Efficacy of Extended-Release 45 mg Oral Minocycline and Extended-Release 45 mg Oral Minocycline Plus 15% Azelaic Acid in the Treatment of Acne Rosacea

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ABSTRACT

Rosacea is one of the most commonly occurring dermatoses treated by dermatologists. There are multiple therapeutic options available for the treatment of papulopustular rosacea. Rosacea is an inflammatory condition, classically presenting with flushing and/or blushing along with erythema, edema, telangiectasia, papules, pustules, and nodules of the face. Minocycline, a member of the tetracycline family, has demonstrated benefit in the treatment of inflammatory lesions in patients with rosacea. This manuscript highlights the use of a new sustained-release low-dose minocycline 45 mg tablet, with or without azelaic acid, for the treatment of papulopustular rosacea.

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INTRODUCTION

Rosacea is one of the most commonly occurring dermatoses treated by dermatologists and affects approximately 16 million people in the United States[1] and 45 million people worldwide. Rosacea is an inflammatory dermatologic condition, classically presenting with flushing and/or blushing along with erythema, edema, telangiectasia, papules, pustules, and nodules of the face.[2] Although the underlying cause of this disorder is currently unknown, genetic and environmental factors are thought to contribute to its pathogenesis.[3] There is evidence that aberrant cathelicidin production plays an important role in the cutaneous findings.[4] The pathophysiology of rosacea is multifactorial, and triggering factors include stress, menopause, alcohol consumption, environmental exposures such as temperature extremes and sun exposure, certain foods such as spices, wind, and temperature extremes. The cutaneous findings are usually in the central face and composed of persistent erythema, telangiectasia, papules, and or pustules. The associated symptoms include pruritus, burning, and flushing.[5,6] There are 4 main subtypes of rosacea: erythematotelangiectatic, papulopustular, phymatous, and ocular.[7]

It is well established that rosacea is a chronic disease that may require long-term therapy such as topical and oral antibiotics, but this may lead to the development of antibiotic-resistant organisms.[8] Inflammation plays a central role in the pathogenesis of rosacea and is usually treated with anti-inflammatory agents; flushing episodes are treated with vasoconstrictor agents, and telangiectasias with laser and light therapy.[9]

It has been well documented that rosacea is an inflammatory response to local factors and not an infectious disease.[3,5] It is important to utilize an agent that does not affect antimicrobial resistance while also impacting the disease. There are a variety of topical medications approved for the treatment of rosacea, but currently there is only one oral medication approved by the US Food and Drug Administration for the treatment of papulopustular rosacea, a subantimicrobial dose of doxycycline. Its effect has been demonstrated beyond its antimicrobial effects and may be more related to its anti-inflammatory capabilities, including but not limited to protease inhibtion.[10] There are other oral agents utilized for the treatment of rosacea, including minocyline, tetracycline, sulfa-based antibiotics, and macrolides. Extended-release (ER) minocycline was formulated to avoid many of the side effects noted with high-dose minocycline. ER minocycline is produced in a variety of doses for use in acne, and dosing is based on weight. At the time of this study, the lowest available dose of ER minocycline, 45 mg, was delivered as a once-daily oral tablet.[11,12] The reasoning behind this study was to demonstrate the efficacy of the lowest possible dose utilizing the anti-inflammatory effects of minocycline in the treatment of patients with papulopustular rosacea, while avoiding the impact and side effects of high-dose minocycline (100-200 g/day). Azelaic acid has been utilized in the treatment of rosacea and was used topically once daily in the comparison group.[13,14] The objective of this study was to evaluate the safety, efficacy, and tolerability of ER 45 mg oral minocycline as monotherapy or combined with azelaic acid 15% in the treatment of rosacea.

METHODS

Study Design

This was a randomized, double-blind study of ER minocycline 45 mg and ER minocycline 45 mg plus 15% azelaic acid for the treatment of rosacea. The study consisted of 12 weeks of treatment plus a 4-week follow-up period (total of 16 weeks). Sixty patients were enrolled at 2 investigational centers (n=30 at each center) and completed the 12 weeks of double-blind treatment with a 4-week follow-up. Patients were randomized to receive ER 45 mg minocycline administered as a once-daily oral dose, or ER 45 mg minocycline as a once-daily oral dose plus azelaic acid 15% once daily via topical application each night.

Study Drug

The following medications will be used in this study:

- Group 1: Once-daily 45 mg oral minocycline as monotherapy.
- Group 2: Once-daily 45 mg oral minocycline plus topical 15% azelaic acid administered once daily at bedtime.

Patient Selection

Inclusion Criteria

1. Postpubescent male and females, aged 18 years or older, with rosacea, 10 to 40 papules and pustules and ≤2 nodules.
2. A score of 2 to 4 on the Investigator's Global Assessment (IGA) Scale (a 0 to 5 scale where 0 = clear, no evidence of facial lesions; 3 = moderate, papules and pustules are a predominant feature (nodules may be present), and some perilesional erythema should be present, and 5 = very severe, numerous papules and pustules present, nodules may be present, and perilesional erythema is a hallmark of this patient.)
3. A score of ≥2 on the Clinical Erythema Assessment (CEA) Scale (a 0 to 4 scale where 0 = none, no redness present; 1 = mild, slight pinkness; 2 = moderate, definite redness; 3 = significant, marked erythema, and 4 = severe, fiery redness.)
4. Female patients of childbearing potential, defined as having an intact uterus and ovaries, older than 50 years, and had menses within the last 12 months, must utilize 2 of the following methods of birth control throughout the study: intrauterine device, diaphragm, a condom plus the use of a spermicidal gel or foam, oral contraceptives (provided patient has been utilizing this method for at least 4 months before baseline and has not changed the brand within this period), or sign an agreement that they will abstain from sexual intercourse during the course of the study. Bilateral tubal ligation or lack of menses for patients younger than 50 years are considered to be of childbearing potential.
5. Informed consent must be obtained from each subject, and a copy of singed consent was provided to subject.
6. Negative urine pregnancy test and nonlactating.

Exclusion Criteria

1. The initiation of a hormonal method of contraception within 3 months of baseline; or discontinuation during the course of study; or change in the actual product within 3 months of baseline or during the study.
2. The use of systemic antibiotics within 4 weeks of baseline.
3. The use of a systemic investigational drug within 30 days of baseline and an investigational topical drug within 14 days of baseline.
4. Pregnant women or women of childbearing potential who are not using an adequate form of birth control as described in the inclusion criteria.
5. Patients with a known hypersensitivity to tetracyclines.
6. Patients on clinically significant, concomitant drug therapy. (See *Concomitant Medications* below.)
7. The use of any rosacea treatment (over-the-counter or prescription) during the course of the study.
8. The use of facial topical steroids 4 weeks before baseline and during the study.
9. The use of systemic corticosteroids 6 weeks before baseline and during the study.
10. Patients who have had gastric bypass surgery or are considered achlorhydric.
11. Patients who are diagnosed with diseases with known photosensitivity (eg, porphyria, vitiligo, polymorphic light eruption, actinic prurigo, solar urticaria).
12. Patients taking drugs that are known photosensitizers (eg, phenothiazines, amiodarone, quinine, thiazides, sulfonamides, quinolones).
13. The use of a tanning bed.

Concomitant Medications

The following medications were prohibited:

1. The use of tetracycline family antibiotics at any dose is prohibited.
2. Use of <u>any</u> acne or rosacea treatments during the course of the study, including spironolactone.
3. Antacids and vitamins containing aluminum, calcium, or magnesium may impair drug absorption and should be taken at least 1.5 hours before or 3.0 hours after taking study medication.
4. Use of proton pump inhibitors.
5. Use of phenothiazines.
6. Use of amiodarone.
7. Use of thiazides.
8. Products containing iron should be taken at least 1.5 hours before or at least 3.0 hours after taking the study medication.

Study Methods

A complete medical history, lesion score (total number of papules, pustules, and nodules), and the IGA score and CEA score was performed by the investigator for all patients. Urine pregnancy testing was conducted on all women of childbearing potential.

After the baseline visit, each patient was scheduled for return visits at weeks 4, 8, 12, and 16. The following evaluations were conducted at each visit: lesion score, IGA score, and CEA score.

Efficacy Evaluation

Efficacy of the study medication was assessed for each dose group compared with the placebo group on the basis of the following parameters:

Primary Efficacy Parameters

1. Change in total inflammatory lesion count of papules plus pustules plus nodules from baseline to the week 12 visit (end point).

Secondary Efficacy Parameters

1. Change from baseline in the IGA score to the week 12 visit (end point).
2. Proportion of patients achieving a score of 0 or 1 (clear/near clear) on the IGA score at the week 12 visit (end point).
3. Change in CEA score from baseline to the week 12 visit (end point).

Ancillary Efficacy Parameters

1. Change from baseline in total lesion count (papules, pustules, and nodules) at the week 4, 8, 12, and 16 visits.
2. Change from baseline in CEA score at the week 4, 8, 12 and 16 visits.
3. Responder analysis: Percentage of patients achieving at least a 50% reduction from baseline inflammatory lesion count at the week 12 visit (end point).
4. Percent change in total inflammatory lesion count from baseline to the week 12 visit (end point).

Safety Evaluation

Safety was assessed during the study by collection of study events and review of concomitant treatments. All adverse events (AEs) were recorded regardless of their intensity or relationship to the drug. Any patient who suffered a serious AE was withdrawn from the study.

Statistical Considerations

Stating the Problem

The objective of this study is to investigate the therapeutic effect of 45 mg daily oral doses of minocycline vs 45 mg daily oral doses of minocycline plus once daily 15% azelaic acid and their benefits in patients with rosacea.

Study Design

This double-blind, 2-center study was a 2-armed, parallel-group design. Treatment was randomly allocated to patients in blocks of 2. Blocks were centrally assigned to investigators as needed and based on enrollment.

The goal of the analyses was to assess evidence of an overall effect of 45 mg minocycline and the overall effect of 45 mg oral minocycline plus 15% azelaic acid in the therapy of patients with acne rosacea. Two types of study populations were analyzed, namely, the intention-to-treat (ITT) and the per-protocol (PP) populations.

Intention-to-Treat Analysis Population

The ITT population included all randomized patients for whom it could not be excluded that they had taken the study medication at least once after randomization.

The ITT population included patients who had no data at week 12 for any reason, eg, patients withdrawn from treatment before week 12. The last observations (postrandomization) in these patients were used for the ITT end point analysis reflecting each patient's final postrandomization visit, ie, the last observation was carried forward for the end point analysis.

The analysis of safety was performed by evaluating vital signs and adverse drug experiences, based on the ITT population. The ITT analysis provides estimates of treatment effects, which may be more likely to mirror those effects observed in practice. Consequently, this analysis was considered the primary efficacy analysis.

Per-Protocol Analysis Population

The PP population is a subset of the ITT population and was defined by the absence of any major protocol violations, including violations of any inclusion/exclusion criterion.

Possible protocol violations/deviations included those defined as follows:

- Failure to meet the inclusion criteria and pass the exclusion criteria;
- noncompliance of treatment medication, defined as less than 80%;
- use of concomitant drugs not allowed according to the protocol; and
- erroneous unblinding.

Patients who discontinued treatment before week 12 were included in the PP analysis. However, no imputation technique to compensate for missing data was used in the PP analysis.

Primary Efficacy Variables

Total Inflammatory Lesion Count (Papules Plus Pustules Plus Nodules)

Total inflammatory lesion count is the sum of the papule count, pustule count, and the nodule count. The total inflammatory lesion count obtained at week 12 (end point) was used for the primary efficacy evaluation. Any week 12 observation obtained

outside the predefined visit window was used for the ITT analysis but not for the PP analysis.

Randomization

The study enrolled 2 groups of patients treated with oral study drug or oral and topical study drug, respectively. The randomization process assigned equal numbers of patients to each treatment group.

There were 2 centers in the study. Blinded study medication was identified using the patient randomization number.

Secondary and Ancillary Efficacy Variables and Their Statistical Analyses

- Lesion counts: For analysis purposes, we assume that separate papule, pustule, and nodule counts are normally distributed. Papule, pustule, and nodule counts were summarized for each treatment group and at each visit using summary statistics. Change from baseline for papule, pustule, nodule and total inflammatory lesions were analyzed at each postrandomization visit using the same analysis of variance (ANOVA) model as the primary efficacy variable.

- IGA score and CEA score: IGA and CEA ranged from 0 to 5. The primary analysis of IGA and CEA was based on changes from baseline scores at end point and was summarized for each treatment group and at each visit. For each visit, these changes from baseline scores were analyzed using Cochran–Mantel–Haenszel (CMH) tests stratified by center.

- Responders: The analysis of the percentage of patients in the ITT population achieving at least a 50% reduction in inflammatory lesions at the week 12 visit (end point) was conducted using ANOVA test stratified by center.

Demographics and Baseline Characteristics

Demographic variables were age, gender, and race. Baseline characteristics included a complete medical history, lesion score (total number of facial lesions and number of papules, pustules, nodules) and IGA/CEA scores. IGA and CEA scores were summarized using frequency distributions and were tested for baseline comparability of treatment groups using ANOVA. Total number of facial lesions, total number of inflammatory lesions, and numbers of papules, pustules, and nodules were summarized for each treatment group using summary statistics (mean, standard deviation, median, minimum, and maximum).

Adverse Clinical Experiences

AEs will be coded using the MedDRA Dictionary (Medical Dictionary for Regulatory Activities, version 4.1). All AEs and study drug–related AEs will be tabulated by seriousness, death, and discontinuation because of adverse experiences for each treatment group. Study drug–related AEs were defined as AEs considered likely or definitely related to study drug or with missing relation.

Adverse Events

Any AEs, including both observed or volunteered problems, complaints, or symptoms, were to be recorded. AEs resulting from concurrent illnesses or reactions to concurrent medications are also to be recorded. Each AE is to be evaluated for duration, intensity, and relationship with the study medication or other causes. The intensity of the event was characterized as mild, moderate, or severe as follows:

- Mild: Events are usually transient, requiring no special treatment, and do not interfere with the subject's daily activities.
- Moderate: Events traditionally introduce a low level of inconvenience or concern to the subject and may interfere with daily activities, but are usually ameliorated by simple therapeutic measures.
- Severe: Events interrupt subject's usual daily activity and traditionally require systemic drug therapy or other treatment.

One of the following determinations will then be used to document the relationship of the AE to the study drug: not related, possible, probable.

Discontinuation and Replacement of Patients

Any patient found to have entered the study in violation of this protocol was withdrawn from the study. Any female subject who became pregnant during the study was withdrawn from the study. Any subject who required the use of an unacceptable concomitant medication was withdrawn from the study. If a patient was withdrawn from the study, regardless of the cause, all evaluations required at the scheduled end of the study were performed. Patients discontinued from the study were not replaced.

Statistical Methods

All study variables—vital signs data, outcome variables (total lesion count, IGA, CEA—were summarized at each study visit with means and standard deviations, medians, and extrema. The primary outcome variable was the 12-week change in the total lesion count (from baseline to week 12). Additional outcomes include 12-week changes in CEA score and IGA score, as well as changes in IGA, CEA, and lesion counts from baseline to interim weeks (4 and 8) and the follow-up visit (week 16). Comparisons of changes in outcome variables within each treatment group (eg, tests of the efficacy of each treatment) were Wilcoxon signed-rank tests. Comparisons of changes in outcome variables between treatment groups were Wilcoxon rank-sum tests, stratified by study site. Two categorical outcomes were examined—subjects having a week 12 IGA less

TABLE 1.

Summary Statistics for Vital Signs and Outcome Measurements From Baseline Visit[a]

Variable	ER Minocycline (n=30)	ER Minocycline +Azelaic Acid 15% (n=30)	*P* Value
Systolic BP	129 ± 15; 130 [97, 162]	125 ± 13; 126 [100, 155]	.37
Diastolic BP	82 ± 9; 84 [59, 98]	79 ± 9; 78 [56, 107]	.11
Pulse	71 ± 9; 72 [57, 88]	70 ± 9; 70 [57, 86]	.37
Temperature	98 ± 1; 98 [94, 100]	98 ± 1; 98 [96, 99]	.91
Respirations	16 ± 1; 16 [12, 18]	16 ± 1; 16 [12, 18]	.86
Total lesion Count	15 ± 7; 12 [10, 34]	15 ± 5; 12 [10, 31]	.94
IGA score	3 ± 1; 3 [2, 10]	3 ± 1; 3 [2, 4]	.99
CEA score	9 ± 3; 8 [4, 15]	9 ± 3; 10 [3, 15]	.67

[a]Data are given as mean ± standard deviation; median [min, max]. *P* values are from stratified Wilcoxon rank-sum tests.

than 2 and subjects experiencing 50% or greater reduction in lesion count by week 12. The CMH test, stratified by study site, was used to compare these outcomes between treatment groups. The number of subjects experiencing an AE was compared with a CMH test, stratified by study site, and the cumulative number of AEs was compared with a Poisson-linked generalized linear mixed-effects model (Poisson GLMM). All analyses were conducted on the ITT population, defined as all enrolled subjects that took at least one dose of study medication. Missing observations for the ITT analysis were imputed by the last observation carried forward (LOCF) method. A sensitivity analysis of the PP population, defined in the Results, was conducted. All hypothesis tests were conducted at the .05 level, and all analyses were conducted using the open source R software program (R Foundation for Statistical Computing, Vienna, Austria, http://www.r-project.org/).

RESULTS

Enrollment Statistics and Baseline Characteristics

Sixty subjects were enrolled. Thirty were treated with ER minocycline, and thirty with ER minocycline and azelaic acid 15%. Each site enrolled 30 subjects, 15 in each treatment group. All 60 subjects comprised the ITT population. At the screening visit, 12 subjects were taking prohibited medications and thus failed to meet all exclusion criteria. Eleven of these subjects underwent a 2-week washout period before baseline assessment for the prohibited medication, and one subject received a waiver for exclusion criteria violation. Five observations were imputed by LOCF at the week 12 visit because of missed visits or loss to follow-up, 7 at week 8, and 6 at the follow-up visit (week 16).

TABLE 2.

Summary Statistics for 12-Week Reduction in Total Lesion Count, IGA, and CEA[a]

Outcome	ER Minocycline	ER Minocycline + Azelaic Acid 15%	2-Sample *P* Value
Total lesion count	−11 ± 5; −11 [−22, 0]	−12 ± 7; −10 [−30, 0]	.60
IGA score	−2 ± 2; −1 [−9, 0]	−2 ± 1; −2 [−3, 0]	.61
CEA score	−3 ± 3; −3 [−9, 6]	−4 ± 3; −4 [−9, 3]	.49

[a]Data are given as mean ± standard deviation; median [min, max]. *P* values comparing treatment groups are from stratified Wilcoxon tests.

Baseline vital signs and study outcomes did not significantly differ between treatment groups (Table 1), so we inferred that treatment groups were well balanced with respect to baseline characteristics.

Week 12 Efficacy Analyses

Summary statistics for 12-week changes in the outcome variables are in Table 2. In both treatment groups, there were significant 12-week reductions in each outcome variable ($P<.0001$ for all variables in both groups). However, the 2 treatments provided equal reductions in total lesion count ($P=.60$), IGA ($P=.61$), and CEA ($P=.61$).

Seventeen of 30 subjects (57%) in the ER minocycline group and 18 of 30 subjects (60%) in the ER minocycline + azelaic acid 15% group had a week 12 IGA of less than 2. These proportions did not significantly differ (CMH test, $P=.50$). Fifty-two (87%) subjects, 26 in each treatment group, experienced a reduction in total lesion count of 50% or greater by week 12. There was no significant difference between groups in this outcome (CMH test, $P=1.0$).

Analyses at Interim Visits (Week 4 and 8) and Follow-up (Week 16)

Significant reductions in lesion counts, IGA, and CEA occurred in each treatment group (Table 3, Figure 1). For each outcome, reductions were largest in the interval between baseline and week 4 ($P\leq.0002$, all outcomes). Significant reductions in total lesion count and IGA occurred in both treatment groups from week 4 to week 8 ($P\leq.01$), while only the ER minocycline group experienced a significant reduction in CEA from week 4 to week 8 ($P=.002$; $P=.051$ for ER minocycline + azelaic acid 15%). Total lesion counts and CEA did not significantly change from

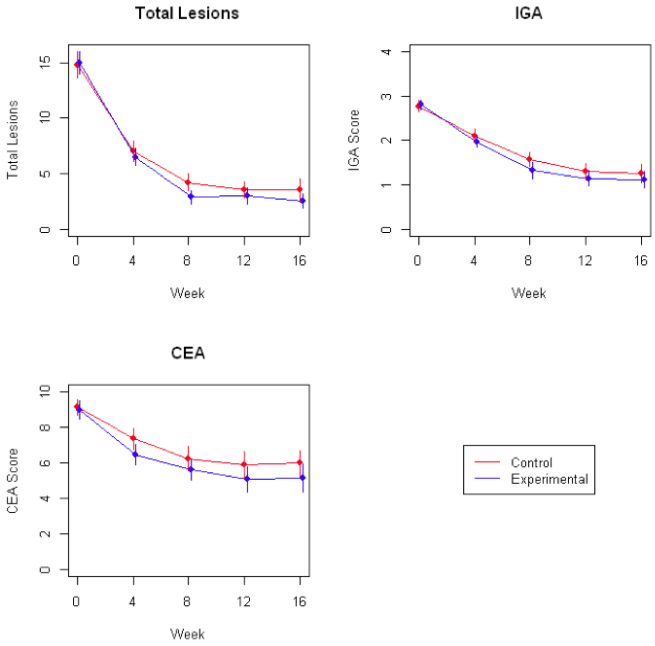
TABLE 3.

Summary Statistics for the Total Lesion Count, IGA, and CEA by Week by Treatment Group[a]

Visit	Total Lesion Count			IGA			CEA		
	ER Minocycline	ER Minocycline + Azelaic Acid 15%	*P* Value	ER Minocycline	ER Minocycline + Azelaic Acid 15%	*P* Value	ER Minocycline	ER Minocycline + Azelaic Acid 15%	*P* Value
Baseline	15 ± 7; 12 [10, 34]	15 ± 5; 12 [10, 31]		3 ± 1; 3 [2, 4]	3 ± 1; 3 [2, 4]		9 ± 2; 9 [6, 15]	9 ± 3; 10 [3, 15]	
Week 4	7 ± 5; 6 [0, 26]	7 ± 4; 6 [0, 18]	.91	2 ± 1; 2 [0, 4]	2 ± 1; 2 [0, 3]	.37	7 ± 3; 7 [2, 15]	7 ± 3; 7 [1, 11]	.33
Week 8	5 ± 4; 4 [0, 21]	4 ± 4; 3 [0, 13]	.58	2 ± 1; 2 [0, 4]	1 ± 1; 2 [0, 3]	.31	6 ± 4; 6 [0, 15]	6 ± 3; 6 [0, 12]	.80
Week 12	4 ± 4; 2 [0, 13]	3 ± 4; 2 [0, 17]	.60	1 ± 1; 1 [0, 3]	1 ± 1; 1 [0, 3]	.61	6 ± 4; 6 [0, 15]	5 ± 3; 6 [0, 13]	.49
Week 16	3 ± 5; 2 [0, 27]	3 ± 4; 2 [0, 12]	.76	1 ± 1; 1 [0, 3]	1 ± 1; 1 [0, 3]	.64	6 ± 4; 6 [0, 13]	6 ± 4; 6 [0, 13]	.32

CEA, Clinical Erythema Assessment score; ER, extended release; IGA, Investigator's Global Assessment score.
[a]Data are given as mean ± standard deviation; median [min, max]. *P* values are from between-group comparisons of the reduction in total lesion count from baseline to the week indicated by the given row (stratified Wilcoxon test).

FIGURE 1. Mean ± standard error plot of total lesion count, Investigator's Global Assessment (IGA), and Clinical Erythema Assessment (CEA) for both treatment groups.



week 8 to week 12 in either treatment group (*P*≥.06). The ER minocycline group experienced a significant week 8 to week 12 decrease in IGA (*P*=.04), while the ER minocycline + azelaic acid 15% group did not (*P*=.22).

Neither treatment was superior with respect to reduction in any outcome variable in any time interval. Specifically, 2-sample comparisons of visit-to-visit changes showed that the ER minocycline and ER minocycline + azelaic acid 15% groups did not significantly differ with respect to visit-to-visit change up to week 12 (*P*>.31).

After discontinuation of treatment at week 12, there were no significant changes in lesion count, IGA, or CEA in either treatment group to week 16 (*P*≥.33), and groups did not differ in changes after week 12 on any study outcome (*P*≥.32).

Safety Analyses

Twenty-seven subjects experienced a total of 44 AEs. Subjects in the ER minocycline + azelaic acid 15% group were more likely to experience an AE (16 of 30, 53%) than those in the ER minocycline group (11 of 30, 37%), although this difference was nonsignificant (CMH test, *P*=.31). The number of AEs also did not significantly differ between groups (Poisson GLMM, *P*=.15).

Two AEs were classified as possibly related to the study medication—an upset stomach and generalized urticaria in separate patients both receiving ER minocycline + azelaic acid 15%. Four AEs in 3 patients (all receiving ER minocycline + azelaic acid 15%) were severe but not suspected to be related to the study medication (bilateral oophorectomy with dermoid cyst removal, gastric erosion after lap band surgery, a severe respiratory infection, and cholecystitis).

Sensitivity Analysis of Per-Protocol Population

The PP population was defined at each week of follow-up as those that did not deviate from the study protocol by (1) missing a visit or (2) having a visit outside of the allowable window for the given

visit (±3 days for weeks 4 and 8, ±4 days for week 12, and ±5 days for week 16). In the sensitivity analysis, missing values for a given visit were not imputed, and patients having a visit outside the allowable time window were thrown out of the analysis. Based on these criteria, there were 50, 41, 42, and 40 subjects in the PP population at weeks 4, 8, 12, and 16, respectively.

The sensitivity analysis was conducted by repeating every analysis conducted on the ITT population in the PP population, and noting changes in the conclusions from the hypothesis tests, ie, whether the null hypothesis was rejected ($P<.05$). With one exception, the conclusions from the PP analysis corresponded with those from the ITT analyses (results not shown). The exception was of minor consequence—the week 4 to week 8 change in IGA in the ER minocycline + azelaic acid 15% group was significant in the ITT population ($P=.01$), but nonsignificant in the PP population ($P=.10$). We thus conclude that protocol deviations had minimal impact on our results.

CONCLUSION

Both ER minocycline 45 mg and ER minocycline 45 mg in combination with 15% azelaic acid provided significant reductions in lesion counts, IGA scores, and CEA scores in patients with rosacea over this 16-week study. Neither study group displayed superior results to the other, as reductions in all measured outcome variables were similar between groups and not statistically significantly different. The treatment groups did not significantly differ with respect to the incidence of AEs, and a negligible number of AEs were possibly suspected to be related to the study medication. The medications were well tolerated in both groups. This study highlights the benefits of ER minocycline 45 mg in patients with rosacea.

DISCLOSURES

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