 to 4: 0 = none (no redness present); 1 = mild (slight pinkness); 2 = moderate (definite redness); 3 = significant (marked erythema); and 4 = severe (fiery redness). Total CEA scores are derived by summing scores over 5 facial areas (forehead, chin, nose, and right and left cheek) and ranged from 0 to 20. In the two studies reported

herein, moderate to severe erythema was defined as at least one area-specific CEA score of 2 or higher and a total CEA score of 5 or higher. Female patients of childbearing potential were eligible for enrollment only if they were using birth control, were not nursing, and had a negative pregnancy test at entry into the studies.

Patients were not eligible for enrollment in the studies if they met any of the following criteria: initiation of or change in hormonal method of contraception within 4 months of baseline or during the study; use of topical acne treatments or topical or systemic antibiotics within 4 weeks of baseline; use of an investigational drug within 90 days of baseline; known hypersensitivity to tetracyclines; use

of clinically significant concomitant drug therapy (eg, long-term use of nonsteroidal anti-inflammatory drugs); use of systemic anti-inflammatories or corticosteroids in the 4 weeks before baseline or during the study; use of vasodilators or α-adrenergic receptor-blocking agents 6 weeks before baseline or during the study; or ocular rosacea and/or blepharitis/meibomianitis requiring treatment by an ophthalmologist.

These studies were conducted in accordance with applicable good clinical practice guidelines and in accordance with the ethical principles described in the Declaration of Helsinki. The original protocol, protocol amendments, and patient's informed consent form were approved by the appropriate institutional review boards for each of the 28 study sites before the screening and enrollment of study participants. Before screening, patients were fully informed both verbally and in writing of the conduct and consequences of the study and signed an institutional review board—approved consent form.

Randomization and blinding procedures

For each study site, a master randomization list in blocks of 4 was prepared by the sponsor for all study sites. With the use of a computer-generated randomization scheme, patients were assigned in equal proportions (1:1) to receive the study drug or placebo. Study drug and placebo capsules were identical in size, shape, and color, and investigators, study site personnel, and patients were blinded with respect to identity of the study medication being taken. All employees of the sponsor and its affiliates who were involved in data monitoring, data entry, or data analysis were blinded as well.

Study medications and treatment regimens

Patients were randomized to receive anti-inflammatory dose doxycycline capsules or placebo once daily in the morning for 16 weeks. Patients were cautioned about exposure to sunlight and were encouraged to apply sunscreen with a sun protection factor value of at least 30 whenever they were outdoors during daylight hours. In addition, patients were instructed that the following medications were prohibited during the studies: long-term use (>14 days) of sulfonamide drugs, erythromycin, cephalosporins, quinolones, and nonsteroidal anti-inflammatory drugs; tetracycline antibiotics; acne treatments, including spironolactone; antimicrobial soaps; penicillin antibiotics; and niacin at a dose of 500 mg or more per day. Antacids and vitamins containing aluminum, calcium, or magnesium were allowed only if taken at least 1.5 hours before or 3 hours after the patient took study medication.

In study 302, patients in both treatment arms were required to discontinue study medication at week 16 and were instructed not to take any systemic or topical medications for the treatment of rosacea or acne or any of the medications prohibited at entry into the study. Patients were re-evaluated at week 20.

Clinical evaluations

Before entry into one of the studies, a complete medical history was obtained from each patient. Baseline evaluations also included a count of inflammatory lesions (papules + pustules + nodules), vital signs, and routine laboratory tests. In addition to these measures, baseline scores were obtained on the CEA scale and on the IGA scale (both described above). Female patients of childbearing potential were given urine pregnancy tests.

In both trials, study medication was distributed at baseline and again at week 12. Patients in both studies returned for evaluations at weeks 3, 6, 12, and 16. In study 302, patients also returned at week 20 for a 4-week posttreatment evaluation. At each visit, patients were evaluated for number and types of lesions, concomitant medication usage, adverse events (AEs), vital signs, height, and weight. IGA and CEA scores were obtained at each visit. At the week-16 visit, female patients of childbearing potential were again given a urine pregnancy test.

Efficacy and safety evaluations

In both studies, the primary efficacy end point was the mean change from baseline in total inflammatory lesion count (papules + pustules + nodules) at week 16. Secondary end points included the mean change from baseline in CEA and IGA scores at week 16. In addition, the static dichotomized IGA score (yes/no), defined as patients who achieved a score of 0 (clear) or 1 (near clear), was analyzed at week 16.

The efficacy variables for the 4-week posttherapy assessment conducted in study 302 included the mean change in total inflammatory lesion count (papules + pustules + nodules) and the mean changes in CEA and IGA scores from week 16 to week 20.

Safety was evaluated at each study visit by recording AEs, concomitant medication use, and vital signs at each study visit and by routine laboratory tests conducted at week 16. AEs were evaluated as mild, moderate, or severe, and the relationships to study medication were determined by the study investigator.

Statistical analysis

The sample size determination for each study was based on a previous placebo-controlled study. It was anticipated that 16 weeks of active treatment would result in a mean change from baseline of −7.0 in total lesion count, whereas treatment with placebo would result in a mean change of −3.5 lesions, with a common standard deviation of 8.0. Hence a total of 111 patients per treatment group would be sufficient to ensure a power of higher than 90% for detecting a significant treatment difference at the two-sided alpha = 0.05 level of significance.

An analysis of variance (ANOVA) was performed on the primary efficacy data (mean change from baseline in number of inflammatory lesions [papules + pustules + nodules]) from the intent-to-treat (ITT) populations in each study to test the null hypothesis of no treatment effect. The dependent variable was the difference from baseline in total lesion count at each study time point. Treatment and center were the main effects examined in the ANOVA model. Differences between the two treatment groups were considered statistically significant at the $P < .05$ level using two-tailed tests. Additionally, the residuals from the ANOVA analyses were studied for deviations from normality at week 16. If the test for normality failed at the .05 level of significance, the Van Elteren test,[16,17] stratified by center, was used to further evaluate the differences between the two treatment groups.

Changes from baseline in IGA scores were evaluated at each visit using frequency distribution data. The distribution of IGA scores was analyzed using the Cochran-Mantel-Haenszel (CMH) test,[18,19] stratified by center, to test for differences between treatment groups. Additional analyses were performed on dichotomized IGA data (yes/no). These data were also analyzed by using the CMH test, stratified by center.

The 4-week posttherapy assessment of efficacy data in study 302 included only those patients who had data available from study visits at week 16 and at week 20. For both total lesion count and CEA scores, within-treatment data from week 16 and from the 4 week posttreatment follow-up visit at week 20 were compared by paired *t* test. Analysis of between-treatment data was performed by using the ANOVA method described above. For IGA scores, within-treatment frequency distribution data were analyzed by using the Wilcoxon signed rank test and between-treatment data were analyzed by using the CMH test, stratified by center. For dichotomized IGA scores, within-treatment data were analyzed by means of McNemar's test and between-treatment data were analyzed by using the CMH test stratified by center.

AEs were coded using MedDRA[20] and incidences were calculated for each treatment group by system organ class and MedDRA preferred term. In this report, safety data (eg, incidence rates of AEs) have been pooled from both studies. Pooling of the safety data is justified as both studies were multicenter studies that followed identical study protocols (with the exception of the 4-week posttreatment assessment in study 302), both studies were conducted over the same time frame (ie, between June 2004 and April 2005), and the incidence rates of AEs by type were similar between the two studies as well as similar between treatment arms in both studies.

RESULTS

Patient population

A total of 537 patients were enrolled in the two studies with 251 patients in study 301 (127 from the active-treatment arm and 124 from the placebo arm) and 286 patients from study 302 (142 from the active-treatment arm and 144 from the placebo arm). A total of 160 patients were enrolled in the 4-week posttherapy assessment conducted in study 302 (84 from the active-treatment arm and 76 from the placebo arm).

Patient demographics and disposition and baseline data for efficacy variables were similar between treatment groups in the two studies and were also similar between the two studies (Table I). More than 40% (239/537) of the patients in each study were 36 to 50 years of age (47% [118/251] in study 301 and 42% [121/286] in study 302). Seventeen percent (42/251) and 20% (57/286) of the patients in studies 301 and 302, respectively, were 18 to 35 years of age, and 32% (79/251) and 33% (95/286) of the patients were 51 to 70 years of age. Seventy percent (375/537) of the patients in the two studies were women and 91% (491/537) were Caucasian. The mean total inflammatory lesion count was 19.9 for the patients participating in study 301 and 20.8 for the patients participating in study 302. The mean CEA score was 9.6 for the patients participating in study 301 and 9.3 for the patients participating in study 302. Approximately half of the patients in each study had an IGA score of 3 (moderate rosacea) and about 90% of the patients had an IGA score of 3 to 4 (moderate to severe rosacea). There were no statistically significant differences between treatment arms in either study in terms of mean lesion counts (papules, pustules, nodules, total lesions) or mean CEA and IGA scores.

Table I. Patient demographics and disposition, baseline values for efficacy assessments, and study medication usage

Parameter	Study 301		Study 302	
	Anti-inflammatory dose doxycycline (n = 127)	Placebo (n = 124)	Anti-inflammatory dose doxycycline (n = 142)	Placebo (n = 144)
Age, y (SD)	46.8 (13.2)	47.6 (11.5)	46.3 (12.7)	47.6
Female, No. (%)	91 (71.7)	95 (76.6)	94 (66.2)	95 (66.0)
Lesion counts, mean (SD)				
Papules	15.2 (7.9)	16.4 (9.2)	17.4 (10.8)	17.8 (10.9)
Pustules	4.1 (5.2)	3.7 (4.7)	3.0 (4.5)	3.3 (6.0)
Nodules	0.2 (0.6)	0.2 (0.5)	0.1 (0.5)	0.1 (0.5)
Total	19.5 (8.8)	20.3 (10.4)	20.5 (11.7)	21.2 (12.5)
CEA score, mean (SD)	9.7 (3.0)	9.5 (2.7)	0.5 (2.9)	9.1 (2.5)
IGA, No. (%)				
0 = Clear	0	0	0	0
1 = Near clear	0	0	0	0
2 = Mild	8 (6.3)	10 (8.1)	17 (12.0)	7 (4.9)
3 = Moderate	67 (52.8)	65 (52.4)	77 (54.2)	80 (55.6)
4 = Severe	52 (40.9)	49 (39.5)	48 (33.8)	57 (39.6)
Exposure to study medication, days, mean (SD)	103.1 (30.1)	106.9 (24.2)	101.2 (29.8)	106.9 (28.7)
Completers, No. (%)*	101 (79.5)	103 (83.1)	115 (81.0)	118 (81.9)
Discontinuations, No. (%)				
AEs	10 (7.9)	4 (3.2)	9 (6.3)	7 (4.9)
Insufficient efficacy	2 (1.6)	2 (1.6)	1 (0.7)	4 (2.8)
Loss to follow-up	4 (3.1)	2 (1.6)	5 (3.5)	5 (3.5)
Protocol violation	2 (1.6)	2 (1.6)	4 (2.8)	5 (3.5)
Other[†]	8 (6.3)	11 (8.8)	8 (5.6)	5 (3.5)
Total	26 (20.5)	21 (16.8)	27 (18.9)	26 (18.2)

AE, Adverse event; *CEA*, Clinician's Erythema Assessment score (range, 0-20); *IGA*, Investigator's Global Assessment.
*Percent of patients taking ≥80% of the assigned study medication.
[†]Other reasons for withdrawal include illness not related to study drug, loss to follow-up, patient withdrawal for personal reasons, and administrative reasons.

The mean exposure to anti-inflammatory-dose doxycycline was 103.1 days in study 301 and 101.2 days in study 302 for a combined exposure to active treatment of 26,377 person-days. Compliance with the per-protocol treatment regimen was generally very good; 474 of the 537 (88%) patients in the two studies took at least 80% of the assigned study medication.

The majority of patients (437/537 [81%]) completed the two studies. The rates of discontinuation because of AEs were higher among patients in the active-treatment groups in both studies (7.9% [10/127] and 6.3% [9/142], in studies 301 and 302, respectively) than among patients in the placebo arms of the studies (3.2% [4/124] and 4.9% [7/144], respectively). Discontinuations because of insufficient efficacy were low in both studies among patients in either treatment arm. Overall, 3 of 269 (1.1%) patients discontinued treatment with doxycycline compared with 6 of 268 (2.2%) patients receiving placebo.

Efficacy assessments
Total inflammatory lesion counts. In both studies, patients in the ITT population who received active treatment demonstrated significantly greater reductions from baseline in total inflammatory lesions at week 16 compared with patients who received placebo. The mean change from baseline in total inflammatory lesions in the active-treatment group was −11.8 in study 301 and −9.5 in study 302 compared with −5.9 and −4.3, respectively, in the placebo arms. These results were statistically significant in both trials ($P < .001$). Figs 2 and 3 depict the reduction in total inflammatory lesion counts that was observed throughout the 16-week study period in both studies. There was a significantly greater decrease in lesion count in the active-treatment group when compared with the placebo group starting at the initial 3-week follow-up visit ($P = .005$) that continued at week 6 ($P < .001$), week 12 ($P < .001$), and week 16 ($P < .001$). To illustrate the
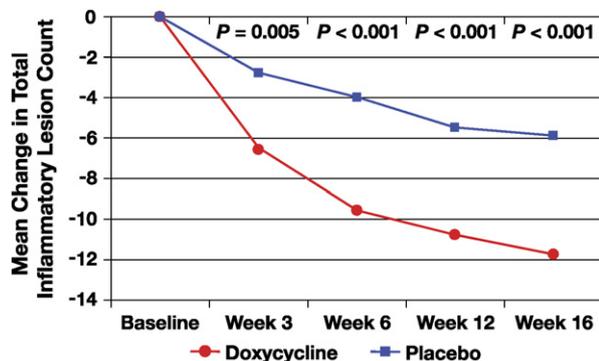
Fig 2. Mean change from baseline in total inflammatory lesion count (papules + pustules + nodules) through week 16 in study 301.
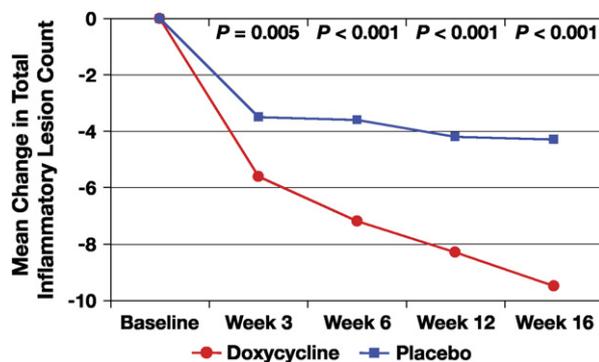

Fig 3. Mean change from baseline in total inflammatory lesion count (papules + pustules + nodules) through week 16 in study 302.

clinical changes seen with use of anti-inflammatory dose doxycycline throughout the 16-week study period, Fig 4 shows the inflammatory lesions and facial erythema of a patient at baseline and then again at week 16.

Total erythema scores. In study 301, the reduction from baseline in the mean total erythema score (defined as the CEA score) was significantly (*P* = .017) greater at week 16 in the active-treatment arm when compared with the placebo arm. At week 16, the mean change from baseline in the total erythema score was −2.7 and −1.8 for the active-treatment and placebo groups, respectively (Fig 5). In study 302, the change from baseline in total erythema scores indicated that facial redness decreased in patients in the active-treatment group (Fig 6); however, the between-group difference did not reach statistical significance.

Investigator global assessment. The active-treatment group demonstrated significantly greater improvement in IGA scores by study end point when compared with the placebo group in both studies. In study 301, 45.7% (58/127) of the patients in the
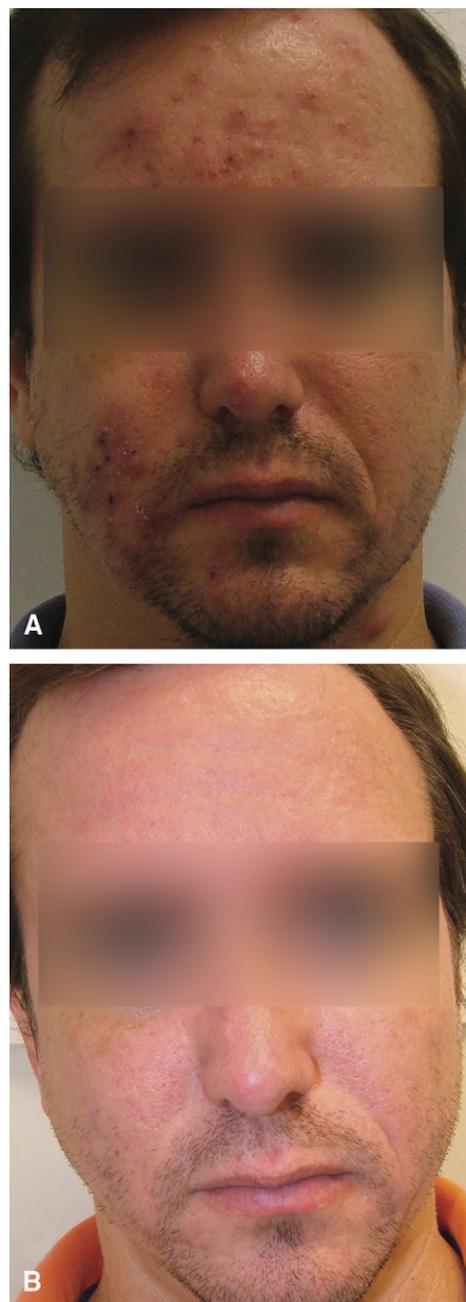

Fig 4. Change in inflammatory lesions throughout the study period (**A**) at baseline in a male patient; (**B**) at week 16 in this same patient.

active-treatment group achieved a 2-point or greater improvement in IGA scores at week 16 compared with 25.8% (32/124) of the patients in the placebo group (*P* < .001). In this same study, a significantly larger percentage of actively treated patients (30.7% [39/127]) achieved an IGA score of 0 (clear) or 1 (near clear) when compared with placebo-treated patients (19.4% [24/124], *P* = .036). In study 302, 22.5% (32/142) of the patients in the active-treatment arm achieved a 2-point or greater improvement in IGA
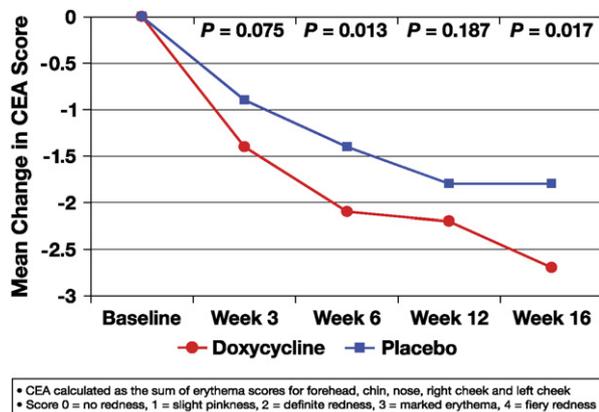
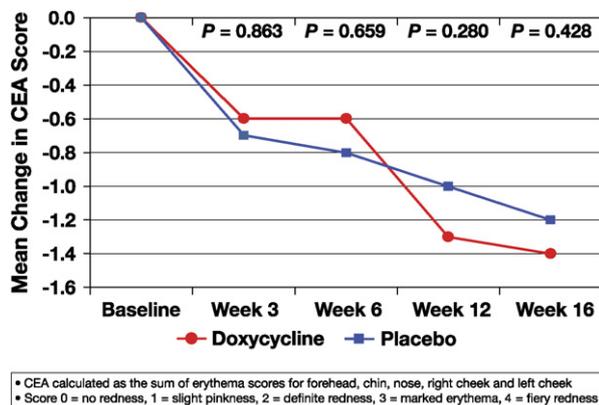**Fig 5.** Mean change from baseline in CEA score through week 16 in study 301.

Fig 6. Mean change from baseline in CEA score through week 16 in study 302.

Table II. Pooled data of treatment-emergent adverse events reported from studies 301 and 302

Adverse event*	Anti-inflammatory dose doxycycline (n = 269) No. (%)	Placebo (n = 268) No. (%)
Nasopharyngitis	13 (4.8)	9 (3.3)
Diarrhea	12 (4.4)	7 (2.6)
Headache	12 (4.4)	16 (5.9)
Upper respiratory tract infection	9 (3.3)	20 (7.4)
Hypertension	8 (2.9)	2 (0.7)
Sinusitis	7 (2.6)	2 (0.7)
↑ AST	6 (2.2)	2 (0.7)
Abdominal pain, upper	5 (1.8)	1 (0.3)
Fungal infection	5 (1.8)[†]	1 (0.3)
Influenza	5 (1.8)	3 (1.1)
Nausea	5 (1.8)	8 (2.9)

AST, Aspartate aminotransferase.
*Reported adverse events not necessarily determined to be probably or possibly related to study drug.
[†]There were no cases of vaginal candidiasis or photosensitivity in the active-treatment arm.

identified during the course of either study, including assessments of reported AEs, vital signs, weight, and laboratory values. Table II lists pooled data of AEs reported during the 16-week treatment period in two or more patients in either treatment group (ITT analysis). No cases of photosensitivity were reported in either treatment group and no cases were suspected by investigators. Among female patients in both studies, vaginal mycotic infections, including candidiasis, were reported in 4 patients in the placebo group and in none of the patients in the active-treatment group.

Adverse events. In study 301, 44.1% (56/127) and 38.7% (48/124) of patients in the active-treatment and placebo groups, respectively, reported AEs over the 16-week study period. Most of these AEs were rated as mild or moderate in severity in both the active-treatment arm (82.1% [46/56]) and placebo arm (87.5% [42/48]). AEs considered by the investigator to be possibly or probably related to study drug were experienced by 19.7% (25/127) of patients in the active-treatment group and 13.7% (17/124) in the placebo group. In study 302, 65.5% (93/142) of the patients in the active-treatment arm and 51.4% (74/144) in the placebo arm noted AEs over the 16-week study period. The majority of these AEs were rated as mild or moderate in severity in both the active treatment group (93.5 % [87/93]) and placebo group (95.9% [71/74]). AEs judged by the investigator to be possibly or probably related to study drug were experienced by 21.8% (31/142) of patients in the

scores at week 16 compared with 16.0% (23/144) of the patients in the placebo arm (*P* = .004). A significantly larger proportion of patients in the active-treatment arm in study 302 (14.8% [21/142]) achieved an IGA score of 0 (clear) or 1 (near clear) when compared with patients in the placebo arm (6.3% [9/144], *P* = .012).

Four-week posttherapy assessment. Of the patients who consented to participate in this study, those in the active-treatment arm maintained a greater overall treatment benefit through week 20. The mean total lesion count at week 20 was 10.3 in the active-treatment group and 15.3 in the placebo group, representing a mean treatment difference of 5 lesions at 4 weeks after discontinuation of therapy. Significant differences in CEA and IGA scores within both study arms recorded at weeks 16 and 20 were not observed.

Safety analysis. Both anti-inflammatory-dose doxycycline administered once daily and placebo were well tolerated throughout both studies 301 and 302. No major safety issues or concerns were

active-treatment group and 14.6% (21/144) in the placebo group. In the 4-week follow-up period from week 16 through week 20, AEs were experienced by 4.8% (4/84) of the patients initially randomized to the active-treatment arm and 9.2% (7/76) of patients initially randomized to the placebo arm.

Vital signs/weight. Vital signs and weight assessments demonstrated only minimal mean changes from baseline with no apparent between-group differences in either study. No changes in blood pressure levels were considered to be AEs, except for one patient in the active-treatment group in study 302. This patient experienced a marked increase in blood pressure that was reported as an AE and was not considered to be related to study drug.

Laboratory evaluations. In both trials, all randomized patients underwent hematology and serum chemistry panels at baseline and week 16. Overall, in both studies, there were no notable changes or emergent trends in abnormal laboratory values in either treatment group from baseline to end point in any hematologic or serum chemistry indices.

DISCUSSION

The results from the two phase III 16-week trials reviewed above demonstrate that anti-inflammatory dose doxycycline administered once daily appears to be effective and safe for the treatment of moderate to severe papulopustular rosacea. Both studies demonstrated the statistically significant superiority of anti-inflammatory dose doxycycline when compared with placebo after 16 weeks based on multiple efficacy end points, including reduction in facial inflammatory lesions as early as week 3, improvements in IGA scores (≥ 2 grade improvement), and proportion of patients rated as clear or near clear (dichotomized IGA). In both studies, actively treated patients achieved lower erythema scores than the placebo groups at weeks 12 and 16, thus displaying a trend toward improvement. The trend in erythema reduction in the active-treatment groups continued progressively through study end point without demonstration of a plateau effect (Figs 5 and 6).

In addition to the results reported herein with anti-inflammatory dose doxycycline, large-scale, randomized, vehicle-controlled, phase III trials have been reported with topical metronidazole[21] and topical azelaic acid.[22] Similar to the present studies of anti-inflammatory dose doxycycline, these topical therapy trials enrolled patients with mostly moderate to severe rosacea (the mean number of lesions was approximately 18 in the 3 trials, compared with approximately 20 lesions in the present studies). In the present studies, the mean total inflammatory lesion count decreased by 61% and

46% in patients receiving active treatment for 16 weeks compared with 29% and 20% in patients receiving placebo. In the 10-week metronidazole 1% gel trial, the mean reductions were 51% with once-daily active treatment and 33% with vehicle ($P < .0001$). In the two 12-week trials of azelaic acid 15% gel, the mean reductions were 58% and 51% with twice-daily active treatment and 40% and 39% with vehicle ($P = .0001$ and $P = 0.02$). It is important to note that it is not entirely valid to directly compare results between independently completed phase III trials evaluating different agents because of several factors that are primarily related to differences in study design, protocol requirements, and patient populations.

The safety analysis indicated that treatment with anti-inflammatory dose doxycycline once daily was very well tolerated over the 16-week period. In both studies, the majority of AEs observed were rated as mild or moderate in severity in both study arms. The percentage of patients discontinuing therapy because of AEs was very low in both trials and was similar in both active-treatment and placebo study arms. Vaginal candidiasis and photosensitivity were not reported in actively treated patients.

As with the phase III studies conducted with topical metronidazole and azelaic acid, the present studies of anti-inflammatory dose doxycycline did not enroll patients with mild inflammatory (subtype 2 papulopustular) rosacea or only erythematotelangiectatic (subtype 1) rosacea. Additionally, disease severity may fluctuate widely over relatively brief periods in patients with rosacea, and patients who met the inclusion criteria for these two trials were most likely at or near the peak of disease activity. Thus it was expected that a heightened placebo effect would be observed because of regression to the mean. The heightened placebo effect tends to reduce the chances of finding a significant treatment effect, though one was found in both of the studies with anti-inflammatory dose doxycycline. In addition, clinical studies may not be fully representative of rosacea therapy in clinical practice, where patients are usually treated regardless of whether or not their symptoms are at their worst. Also of note, although the mean number of inflammatory lesions decreased and plateaued in patients receiving placebo, the declining lesion count did not plateau in patients receiving 16 weeks of active treatment. Thus the efficacy of anti-inflammatory dose doxycycline may have been underestimated. Longer term trials are needed to determine the full therapeutic potential of anti-inflammatory dose doxycycline.

An understanding of how anti-inflammatory dose doxycycline may reverse mechanisms reported to be associated with the pathophysiology of rosacea

Table III. Summary of the biologic effects of tetracycline derivatives*,†

Biologic effects[5,10,12,13,34-37,40-44]	Impact of effect
Reduced activity of ROS	Decreased extracellular matrix (eg, collagen) degradation
	Decreased inactivation of MMP inhibitors
	Reduced activation of pro-MMPs
Inhibition of NOS	Reduced NO production leading to decreased inhibition of extracellular matrix synthesis (eg collagen, proteoglycan)
	Decreased expression of MMPs
	Reduced vasodilation related to decreased NO production by endothelial cells
Decreased cytokine expression	Down-regulation of proinflammatory cytokine production (eg, TNF-α, IL-1 β)
	Reduced inflammatory cell recruitment
Inhibition of activity of several MMP and MMP precursors	Studies in vitro and in vivo demonstrate inhibition of MMP activity, including collagenase-3 (MMP-13), collagenase-2 (MMP-8), collagenase-1 (MMP-1), gelatinase A (MMP-2), gelatinase B (MMP-9), and macrophage metalloelastase (MMP-12), sparing breakdown of the extracellular matrix
Inhibition of protein kinase C activity	Decreased transcriptional activity of several MMPs
Inhibition of Ca^{++}/calmodulin pathway	Decreased MMP-mediated breakdown of extracellular matrix
	Reduced activity of endothelial cNOS
	Decreased production of NO resulting in reduced vasodilation (vascular smooth muscle relaxation)
Reduced proinflammatory activity of PLA_2	Inhibition of arachidonic acid production from glycerophospholipid precursors in cell membranes with decreases in metabolites that serve as proinflammatory cell regulators such as PGE_2
	Reduced inflammatory activity

cNOS, Constitutive nitric oxide synthetase; *IL*, interleukin; *MMP*, matrix metalloproteinase; *NO*, nitric oxide; *NOS*, nitric oxide synthetase; *PGE₂*, prostaglandin E$_2$; *PLA₂*, phospholipase A$_2$; *ROS*, reactive oxygen species; *TNF*, tumor necrosis factor.
*Biologic effects based on multiple in vitro and in vivo experimental models.
†Separation of antibiotic effects and biologic activities confirmed with doxycycline based on pharmacokinetic profile and microbiologic assays evaluating dose-response; confirmed with anti-inflammatory dose doxycycline.

warrants some discussion of these mechanisms. Although the pathophysiology of rosacea, including definitive correlation with specific clinical subtypes, is not completely understood, several intrinsic and extrinsic factors correlate with the pathogenesis of the disease.[4-6,11-13] Reported pathophysiologic findings associated with rosacea include structural alterations of cutaneous vasculature, changes in cutaneous blood flow, altered vascular response to ambient and oral heat exposure, immune responses to pathogenic organisms (eg, follicular *Demodex* mites), temperature-dependent bacterial protein production, degeneration of the dermal matrix, abnormalities of the pilosebaceous unit, and impairment of the epidermal barrier function involving predominantly centrofacial skin.[1,3,5,7,11,23-31] Many pathogenic associations related to rosacea have also been linked with long-term photodamage, including loss of vascular integrity, increased angiogenesis, telangiectasia formation, altered cutaneous oxidation/antioxidant balance, increased generation of reactive oxygen species and increased production of reactive nitrogen intermediates.[5,7,32-36]

The biologic effects of doxycycline that correlate with its anti-inflammatory activities are summarized in Table III. Several of these described modes of action correlate with the inhibition of pathophysiologic mechanisms that have been related to rosacea and appear to explain the therapeutic effects obtained with the use of anti-inflammatory dose doxycycline.[5,10,12,13,32,35-48]

The use of tetracycline antibiotics for rosacea is well recognized based on clinical experience and a limited number of clinical trials.[10,12,13] Anti-inflammatory activity of doxycycline appears to be of major significance in the treatment of inflammatory skin disorders such as rosacea.[36-38,44-48] The completion of two pivotal, phase III clinical trials demonstrating the efficacy and safety of anti-inflammatory dose doxycycline once daily for rosacea establishes the first important body of evidence supporting the use of a systemic therapy for rosacea that is devoid of antibiotic activity.[29] The results of studies 301 and 302 demonstrate important findings regarding the efficacy and safety of anti-inflammatory dose doxycycline in patients with rosacea for a 16-week period.

Anti-inflammatory dose doxycycline has a rapid onset of action and produced a significant reduction in inflammatory lesions within the first 3 weeks of therapy, followed by a progressive continued reduction over the entire study period. Marked improvement was noted over a wide range of clinical severity. Reduction in erythema was also observed in both studies. Anti-inflammatory dose doxycycline proved to be safe in both studies, with the frequency of AEs similar to those of patients who received placebo. Vaginal candidiasis and photosensitivity were not observed in patients treated with anti-inflammatory dose doxycycline in either study.[44,45,48] Finally, an inverse relationship exists between compliance and dosing frequency, and therefore once-daily administration has been shown, based on a review of several studies, to be the dosing regimen associated with the highest rate of compliance.[49,50]

Anti-inflammatory dose doxycycline is the only tetracycline agent proven to be effective for the treatment of rosacea in pivotal phase III clinical trials that exhibits a pharmacokinetic profile that separates the anti-inflammatory effects from antibiotic activities.[15,36,51] The antibacterial effects of doxycycline or other antibiotics have not been shown to be of therapeutic importance in rosacea; therefore an effective and safe once-daily formulation of this drug that does not exhibit antibiotic selection pressure is clinically significant.[3-6,11,15,48] The data suggest that anti-inflammatory dose doxycycline may be used as first-line therapy for patients with rosacea. Although studies of combination therapy for rosacea are limited, concomitant use of topical therapy, such as metronidazole,[44] azelaic acid, or sulfacetamide-sulfur with anti-inflammatory dose doxycycline, has the potential to produce additive therapeutic benefits and is worthy of investigation.

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