COMPARISON OF ANTI-INFLAMMATORY DOSE DOXYCYCLINE VERSUS DOXYCYCLINE 100 MG IN THE TREATMENT OF ROSACEA

James Q. Del Rosso DO,[a] Joel Schlessinger MD,[b] Philip Werschler MD[c]

a. Dermatology Residency Director, Valley Hospital Medical Center, Las Vegas, NV

Clinical Associate Professor, Dermatology, University of Nevada School of Medicine, Touro University College of Osteopathic Medicine, Las Vegas, NV

b. President, Advanced Skin Research Center, Omaha, NE

c. Assistant Clinical Professor (Medicine/Dermatology), University of Washington, Seattle, WA

Editor's Note: This study was previously presented in a poster at the 7th Annual Caribbean Dermatology Symposium, January 15-19, 2008; St Thomas, US Virgin Islands, and parts of the study data have been previously published. The *Journal of Drugs of Dermatology* (JDD) is publishing the study in its entirety in cooperation with the original authors.

Rosacea is a chronic inflammatory dermatosis, but the exact etiology of rosacea remains unknown. It has been described as a result of "a disparate assortment of stimuli acting in concert on a genetically susceptible host" with a constitutional diathesis.[1] Among the many investigations into its pathophysiology, much interest has been focused on the role of the collagen-degrading matrix metalloproteinases (MMPs) and proteases that are involved in many aspects of tissue remodeling and local tissue inflammation. New research findings suggest that an upregulation of local inflammatory mediators play a key role in the pathophysiology of this chronic disease.[2,3]

Tetracyclines have historically been used to treat rosacea.[4] No causative organisms have been definitively implicated as an etiologic factor in rosacea. Thus, it is thought that tetracyclines treat the disease primarily via multiple anti-inflammatory mechanisms. These mechanisms include MMP inhibition, reduced cytokine expression, and indirect inhibition of serine proteases. Animal model research has shown these effects to be exerted in the absence of antibiotic activity, and results from clinical trials support these findings.[4-9]

Traditional doses of doxycycline (≥50 mg) can exert selection pressure, increasing the risk of bacterial resistance, and can alter normal commensal microflora.[7] A recent prospective, placebo-controlled, randomized, double-blind trial in 29 healthy volunteers demonstrated that daily administration of oral doxycycline 100 mg was associated with a significant increase in doxycycline-resistant nasopharyngeal flora measured at days 7 and 14, and continuing for at least 2 weeks after cessation of therapy.[8] In contrast, research has shown that even long-term treatment with an anti-inflammatory dose of doxycycline (40 mg delayed-release) does not alter susceptibility of bacteria to antibiotics in a 9-month trial.[5-7,9]

Overview and Objectives

The following study evaluated the safety and efficacy of an anti-inflammatory dose of doxycycline (40 mg delayed-release) administered once daily versus doxycycline 100 mg administered once daily in the treatment of moderate to severe rosacea for 16 weeks. In addition, both groups also applied

Table 1. Investigator's Global Assessment.

Score	Definition	Assessment guideline
0	Clear	Skin is completely clear of inflammatory lesions
1	Near clear	1-4 papules and pustules; no nodules
2	Mild	5-10 papules and pustules; no nodules
3	Moderate	11-17 papules and pustules; 0 or 1 nodule may be present
4	Severe	18-25 papules and pustules; 1 or 2 nodules must be present; perilesional erythema is present
5	Very severe	>25 papules and pustules; nodules must be present; perilesional erythema plus edema are a hallmark of this patient

Table 2. Clinician's erythema assessment scale.

Score	Definition	Assessment guideline
0	None	No redness present
1	Mild	Slight pinkness
2	Moderate	Definite redness
3	Significant	Marked erythema
4	Severe	Fiery redness

Table 3. Subject demographics (N=91).

	Group 1 (100 mg) subjects (n=47)	Group 2 (40 mg) subjects (n=44)
Completed	37	30
Gender		
Male	12	15
Female	35	29
Race		
Caucasian	44	43
Mean age (years)	45.2	44.3

Table 4. Reasons for discontinuation.

	Group 1: n (%)	Group 2: n (%)	Total: N (%)
Discontinued from study	10 (21.3)	14 (31.8)	24 (26.4)
Adverse or serious adverse event	4 (8.5)	5 (11.4)	9 (9.9)
Protocol violation	1 (2.1)	3 (6.8)	4 (4.4)
Lost to follow-up	0 (0.0)	4 (9.1)	4 (4.4)
Patient withdrew consent	4 (8.5)	0 (0.0)	4 (4.4)
Other	1 (2.1)	2 (4.5)	3 (3.3)

Table 5. Top 10 most common adverse events.

Adverse Event	Group 1	Group 2
Nausea	8	-
Headache	3	2
Influenza	3	-
Nasopharyngitis	2	3
Urticaria	2	1
Diarrhea	2	-
Esophageal pain	2	-
Vomiting	2	-
Abdominal pain	1	-
Abdominal pain upper	1	-

topical metronidazole 1% gel once daily. This was a multicenter, outpatient, prospectively randomized, double-blind, active-control study of 91 subjects. The primary objective of the study was to evaluate, in subjects with inflammatory rosacea, the relative efficacy and onset of anti-inflammatory dose doxycycline (40 mg delayed-release), which does not exert an antibiotic effect, as compared to a conventional dose of doxycycline (100 mg daily), which does exert antibiotic activity. Additionally, an important objective of the study was to compare safety and adverse reactions between the 2 study arms.

Design

Subjects were randomized to receive daily administration of drugs in the following groups: 100 mg doxycycline and topical metronidazole 1% gel (Group 1) and 40 mg delayed-release doxycycline and topical metronidazole 1% gel (Group 2). Both the doxycycline 100 mg capsules and 40 mg delayed-release capsules were over encapsulated to ensure the capsules were indistinguishable during administration and maintain a double-blind study.

Inclusion/Exclusion Criteria

The study population included healthy, postpubescent males and females ≥18 years of age with inflammatory (papulopustular) rosacea, 8 to 40 papules and pustules, ≤2 nodules, a score of 2 to 5 on the Investigator's Global Assessment (IGA) (Table 1), a total erythema score of 5 to 20 with at least 1 pentad (1 of 5 facial areas) specific score of ≥2 on the Clinician's Erythema Assessment (CEA) scale (Table 2), and the presence of telangiectasia. Conventional precautions regarding the use of contraceptives, negative pregnancy test, and nonlactation were applied.

Exclusion criteria included changes in hormonal contraception methods within 4 months of baseline, the use of any rosacea treatments within 2 weeks of baseline, subjects with a known sensitivity to study drugs, and use of clinically significant concomitant drug therapy including corticosteroids and vasodilatory agents.

Demographics

Subject demographics are summarized in Table 3. A total of 24 subjects discontinued the study prematurely (Table 4).

Endpoints

The primary efficacy endpoint was the change in total lesion count (papules, pustules, and nodules) from baseline to week 16. The secondary efficacy endpoints were changes in IGA from baseline, changes in CEA from baseline, and changes in total lesion counts at each time point including weeks 4, 8, 12, and 16. Adverse events were monitored throughout the study.

Statistical Methodology

The purpose of the study was to determine whether there was any statistically significant difference between the 2 treatment groups at each visit and study endpoint with regard to the primary efficacy parameter. An ANOVA model with

terms for the treatment group and investigator center was used to evaluate the efficacy parameters, with 2-tailed alpha set to 0.05. SAS Software (SAS® software, version 8.2) was used to perform all statistical analyses.

Results

Primary Efficacy Variables

Figure 1 shows the total inflammatory lesion count by visit for the per protocol population, ie, without imputation. "Endpoint" represents the primary efficacy endpoint using a last observation carried forward (LOCF) approach to account for missing data of those subjects who discontinued early. As shown in Figure 1, the mean change from baseline to week 16 in inflammatory lesion count was similar in both study groups and at all study visits. Small differences that were observed are neither statistically nor clinically significant with a P value of ≥.8 for the primary efficacy analysis.

Secondary Efficacy Variables

There were no significant inter-group differences in IGA. Figure 2 shows the mean change from baseline in IGA score. The mean change from baseline in erythema score was slightly greater at all time points in the 40 mg group. This was statistically significant at week 12 when the mean decrease in erythema score was -4.97 in the 40 mg group and -3.47 in the 100 mg group (P<.04), but not at week 16 (Figure 3).

Treatment-Emergent Adverse Events

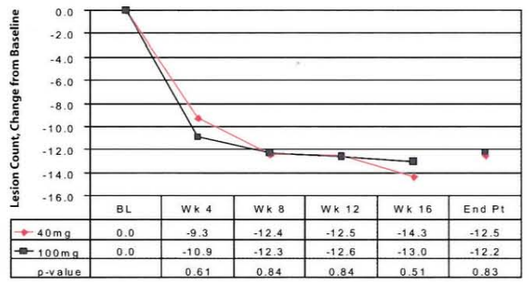
The 10 most frequent adverse events (AEs) included nausea, headache, influenza, nasopharyngitis, urticaria, diarrhea, esophageal pain, vomiting, abdominal pain, and upper abdominal pain in a total of 32 subjects. Of those, 26 subjects were in the 100 mg group and 6 subjects in the 40 mg group as depicted in Table 5. Figure 4 shows the number of treatment-emergent AEs for the 100 mg and 40 mg groups. Figure 5 shows the types of gastrointestinal AEs and the percentage of subjects that reported them in each group. Both the number of AEs and the number of subjects with AEs were greater in the 100 mg group. While the majority of AEs were mild or moderate, the 100 mg group had a higher incidence of moderate side effects that were rated as "possibly" or "probably" related (Figure 6) to the combination drug treatment. The 2 serious adverse events reported in the 40 mg group were myocardial infarction and hysterectomy, and neither were deemed to be related to treatment. The majority of AEs were gastrointestinal disorders, followed by infections and infestations.

Conclusions

Both anti-inflammatory dose doxycycline (40 mg delayed-release) and 100 mg doxycycline are equally effective once-daily treatments for moderate to severe rosacea for up to 16 weeks. Doxycycline at a dosage of 100 mg does not have a more rapid onset of action than 40 mg delayed-release, and is associated with a higher incidence of AEs than the 40 mg delayed-release dosage (eg, 5% of the subjects receiving 40 mg delayed-release doxycycline exhibited GI symptoms compared to 26% of those receiving the 100 mg dose).

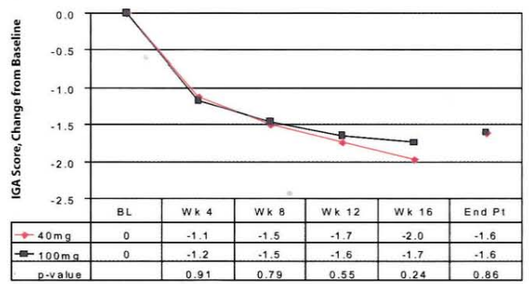
With equivalent therapeutic results to doxycycline 100 mg, anti-inflammatory dose doxycycline (40 mg delayed-release) offers clinically relevant advantages for the treatment of rosacea due to lower risk for AEs, especially gastrointestinal side effects, and noncontributory effects toward the development of bacterial resistance.

Figure 1. Total inflammatory lesion count: mean change from baseline.



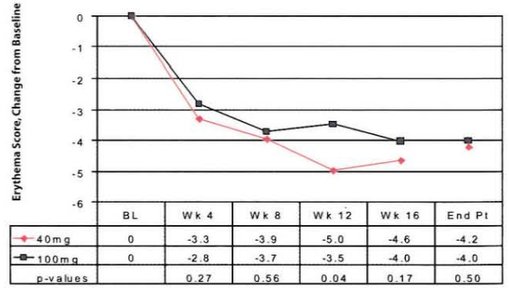
	BL	Wk 4	Wk 8	Wk 12	Wk 16	End Pt
40mg	0.0	-9.3	-12.4	-12.5	-14.3	-12.5
100mg	0.0	-10.9	-12.3	-12.6	-13.0	-12.2
p-value		0.61	0.84	0.84	0.51	0.83

Figure 2. Investigator's global assessment: mean change from baseline.



	BL	Wk 4	Wk 8	Wk 12	Wk 16	End Pt
40mg	0	-1.1	-1.5	-1.7	-2.0	-1.6
100mg	0	-1.2	-1.5	-1.6	-1.7	-1.6
p-value		0.91	0.79	0.55	0.24	0.86

Figure 3. Mean change from baseline in erythema.



	BL	Wk 4	Wk 8	Wk 12	Wk 16	End Pt
40mg	0	-3.3	-3.9	-5.0	-4.6	-4.2
100mg	0	-2.8	-3.7	-3.5	-4.0	-4.0
p-values		0.27	0.56	0.04	0.17	0.50

Figure 4. Treatment-emergent adverse events.

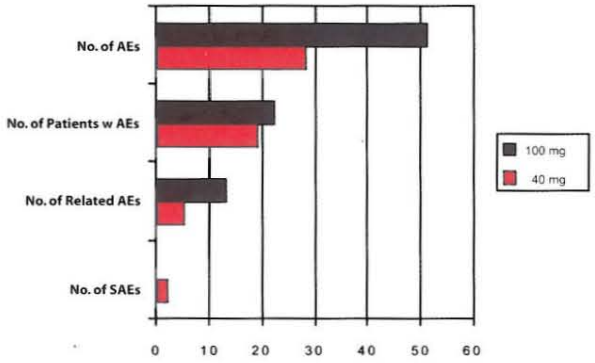


Figure 5. Percentage of subjects with gastrointestinal adverse events.

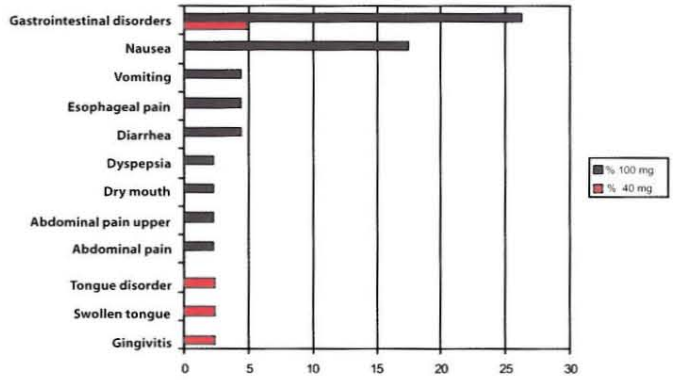
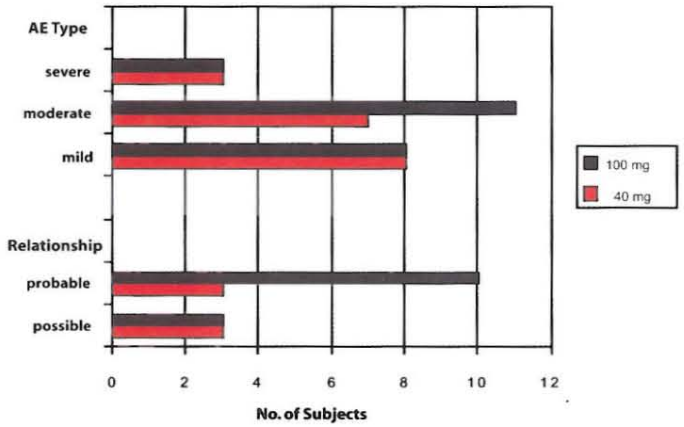


Figure 6. Severity of adverse events and relationship to study drug.



Acknowledgments

The authors would like to acknowledge the following co-investigators for their participation in this study: William Abramovits MD, Douglas Forsha MD, Bernard Goffe MD, and Angela Moore MD.

Disclosure

The study was supported through educational grants from CollaGenex Corporation.

References

1. Landow K. Unraveling the mystery of rosacea. *Postgrad Med.* 2002;112:51-58.
2. Yamasaki K, Di Nardo A, Bardan A, et al. Increased serine protease activity and cathelicidin promotes skin inflammation in rosacea. *Nat Med.* 2007;13:975-980.
3. Aroni K, Tsagroni E, Kavantzas N, et al. A study of the pathogenesis of Rosacea: how angiogenesis and mast cells may participate in a complex multifactorial process. *Arch Dermatol Res.* 2008;300: 125-131.
4. Pelle MT, Crawford GH, James WD. Rosacea: II. Therapy. *J Am Acad Dermatol.* 2004;51:499-512.
5. Golub LM, Lee HM, Ryan ME, et al. Tetracyclines inhibit connective tissue breakdown by multiple non-antimicrobial mechanisms. *Adv Dent Res.* 1998;12:12-26.
6. Del Rosso JQ, Webster GF, Jackson M, et al. Two randomized phase III clinical trials evaluating anti-inflammatory dose doxycycline (40-mg doxycycline, USP capsules) administered once daily for treatment of rosacea. *J Am Acad Dermatol.* 2007;56:791-802.
7. Skidmore R, Kovach R, Walker C, et al. Effects of subantimicrobial-dose doxycycline in the treatment of moderate acne. *Arch Dermatol.* 2003;139:459-464.
8. Walker C, Bradshaw M. The effect of oral doxycycline 100 mg once-daily for 14 days on the nasopharyngeal flora of healthy volunteers: a preliminary analysis. Poster presented at: 26th Anniversary Fall Clinical Dermatology Conference; October 18-27, 2007; Las Vegas, Nevada.
9. Walker C, Webster G. The effect of anti-inflammatory dose doxycycline 40mg once-daily for 9 months on bacterial flora: subset analysis from a multicenter, double-blind, randomized trial. Poster presented at: 26th Anniversary Fall Clinical Dermatology Conference; October 18-27, 2007; Las Vegas, NV.

ADDRESS FOR CORRESPONDENCE

James Q. Del Rosso DO
Dermatology Residency Director
Valley Hospital Medical Center, PMB-531
3230 E. Flamingo #8
Las Vegas, NV 89121
Phone: 702-585-6732
e-mail: jqdelrosso@yahoo.com