

CUTANEOUS
MEDICINE
FOR THE
PRACTITIONER

VOL. 86 NO. 5S[i]

NOVEMBER 2010

A SUPPLEMENT TO

cutis®

The ORCA (Oracea® for Rosacea: A Community-Based Assessment) Trial:

A Large-Scale, Phase 4 Trial in Papulopustular Rosacea



Supported by an educational grant from Galderma Laboratories, L.P.

A SUPPLEMENT TO
cutis[®]

CUTANEOUS MEDICINE
FOR THE PRACTITIONER
VOL. 86 NO. 5S[j]

NOVEMBER 2010

Cutis[®] Cutaneous Medicine for the Practitioner, November 2010,
Volume 86 Number 5S[j]

TRADEMARK: *Cutis*[®] is a registered trademark of Quadrant HealthCom Inc.

PUBLISHER: *Cutis*[®] (ISSN-0011-4162) (GST #128741063) is published monthly by Quadrant HealthCom Inc., with business offices at 7 Century Dr, Suite 302, Parsippany, NJ 07054-4609; telephone 973-206-3434; fax 973-206-9378.

COPYRIGHT: Copyright Quadrant HealthCom Inc. 2010. All rights reserved. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, mechanical, computer, photocopying, electronic recording, or otherwise, without the prior written permission of Quadrant HealthCom Inc. The copyright law of the United States (Title 17, U.S.C., as amended) governs the making of photocopies or other reproductions of copyrighted material.

PHOTOCOPY PERMISSIONS POLICY: This publication has been registered with Copyright Clearance Center, Inc (CCC), 222 Rosewood Dr, Danvers, MA 01923, telephone 508-750-8400. Permission is granted for the photocopying of specified articles provided that the base fee is paid directly to CCC (ref. *Cutis*[®], ISSN-0011-4162, specifying volume, date, and title of article). This consent does not extend to other kinds of copying, such as for general distribution, resale, advertising, and promotional purposes, or for creating new collective works.

OPINIONS: Opinions expressed in articles are those of the authors and do not necessarily reflect those of Quadrant HealthCom Inc. or the Editorial Board. Quadrant HealthCom Inc. assumes no liability for any material published herein.

REPRINTS: Contact Sharon Finch at sharon.finch@qhc.com.

PAID SUBSCRIPTIONS: All prices listed are for one-year subscription. Individual, USA, \$151; Individual, Canada/Mexico, \$232; Individual, all other nations, \$276 surface, \$355 air; Student/Resident, USA, \$45; Institution, USA, \$223; Institution, Canada/Mexico \$289; Institution, all other nations, \$350. For single issues: USA, \$26; Canada/Mexico, \$31; all other nations, \$36.

BACK ISSUES: For back issues (subject to availability), call 800-480-4851 to charge your credit card. Written requests will be accepted and must be accompanied by a check or money order. Send payment and request to *Cutis*[®], Subscription Service, 151 Fairchild Ave, Suite 2, Plainview, NY 11803-1709. Claims for free replacement of missing copies of *Cutis*[®] must be made within 3 months of the date of the missing issue requested. Otherwise, the cost of replacement is \$31 per copy, USA; \$36, Canada/Mexico; \$41, all other nations.

For subscriptions, please call 800-480-4851, Subscription Service, 151 Fairchild Ave, Suite 2, Plainview, NY 11803-1709; or e-mail quadrantcut@emscirc.com.

POSTMASTER: Send address changes to:
Cutis[®], Subscription Service, 151 Fairchild Ave,
Suite 2, Plainview, NY 11803-1709. Periodicals
postage paid at Parsippany, New Jersey, and at
additional mailing offices.



EDITOR Melissa Steiger
973-206-8096

**ASSISTANT
MANAGING EDITOR** Brandi Ragas
973-206-2344

EDITORIAL ASSISTANT Alicia Wendt
973-206-8098

PROOFREADER Michele V. Murray

CREATIVE DIRECTOR Mary Ellen Niatas
973-206-8973

PRODUCTION MANAGER Jaime Serra
973-206-8011

**CORPORATE
CIRCULATION DIRECTOR** Donna Sickles

SUBSCRIBER INQUIRY LINE 800-480-4851

**DIRECTOR,
MARKETING RESEARCH** Lori Raskin
973-206-8013

**SENIOR VICE PRESIDENT/
GROUP PUBLISHER** Sharon Finch
973-206-8952

PUBLISHING CONSULTANT Claudia Shayne-
Ferguson
914-522-3188

ADMINISTRATIVE ASSISTANT Nikki Vargas

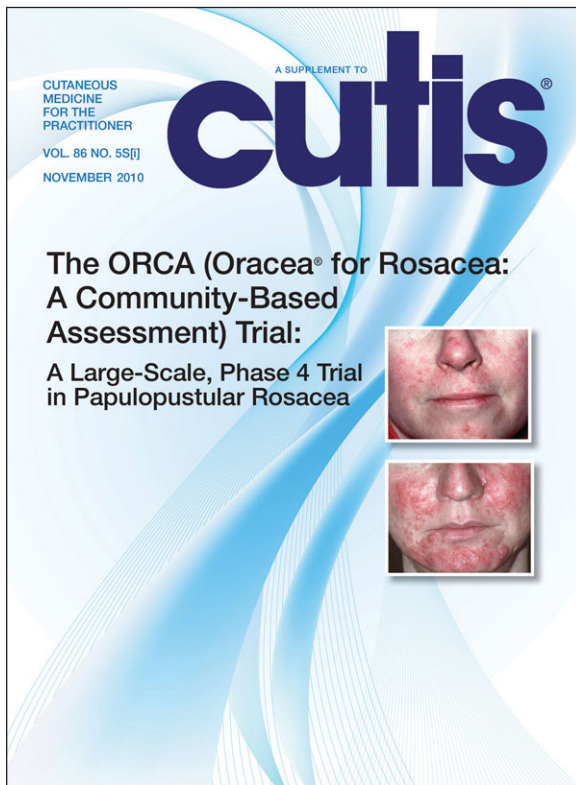
**ADVERTISING/BILLING
DIRECTOR** Tracy O'Keefe
973-206-8022
Fax 973-206-9378

REPRINT INQUIRIES Sharon Finch
sharon.finch@qhc.com



PRESIDENT AND CEO
Stephen Stoneburn

**american
business
media**
The Association of Business Information Companies



The ORCA (Oracea® for Rosacea: A Community-Based Assessment) Trial: A Large-Scale, Phase 4 Trial in Papulopustular Rosacea

Supported by an educational grant from Galderma Laboratories, L.P.

Photographs on cover courtesy of the National Rosacea Society.

4 Introduction

James Q. Del Rosso, DO

7 An Open-Label, Community-Based, 12-Week Assessment of the Effectiveness and Safety of Monotherapy With Doxycycline 40 mg (30-mg Immediate-Release and 10-mg Delayed-Release Beads)

Guy F. Webster, MD, PhD

Rosacea is a common inflammatory disorder of the skin of middle-aged and older adults. A unique 40-mg formulation of doxycycline (30-mg immediate-release and 10-mg delayed-release beads) developed for its anti-inflammatory properties is the only US Food and Drug Administration–approved oral medication for the disorder. This report describes the results of the Oracea® for Rosacea: A Community-Based Assessment (ORCA) trial, a phase 4 trial of the 40-mg formulation as monotherapy in adults with mild to severe papulopustular rosacea. A total of 1197 participants were enrolled in the monotherapy arm of the 12-week open-label study at 271 community-based investigational sites. The primary outcome measure was a change in the 5-point investigator global assessment (IGA) score from baseline to end point (week 12). Secondary outcome measures included change in the 5-point clinician erythema assessment (CEA) score from baseline to end point, IGA success, and adverse events (AEs). The monotherapy per-protocol (PP) population was selected a priori as the primary analysis population and safety assessments were performed on all participants who received at least 1 dose of the study drug. In the PP population of 826 monotherapy participants who completed the trial, approximately 75% of participants with mild to severe rosacea at baseline were clear or near clear by week 12,

according to IGA scores. Furthermore, approximately 75% of participants had CEA scores reflecting none or mild erythema after 12 weeks. In the safety population of 1196 participants, treatment-related AEs were reported in 6.7% of participants that were mainly mild or moderate in severity. Adverse events that occurred in more than 1% of the safety population included diarrhea (1.2%), nausea (1.3%), and headache (1.0%). The incidence of fungal and yeast infections was 0.4%. The results of the ORCA trial support the effectiveness and safety of the 40-mg formulation of doxycycline in patients with papulopustular rosacea.

16 Effectiveness and Safety of Doxycycline 40 mg (30-mg Immediate-Release and 10-mg Delayed-Release Beads) Once Daily as Add-on Therapy to Existing Topical Regimens for the Treatment of Papulopustular Rosacea: Results From a Community-Based Trial

James Q. Del Rosso, DO

Rosacea is a prevalent inflammatory skin disorder that affects approximately 16 million individuals in the United States. Although its exact etiology is unknown, basic science, histologic evidence, and clinical evidence suggest that it is inflammatory in nature. In this 12-week, open-label, multicenter, community-based, phase 4 trial, we evaluated the anti-inflammatory effects of once daily subantimicrobial-dose doxycycline 40 mg (30-mg immediate-release and 10-mg delayed-release beads) in participants with papulopustular rosacea (PPR) who were receiving topical therapy (metronidazole, azelaic acid, and/or sodium sulfacetamide-sulfur) at the time of the study entry but whose rosacea symptoms were still present. The primary outcome measure was the change in the investigator global assessment (IGA) score from baseline to end of study (week 12). Secondary outcome measures were changes from baseline to end of study in the clinician erythema assessment (CEA) score, treatment responders (IGA score of clear, near clear), and safety. After week 12, 75.7% of participants in the per-protocol (PP) population had IGA scores of clear or near clear. In addition, there were significant differences in the distribution of baseline and week 12 IGA scores in the PP group ($P=.0012$). At week 12, most participants (63.6%) had mild CEA scores; the distribution was significantly different from baseline ($P=.0407$). Only 7% of participants had treatment-related adverse events (AEs), mostly mild or moderate in severity. Thus the 40-mg formulation of doxycycline proved to be effective and well-tolerated in a real-world setting in participants with rosacea who were receiving topical therapy but still experiencing symptoms.

26 A Community-Based Study of the Effectiveness of Doxycycline 40 mg (30-mg Immediate-Release and 10-mg Delayed-Release Beads) on Quality of Life and Satisfaction With Treatment in Participants With Rosacea

Hilary E. Baldwin, MD

Changes to the skin of the face in patients with rosacea have the potential to substantially impair multiple domains of quality of life (QOL); however, the number of publications providing evidence for this topic is limited. This 12-week, open-label, community-based, phase 4 trial of 1421 participants is the largest study of the disease to date. It explores the effects of mild to severe rosacea and its treatment on QOL. Participants were treated with doxycycline 40 mg (30-mg immediate-release and 10-mg delayed-release beads) as monotherapy or add-on treatment to existing topical therapy. This article examines QOL issues in the primary analysis population consisting of 966 participants who completed the trial without a major protocol violation. Quality of life was assessed at baseline and study end (week 12) with the RosaQoL™, a validated 21-question instrument. Participant and investigator satisfaction with treatment also were evaluated. In the monotherapy group, the mean RosaQoL score was 3.3 at baseline and 2.8 at end of study. In the add-on therapy group, the mean RosaQoL score was 3.2 at baseline and 2.8 at end of study. The improvement in QOL was both clinically and statistically significant ($P<.0001$) and was similar in both monotherapy and add-on therapy groups. Most participants expressed satisfaction with treatment and approximately 90% of the community-based investigators reported that they were likely or very likely to continue prescribing this formulation. The study demonstrates that the impaired QOL in patients with rosacea can be substantially improved during a 3-month period by once-daily treatment with the anti-inflammatory activity of subantimicrobial-dose doxycycline.

Introduction

James Q. Del Rosso, DO

Dermatologists in clinical practice regularly encounter patients presenting with rosacea, a chronic, recurrent, inflammatory dermatosis that primarily involves the central face in adults.^{1,3} The most common subtypes of rosacea are erythematotelangiectatic and papulopustular rosacea (PPR). Although the prevalence of rosacea in the United States is not precisely known, it has been estimated to affect as many as 16 million individuals.⁴ In addition to the visible signs and symptoms of rosacea, psychosocial implications of the condition should not be overlooked. Surveys have noted that lowered self-esteem and avoidance of interpersonal interaction affects more than 76% and 41% of patients, respectively, who experience rosacea.⁴ Interestingly, when shown photographs of women with and without rosacea, survey respondents reported that affected women often appeared to be insecure, unhappy, and more stressed than those without the disease.⁵ As both erythematotelangiectatic and PPR affect the face; tend to be diffuse; flare without warning; tend to be exacerbated by a variety of commonly encountered trigger factors; and are associated with erythema, which is difficult to mask with makeup, the physical and psychosocial frustrations experienced by many affected patients are understood.²

Several factors have been associated with the pathogenesis of different rosacea subtypes; however, many unanswered questions remain about the etiology of all clinical forms of rosacea. Potential pathogenic factors associated with PPR include augmented innate immune response, epidermal barrier dysfunction, environmental factors such as UV light exposure, cutaneous vascular hyperreactivity, aberrations in neurovascular response, increased cutaneous levels of cathelicidins and their pro-inflammatory peptide by-products, increased activity of serine protease enzyme activity (kallikrein 5), up-regulation of certain matrix metalloproteinase enzymes involved in dermal matrix degradation,

depletion of antioxidant reserve, and suggested association with proliferation of certain microbial organisms such as *Demodex folliculorum*.⁶⁻¹²

Because of the successful treatment of patients with acne vulgaris via topical and systemic antibiotics, the use of antibiotic agents subsequently has expanded over time to also include the treatment of PPR and other rosacea subtypes.^{12,13} The effectiveness of oral antibiotics, primarily tetracycline agents, led to the assumption that treatment of rosacea requires antibiotic activity, as even topical agents used to treat rosacea across the years (eg, erythromycin, metronidazole, azelaic acid, sodium sulfacetamide-sulfur) exhibit antibiotic properties.¹⁴ In fact, there is no definitive evidence that any clinical subtype of rosacea, including PPR, is associated with the need to suppress a bacterium; instead, antibiotics used to treat rosacea are believed to provide therapeutic benefit via inherent anti-inflammatory properties and not antibiotic activity.¹²

The tetracycline agents exhibit a variety of anti-inflammatory properties, with some believed to be operative in the treatment of certain subtypes of rosacea such as PPR and ocular rosacea.¹² Of the available tetracycline derivatives, dose response and pharmacokinetic separation of antibiotic effect and anti-inflammatory properties have been determined with doxycycline based on multiple pharmacokinetic analyses, short-term and long-term microbiologic studies, and assays evaluating specific anti-inflammatory mechanisms.^{6-10,15-20} Once daily doxycycline 40 mg (30-mg immediate-release and 10-mg delayed-release beads) produces steady-state concentrations below the antimicrobial threshold. Treatment with subantimicrobial-dose doxycycline has been shown to be effective in reducing both inflammatory lesions in PPR and perilesional erythema.²¹ The anti-inflammatory activity of doxycycline 40 mg has been demonstrated to down-regulate several potentially operative pathogenic mechanisms in rosacea such as cytokine release, matrix metalloproteinase activity, nitric oxide production, inflammatory cell migration and proliferation, granuloma formation, angiogenesis, and generation of reactive oxygen species.

Concerns regarding antibiotic resistance progressively have increased worldwide because of the rising prevalence of hospital-based and community-acquired pathogens that are now less sensitive to commonly used antibiotics, despite known efficacy

From Valley Hospital Medical Center, Las Vegas, Nevada.

The study described in this report was funded by Galderma Laboratories, LP. Dr. Del Rosso has served as a consultant for, has been a speaker or a member of the speakers bureau for, and has received grants for clinical research from Allergan, Inc; Coria Laboratories, LLC; Galderma Laboratories, LP; Graceway Pharmaceuticals, LLC; Intendis, Inc; Medicis Pharmaceutical Corporation; Onset Therapeutics; Ortho Dermatologics, a division of Ortho-McNeil-Janssen Pharmaceuticals, Inc; PharmaDerm; Promius Pharma; Ranbaxy Laboratories Ltd; Stiefel, a GSK company; Triax Pharmaceuticals, LLC; Unilever; and Warner Chilcott.

in the past.^{22,23} Importantly, dedicated efforts supporting more rational and scientifically directed use of antibiotics have led to a reduction in antibiotic resistance across time in studied populations of specific geographic locations.²⁴ In an effort to decrease the development of antibiotic-resistant bacterial strains and preserve antibiotic options, clinicians have been encouraged to practice antibiotic stewardship as best as possible.^{25,26} With regard to dermatology practice, there may be scientific justification for antibiotic therapy for acne vulgaris, as proliferation of *Propionibacterium acnes* is accepted as an integral component of acne pathogenesis, and suppression of *P. acnes* has been correlated with therapeutic benefit.^{22,27} However, as the presence of a pathogenic bacterium has not been definitively identified in any subtype of rosacea, it is rational to consider that antibiotic activity is not needed to achieve therapeutic benefit and that use of an oral agent in an antibiotic dosage range for rosacea is best avoided whenever possible to reduce the emergence of antibiotic-resistant bacterial strains, which is especially important with rosacea because of the chronicity of this disorder, warranting prolonged duration of therapy.

Oracea[®] is a 40-mg oral formulation of anti-inflammatory-dose doxycycline administered once daily and is the only oral product approved by the US Food and Drug Administration for the treatment of PPR.²⁸ In phase 3, randomized, placebo-controlled, double-blind trials, the unique formulation was demonstrated to be effective and safe for the treatment of PPR.²¹ It also has been shown to have efficacy comparable with doxycycline 100 mg once daily regarding onset and magnitude of therapeutic improvement over 12 weeks. However, the use of doxycycline 40 mg once daily produced markedly fewer adverse reactions compared with doxycycline 100 mg, especially gastrointestinal tract side effects.¹⁵ Additionally, unlike doxycycline 100 mg once daily, which is a functional antibiotic dose, the plasma concentrations produced by anti-inflammatory-dose doxycycline were not associated with induction of antibiotic resistance during study duration up to 9 months.¹⁷ Thus the clinician wanting to use an oral agent for PPR can prescribe anti-inflammatory-dose doxycycline with the confidence that the therapeutic benefits of treatment can be achieved while simultaneously decreasing the potential for the emergence of antibiotic resistance to the drug.

The Oracea for Rosacea: A Community-Based Assessment (ORCA) trial described in this supplement was designed to extend the database on the effectiveness and safety of anti-inflammatory-dose doxycycline by incorporating results from a community-based 12-week clinical study that is more reflective of real-world experience. As such, it provides dermatologists with a reasonable expectation of the outcomes that they can achieve in their daily practice when treating patients with PPR. The ORCA trial included a total of 1421 participants with a range of clinical severity noted at baseline that consisted of mild, moderate, and severe PPR; of these enrolled participants, 966 completed the study without a major protocol deviation and were assessed in the per-protocol analysis. In this supplement, Webster²⁹ describes the efficacy and safety of doxycycline 40 mg once daily used as monotherapy for PPR. As the study also allowed for continuation of conventional topical agents used for rosacea in participants receiving established topical treatment at the time of enrollment, Del Rosso³⁰ reports on results from the ORCA trial in participants who received anti-inflammatory-dose doxycycline once daily as add-on treatment to existing topical therapy with metronidazole, azelaic acid, and sodium sulfacetamide 10%-sulfur 5%. Lastly, the ORCA trial provided a unique opportunity to explore the effects of PPR and its oral and topical treatment on quality of life by capturing the thoughts and experiences from the large number of enrolled participants. Baldwin³¹ describes the impact of the disease and its treatment on quality of life as assessed by the validated RosaQoL[™] instrument and also provides insight on participant and investigator satisfaction with treatment.

The ORCA trial was a large project involving the dedication of several investigators and the enrollment of many participants with PPR. The authors are hopeful that the information in this supplement will assist physicians in managing patients with PPR in their daily practice.

REFERENCES

1. Berg M, Liden S. An epidemiological study of rosacea. *Acta Derm Venereol.* 1989;69:419-423.
2. Crawford GH, Pelle MT, James WD. Rosacea: I. etiology, pathogenesis, and subtype classification. *J Am Acad Dermatol.* 2004;51:327-341.
3. Powell FC. Clinical practice. rosacea. *N Engl J Med.* 2005;352:793-803.

4. Rosacea riddle now threatens more than 16 million Americans [news release]. Chicago, IL: National Rosacea Society; April 1, 2010. <http://www.rosacea.org/press/archive/20100401.php>. Accessed April 27, 2010.
5. New survey reveals first impressions may not always be rosy for people with the widespread skin condition rosacea [new release]. Barrington, IL: National Rosacea Society; <http://www.prnewswire/news-releases/new-survey-reveals-first-impressions-may-not-always-be-rosy-for-people-with-the-widespread-skin-condition-roseacea-90829299.html>. Accessed October 13, 2010.
6. Akamatsu H, Asada M, Komura J, et al. Effect of doxycycline on the generation of reactive oxygen species: a possible mechanism of action of acne therapy with doxycycline. *Acta Derm Venereol.* 1992;72:178-179.
7. Cazalis J, Bodet C, Gagnon G, et al. Doxycycline reduces lipopolysaccharide-induced inflammatory mediator secretion in macrophage and ex vivo human whole blood models. *J Periodontol.* 2008;79:1762-1768.
8. Dan L, Shi-long Y, Miao-li L, et al. Inhibitory effect of oral doxycycline on neovascularization in a rat corneal alkali burn model of angiogenesis. *Curr Eye Res.* 2008;33:653-660.
9. Hoyt JC, Ballering J, Numanami H, et al. Doxycycline modulates nitric oxide production in murine lung epithelial cells. *J Immunol.* 2006;176:567-572.
10. Pruzanski W, Greenwald RA, Street IP, et al. Inhibition of enzymatic activity of phospholipases A₂ by minocycline and doxycycline. *Biochem Pharmacol.* 1992;44:1165-1170.
11. Ueyama Y, Misaki M, Ishihara Y, et al. Effects of antibiotics on human polymorphonuclear leukocyte chemotaxis in vitro. *Br J Oral Maxillofac Surg.* 1994;32:96-99.
12. Webster G, Del Rosso JQ. Anti-inflammatory activity of tetracyclines. *Dermatol Clin.* 2007;25:133-135.
13. Sneddon IB. A clinical trial of tetracycline in rosacea. *Br J Dermatol.* 1966;78:649-652.
14. Pelle MT, Crawford GH, James WD. Rosacea: II. therapy. *J Am Acad Dermatol.* 2004;51:499-512.
15. Del Rosso JQ, Schlessinger J, Werschler P. Comparison of anti-inflammatory dose doxycycline versus doxycycline 100 mg in the treatment of rosacea. *J Drugs Dermatol.* 2008;7:573-576.
16. Liu Y, Ramamurthy N, Marecek J, et al. The lipophilicity, pharmacokinetics, and cellular uptake of different chemically-modified tetracyclines (CMTs). *Curr Med Chem.* 2001;8:243-252.
17. Preshaw PM, Novak MJ, Mellonig J, et al. Modified-release subantimicrobial dose doxycycline enhances scaling and root planing in subjects with periodontal disease. *J Periodontol.* 2008;79:440-452.
18. Raza M, Ballering JG, Hayden JM, et al. Doxycycline decreases monocyte chemoattractant protein-1 in human lung epithelial cells. *Exp Lung Res.* 2006;32:15-26.
19. Ryan ME, Usman A, Ramamurthy NS, et al. Excessive matrix metalloproteinase activity in diabetes: inhibition by tetracycline analogues with zinc reactivity. *Curr Med Chem.* 2001;8:305-316.
20. TeKoppele JM, Beekman B, Verzijl N, et al. Doxycycline inhibits collagen synthesis by differentiated articular chondrocytes. *Adv Dent Res.* 1998;12:63-67.
21. 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.
22. Del Rosso JQ, Leyden JJ. Status report on antibiotic resistance: implications for the dermatologist. *Dermatol Clin.* 2007;25:127-132.
23. Steinberg I. Clinical choices of antibiotics: judging judicious use. *Am J Manag Care.* 2000;6(suppl 23):S1178-S1188.
24. Del Rosso JQ. Update from the Scientific Panel on Antibiotic Use in Dermatology: clinical considerations for the dermatologist. *Cutis.* 2008;82(suppl 2):3-4.
25. MacDougall C, Polk RE. Antimicrobial stewardship programs in health care systems. *Clin Microbiol Rev.* 2005;18:638-656.
26. Shlaes DM. Role of Antimicrobial Stewardship in Prevention and Control of Antibiotic Resistance. *Curr Infect Dis Rep.* 1999;1:334-337.
27. Leyden JJ, Del Rosso JQ, Webster GF. Clinical considerations in the treatment of acne vulgaris and other inflammatory skin disorders: focus on antibiotic resistance. *Cutis.* 2007;79(suppl 6):9-25.
28. Oracea [package insert]. Fort Worth, TX: Galderma Laboratories, LP; 2008. <http://oracea.com/Includes/PDF/PrescribingInformation.pdf>. Accessed April 27, 2010.
29. Webster GF. An open-label, community-based, 12-week assessment of the effectiveness and safety of monotherapy with doxycycline 40 mg (30-mg immediate-release and 10-mg delayed-release beads). *Cutis.* 2010;86(suppl 5[i]):7-15.
30. Del Rosso JQ. Effectiveness and safety of doxycycline 40 mg (30-mg immediate-release and 10-mg delayed-release beads) once daily as add-on therapy to existing topical regimens for the treatment of papulopustular rosacea: results from a community-based trial. *Cutis.* 2010;86(suppl 5[i]):16-25.
31. Baldwin HE. A community-based study of the effectiveness of doxycycline 40 mg (30-mg immediate-release and 10-mg delayed-release beads) on quality of life and satisfaction with treatment in participants with rosacea. *Cutis.* 2010;86(suppl 5[i]):26-36.

An Open-Label, Community-Based, 12-Week Assessment of the Effectiveness and Safety of Monotherapy With Doxycycline 40 mg (30-mg Immediate-Release and 10-mg Delayed-Release Beads)

Guy F. Webster, MD, PhD

Rosacea is a common inflammatory disorder of the skin of middle-aged and older adults. A unique 40-mg formulation of doxycycline (30-mg immediate-release and 10-mg delayed-release beads) developed for its anti-inflammatory properties is the only US Food and Drug Administration–approved oral medication for the disorder. This report describes the results of the Oracea® for Rosacea: A Community-Based Assessment (ORCA) trial, a phase 4 trial of the 40-mg formulation as monotherapy in adults with mild to severe papulopustular rosacea. A total of 1197 participants were enrolled in the monotherapy arm of the 12-week open-label study at 271 community-based investigational sites. The primary outcome measure was a change in the 5-point investigator global assessment (IGA) score from baseline to end point (week 12). Secondary outcome measures included change in the 5-point clinician erythema assessment (CEA) score from baseline to end point, IGA success, and adverse events (AEs). The monotherapy per-protocol (PP) population was selected a priori as the primary analysis population and safety assessments were performed on all participants who received at least 1 dose of the study drug. In the PP population of 826 monotherapy participants who completed the trial, approximately 75% of participants with mild to severe rosacea at baseline

were clear or near clear by week 12, according to IGA scores. Furthermore, approximately 75% of participants had CEA scores reflecting none or mild erythema after 12 weeks. In the safety population of 1196 participants, treatment-related AEs were reported in 6.7% of participants that were mainly mild or moderate in severity. Adverse events that occurred in more than 1% of the safety population included diarrhea (1.2%), nausea (1.3%), and headache (1.0%). The incidence of fungal and yeast infections was 0.4%. The results of the ORCA trial support the effectiveness and safety of the 40-mg formulation of doxycycline in patients with papulopustular rosacea.

Cutis. 2010;86(suppl 5[i]):7-15.

Rosacea is a chronic dermatosis of middle-aged and older adults that affects approximately 16 million individuals in the United States, a prevalence that is approximately 4-fold greater than psoriasis.^{1,3} A family history of the disease is reported in approximately 30% of patients.^{4,5} Rosacea is characterized by dilation of blood vessels of the central face and is more common in patients who experience frequent flushing or blushing.⁵ The etiology of rosacea is unknown; however, it is associated with factors that trigger the skin's innate immune response.⁶ Rosacea is histologically characterized by inflammation and vascular changes.⁷ Patients with rosacea have increased expression of epidermal cathelicidins.⁸ These peptides have been demonstrated to have antimicrobial, chemotactic, and angiogenic activities.⁹⁻¹¹ It has been suggested that increased expression of cathelicidin

From Jefferson Medical College, Philadelphia, Pennsylvania.
The study described in this report was funded by Galderma Laboratories, LP. Dr. Webster is an advisory board member, investigator, and speaker for Galderma Laboratories, LP, and a consultant for and has received research grants from Medicus Pharmaceutical Corporation.

and its trypsinlike proteolytic processing enzyme, stratum corneum tryptic enzyme (SCTE), are central elements in the pathogenesis of the disease. This hypothesis is supported by immunohistochemical evidence of increased cathelicidin and SCTE in rosacea-affected skin. In a murine model, subcutaneous injections of SCTE produced cutaneous changes and antimicrobial peptide profiles similar to rosacea in humans.⁸

Doxycycline has been shown to have both antibacterial and anti-inflammatory properties. Pro-inflammatory mediators modulated by tetracyclines include phospholipase A₂, endogenous nitric oxide, IL-6, and serine proteases such as SCTE.^{12,13} In addition, the drug down-regulates matrix metalloproteinase activity, inhibits chemotaxis and granuloma formation, and acts as a scavenger to protect cells against reactive oxygen species.¹⁴⁻²¹ Oracea[®] is a low-dose 40-mg capsule of doxycycline monohydrate containing 30-mg immediate-release and 10-mg delayed-release beads (hereinafter referred to as doxycycline 40 mg).²² Its formulation and pharmacokinetic profile are unique in that plasma concentrations do not reach levels producing antibiotic activity that would encourage the development of resistant organisms.²²

Tetracyclines have been important elements of rosacea therapy for more than 50 years.²³ The US Food and Drug Administration approved the 40-mg formulation of doxycycline in 2006 for the treatment of inflammatory papules and pustules in adults with rosacea.²⁴ The approval was based on the results of 2 randomized, multicenter, 16-week, placebo-controlled, phase 3 trials of participants with rosacea.²² Although the drug has been available for decades and this formulation for almost 5 years, there have been no phase 4 trials of its use as monotherapy in routine clinical practice.²⁵ This report describes the phase 4 Oracea for Rosacea: A Community-Based Assessment (ORCA) trial, which was designed to evaluate the effectiveness and safety of doxycycline 40 mg in a large rosacea population used as either monotherapy or add-on therapy. This report describes the doxycycline 40 mg monotherapy arm of this large community-based population.

METHODS

This 12-week, open-label, multicenter, community-based trial evaluated doxycycline 40 mg in participants with mild to severe rosacea (participants who otherwise would have been treated with antibiotic-dose doxycycline) with the drug administered as monotherapy. This study was conducted in accordance with the Declaration of Helsinki,

Good Clinical Practice guidelines, US Food and Drug Administration Code of Federal Regulations, and local regulatory requirements. The protocol was approved by a central institutional review board or the investigator's local institutional review board. All participants were fully informed about the study and provided written consent prior to participation.

Study Population

Adults 18 years and older were eligible for the study if they had a diagnosis of mild to severe papulopustular rosacea with moderate to severe perilesional erythema. Candidates were excluded if they were pregnant or planning to become pregnant during the study; used a topical or systemic acne therapy (ie, retinoids, isotretinoin) within 4 months of the baseline visit; used topical or systemic antibiotics within 4 weeks of the baseline visit; had laser or intense pulsed light treatments within 3 months of the baseline visit or anticipated this intervention during the time of the trial; used an investigational drug or device within 90 days of baseline; used a topical or systemic corticosteroid within 2 weeks or 4 weeks, respectively, of the baseline visit and during the study; had a known hypersensitivity to tetracyclines; were receiving treatment for concomitant conditions and were not on a stable dose of medication for at least 3 months; or had any condition that the investigator deemed to place the participant at risk or interfere with the study outcome. Other causes for exclusion included kidney disease, achlorhydria, gastrointestinal tract problems including surgery that bypassed the duodenum, active systemic fungal infection, vaginal yeast infection, concurrent diseases, or α -adrenergic blocker therapy in which dosing was not stable or was anticipated to change.

Participants were instructed to take 1 capsule of doxycycline 40 mg daily in the morning on an empty stomach for the duration of the 12-week trial. Participants were cautioned not to take drugs that may interfere with absorption of the study medication (eg, aluminum, calcium, magnesium, iron) up to 1.5 hours before and up to 3 hours after the study medication. Investigators evaluated each participant's rosacea severity and erythema at baseline and at weeks 2, 4, 8, and 12 (study end). Severity of rosacea was assessed on a 5-point investigator global assessment (IGA) scale (Table 1). At the time of the IGA assessment, the investigator also characterized disease-associated erythema on a 5-point clinician erythema assessment (CEA) scale (Table 2). Safety was assessed by the incidence of adverse events (AEs) that were descriptively summarized with incidence rates tabulated using the Medical

Table 1.

Investigator Global Assessment Scale

Score	Definition	Guideline
0 (clear)	No signs or symptoms present	Completely clear of inflammatory lesions
1 (near clear)	1 or 2 papules	1–2 small noninflammatory papules
2 (mild)	Some papules and pustules	3–10 papules and pustules
3 (moderate)	Moderate number of papules and pustules	11–19 papules and pustules
4 (severe)	Numerous papules and pustules, nodules	≥20 papules and pustules, nodules

Dictionary for Regulatory Activities® system organ class and preferred term.

End Points

The primary outcome measure was the change in IGA score from baseline to end point (week 12). Secondary outcome measures included change in CEA score from baseline to end point, success, and safety. For purposes of analyses, success could be defined as the proportion of treatment responders at end point with an IGA score of 0 (clear) or 1 (near clear).

Statistical Analysis

This study was not powered. A large number of investigators participated in the trial to obtain a substantial body of evidence regarding the effectiveness and safety of doxycycline 40 mg when used in normal dermatologic practice. As discontinuation rates in a large open-label trial were anticipated to be relatively high compared with smaller controlled trials, the per-protocol (PP) population was selected a priori for all effectiveness analyses. The PP population consisted of all participants who completed the 12-week trial without major protocol deviations. The safety population was defined as all participants who received at least 1 dose of the study drug. Discrete variables such as certain demographics, AEs, and categorical effectiveness were summarized by frequencies (number and percentage). Continuous categorical effectiveness variables were summarized by mean, median, standard deviation, number, and range (minimum,

Table 2.

Clinician Erythema Assessment Scale

Score	Definition
0 (none)	No redness present
1 (mild)	Slight pinkness
2 (moderate)	Definite redness
3 (significant)	Marked erythema
4 (severe)	Fiery redness

maximum). Baseline IGA scores were compared with subsequent IGA scores using the Cochran-Mantel-Haenszel (CMH) test. Similarly, baseline CEA scores were compared with subsequent CEA scores using the CMH test. The baseline dichotomized IGA scores were compared with subsequent visits using the CMH test. Significance for all hypotheses testing, except normal distribution, was

Table 3.

**Participant Demographics
(Per-Protocol Population)**

	Monotherapy Group (n=826)
Age, y	
Mean (SD)	50.3 (13.6)
Median	50.0
Minimum, maximum	18.0, 87.0
Sex, n (%)	
Female	591 (71.5)
Male	235 (28.5)
Ethnicity, n (%)	
Hispanic or Latino	72 (8.7)
Not Hispanic or Latino	754 (91.3)
Race, n (%)	
White	768 (93.0)
Black or African American	6 (0.7)
Asian	11 (1.3)
American Indian/Alaskan native	1 (0.1)
Native Hawaiian/other Pacific Islander	3 (0.4)
Other	37 (4.5)
Fitzpatrick skin type, n (%)	
I	67 (8.1)
II	321 (38.9)
III	275 (33.3)
IV	130 (15.7)
V	30 (3.6)
VI	3 (0.4)

Abbreviation: SD, standard deviation.

at $\alpha=.05$. For normal distribution testing, significance was $\alpha=.01$.

RESULTS

Participant Disposition

A total of 1421 participants from 271 investigational sites were enrolled in the study with 1197 participants in the monotherapy arm. The monotherapy safety population was composed of 1196 participants because a single enrollee withdrew without receiving a dose of the study drug. Of the 1197 enrolled participants, 826 (69.0%) completed the trial without a major protocol deviation and were included in the PP analyses (Table 3). The mean age of participants in this population was 50.3 years; most participants were women (71.5%). More than 90% of participants were white and were not of Hispanic or Latino ethnicity. Most participants had skin that was classified as normal or combination type. In this group, the mean duration of disease was 5.0 years.

Effectiveness Assessments

Investigator Global Assessment—Most PP participants (74.6%) treated with monotherapy had clear (35.5%) or near clear (39.1%) IGA scores at week 12 (Figure 1). There was a significant difference between the distribution of baseline IGA and week 12 IGA scores in the group ($P<.0001$).

Clinician Erythema Assessment—At week 12, 74.5% of PP participants treated with monotherapy had CEA scores of none (17.7%) or mild (56.8%) (Figure 2). There was a significant difference between the distribution of baseline CEA and week 12 CEA scores in the group ($P<.0001$).

Proportion of Treatment Responders—When success was defined as an IGA score of clear, 35.5% of the monotherapy PP participants were successful at week 12. When success was defined as an IGA score of clear or near clear, 74.6% of the PP population was successful at week 12 (Figure 3).

Safety Assessments

Safety assessments were performed on 1196 participants who received at least 1 dose of the study drug. In the monotherapy safety population, there were reports of 221 AEs in 143 participants (12.0%)(Table 4). The AEs were mainly mild or moderate in severity. Of all AEs in the monotherapy safety population, 50 participants had AEs involved with the gastrointestinal tract; of these, 3.6% were considered to be possibly ($n=23$), probably ($n=10$), or definitely ($n=10$) related to the study drug. There was 1 report of vulvovaginal candidiasis (0.1%) and 1 report of oral candidiasis (0.1%); 5 reports coded as fungal infection (and further classified as yeast infections)(0.4%);

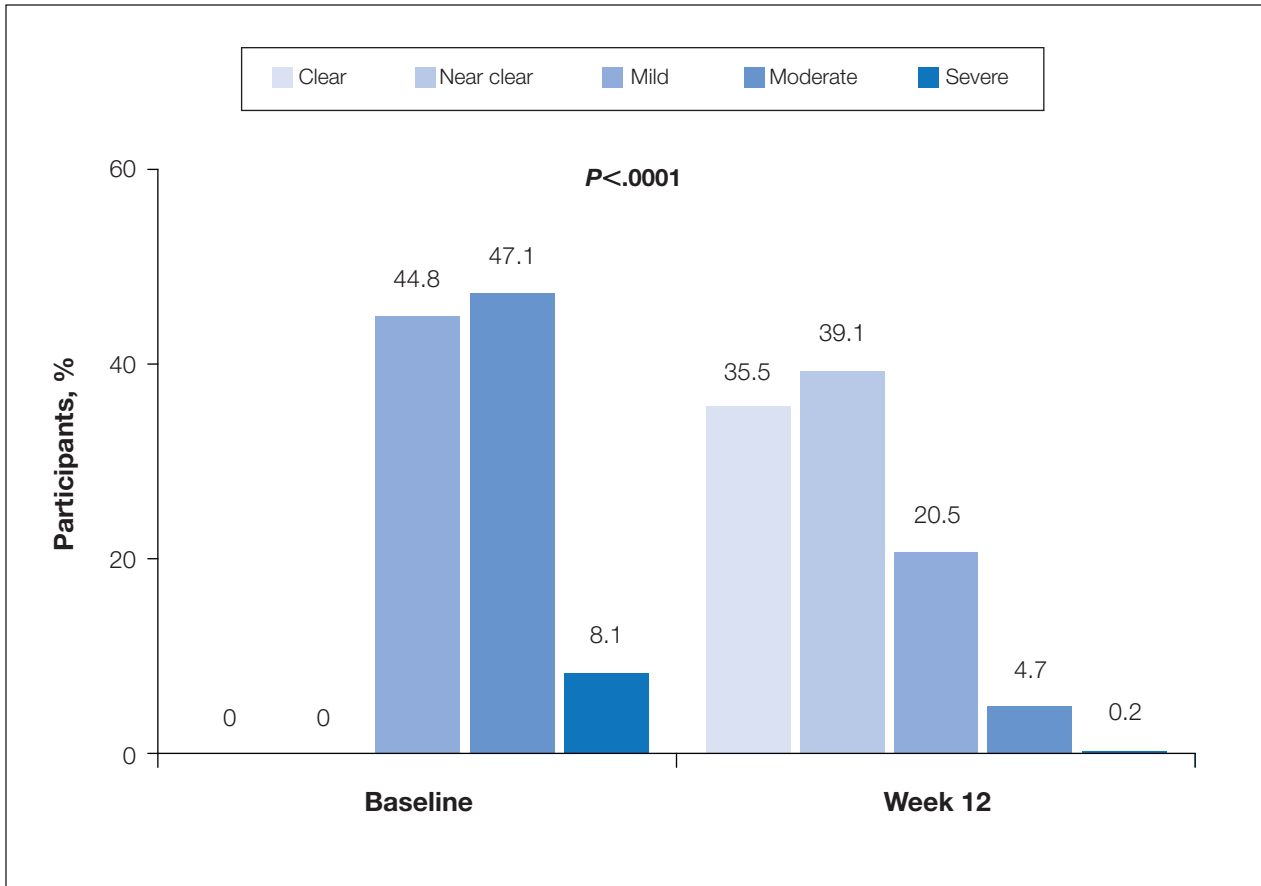


Figure 1. Distribution of investigator global assessment (IGA) scores at baseline and week 12 in the monotherapy per-protocol population (n=826). P value was calculated (Cochran-Mantel-Haenszel test) comparing the distribution of baseline IGA scores with the distribution of week 12 IGA scores; there was a significant difference ($P<.0001$).

and 1 report of a photosensitivity reaction (0.1%) in the safety population. Eighty participants (6.7%) discontinued the study treatment because of an AE. Five serious AEs (superficial venous thrombosis, hospitalization for possible cardiac event, cerebrovascular accident, a new diagnosis of breast cancer on routine screening, angina) were reported and none were related to study treatment.

COMMENT

The ORCA trial is the largest rosacea trial conducted to date. It demonstrates that the 40-mg formulation of doxycycline was effective as monotherapy in participants with mild to severe rosacea. Investigators assessed the severity of disease in a manner that fits well in clinical practice by classifying it by overall severity at each visit. During the course of the trial, IGA scores improved and the changes were clinically and statistically significant ($P<.0001$). By the end of the trial, approximately 75% of participants had achieved clear or near clear IGA scores. Erythema, a

primary feature of rosacea, also was evaluated in the study. Monitoring of perilesional erythema during the course of the trial demonstrated a reduction of this disease marker across time; CEA scores of moderate to severe at presentation had decreased to none or mild in approximately 75% of participants by the end of the study.

The present trial builds on the existing evidence of the effectiveness and safety of once-daily administration of doxycycline 40 mg in participants with rosacea. The 40-mg once-daily formulation was approved based on two 16-week, randomized, phase 3 clinical trials.²⁶ Participants in both studies (N=537) had moderate to severe rosacea (10–40 papules or pustules, ≤ 2 nodules) and were treated with either the study drug (n=269) or placebo (n=268). Compared with placebo, the populations in both studies had significant reductions in mean lesion counts ($P<.001$). The difference between the efficacy of study drug and placebo on mean lesion counts could be observed as early as

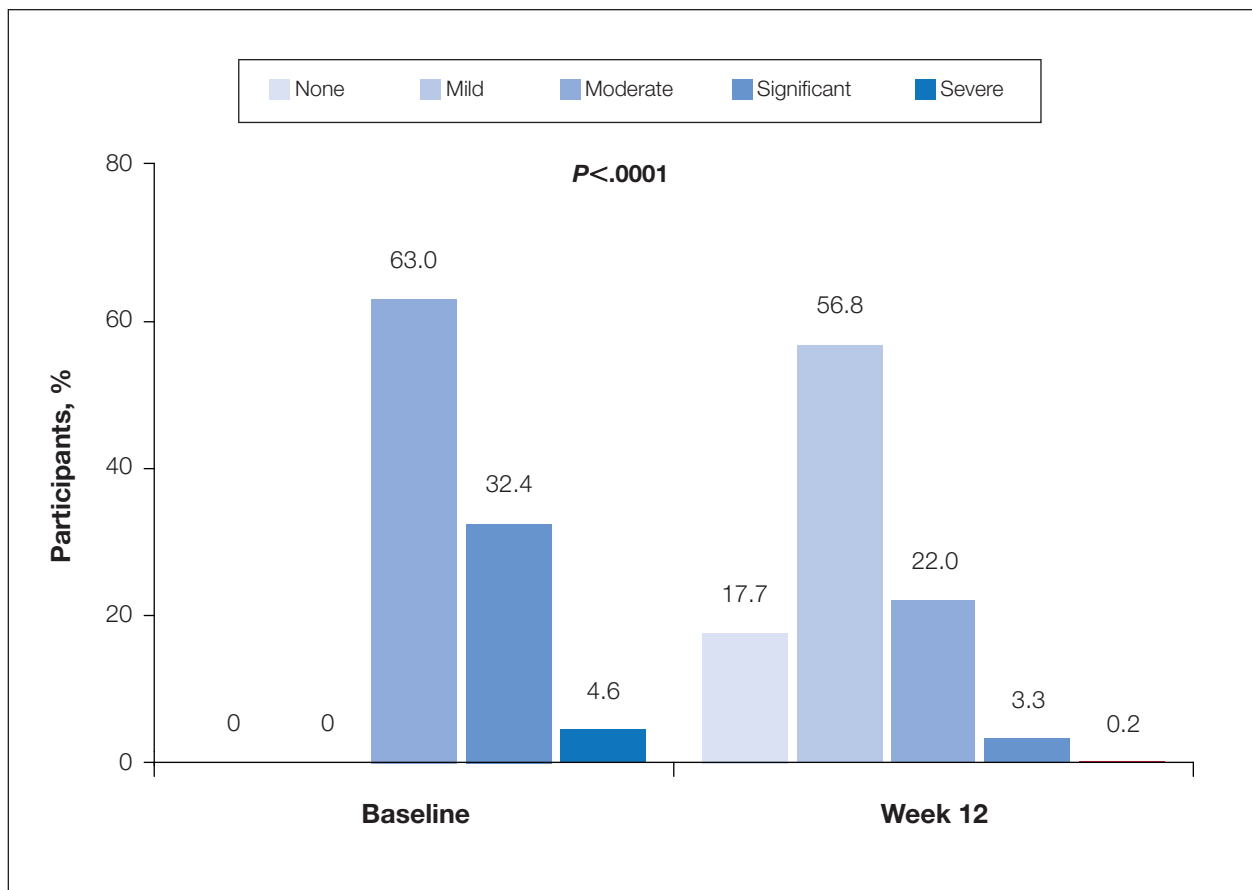


Figure 2. Distribution of clinician erythema assessment (CEA) scores at baseline and week 12 in the monotherapy per-protocol population (n=826). *P* value was calculated (Cochran-Mantel-Haenszel test) comparing the distribution of baseline CEA scores with the distribution of week 12 CEA scores; there was a significant difference ($P<.0001$).

week 3 and continued to diverge for the remainder of the study. The overall benefits of treatment persisted through week 20 in participants who were evaluated 4 weeks after treatment had been discontinued.²⁶ A meta-analysis of the 2 trials demonstrated that the efficacy of doxycycline 40 mg confers clinically significant anti-inflammatory efficacy in rosacea.²⁷ A randomized, double-blind, parallel-group, multicenter study also has compared the efficacy and safety of once daily subantimicrobial-dose doxycycline 40 mg (n=44) with conventional doxycycline 100 mg (n=47) in participants with moderate to severe rosacea.²⁸ Results of the trial demonstrated that the anti-inflammatory effect of treatment with subantimicrobial-dose doxycycline in the 40-mg formulation produced equivalent decreases in inflammatory lesion counts and CEA scores. Furthermore, participants treated with the unique formulation had a 5-fold lower incidence of gastrointestinal tract AEs.²⁸

Key features of the current trial include the large size of the study population and its community-based

setting. Large-scale, randomized, controlled trials have provided evidence to guide clinicians in the treatment of a variety of disorders of the skin and other organ systems; however, there has been a recent recognition that community-based clinicians should help guide and participate in clinical trials.²⁹ These studies may include large numbers of patients seen and treated in community settings, enabling investigators to confirm the effectiveness of various interventions, answer questions about utilization, and help identify uncommon or new AEs. The results of the ORCA trial provide additional support on the benefits and safety of this treatment that were first reported in the phase 3 trials.²⁶ Potential limitations of this trial include choice of the specific outcome measures and decision to use the PP population for the primary analyses. Although use of the PP participants would exclude the most serious protocol violations, it was selected as the primary outcome measure during design of the study because larger numbers of participant dropouts and/or protocol deviations were expected in this

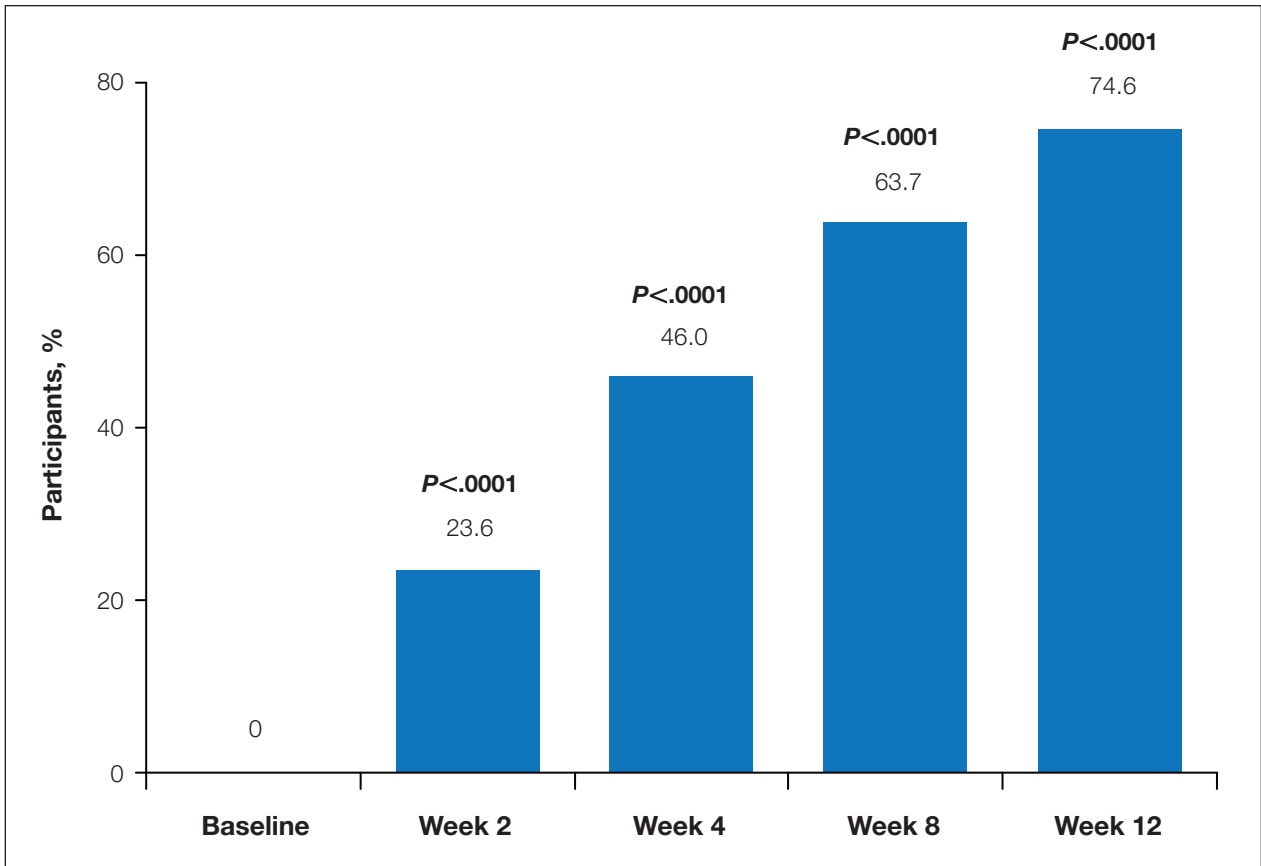


Figure 3. Percentage of participants with clear or near clear investigator global assessment scores at each visit in the monotherapy per-protocol population (n=826). There was a significant difference between baseline and all postbaseline scores ($P < .0001$) (Cochran-Mantel-Haenszel test). This study was not designed to make comparisons between the monotherapy and add-on therapy groups. Treatment response was evaluated from baseline to 12 weeks.

Table 4.

Summary of Adverse Events (AEs)^a

	Monotherapy Group (n=1196)
Participants with any AEs, n (%)	143 (12.0)
Total no. of AEs	221
Gastrointestinal tract disorders, n (%)	50 (4.2)
Nausea, n (%)	16 (1.3)
Diarrhea, n (%)	14 (1.2)
Skin and subcutaneous tissue disorders, n (%)	32 (2.7)
Nervous system disorders, n (%)	20 (1.7)
Headache, n (%)	12 (1.0)

^aAEs were descriptively summarized by system organ class and preferred term; occurred in >1% of the monotherapy group safety population.

type of trial. Overall, the results of this trial make a substantial contribution to the evidence base that has accumulated about the effectiveness and safety of doxycycline 40 mg in participants with mild to severe rosacea who are treated with the drug as monotherapy.

CONCLUSION

The results of this study indicate that 12 weeks of treatment with doxycycline 40 mg is effective and that its subantimicrobial formulation exerts a clinically significant anti-inflammatory effect. In addition, it has been demonstrated that the study drug can be used as monotherapy in the routine treatment of patients with rosacea. Lastly, the results provide additional confirmation of the safety profile of the drug.

Acknowledgments—The ORCA steering committee assisted in the design of the study and participated in its monitoring: James Q. Del Rosso, DO; Hilary E. Baldwin, MD; Guy F. Webster, MD, PhD; John E. Wolf Jr, MD; and James J. Leyden, MD.

The study described in this report was funded by Galderma Laboratories, LP. The authors thank Jodie Macoun, PhD, of Evince Communications for her support in the preparation of this article. Her work was funded by Galderma Laboratories, LP. The authors also would like to acknowledge Luz E. Colon and Kelley Collins-Winters for their significant effort in the conduct of this study, and Norman J. Preston, PhD, for assistance with statistical analyses. Revisions of the manuscript for important intellectual content were performed by each of the listed authors.

REFERENCES

1. Rosacea riddle now threatens more than 16 million Americans [news release]. Chicago, IL: National Rosacea Society; April 1, 2010. <http://www.rosacea.org/press/archive/20100401.php>. Accessed April 27, 2010.
2. Nestle FO, Kaplan DH, Barker J. Psoriasis. *N Engl J Med*. 2009;361:496-509.
3. Bickers DR, Lim HW, Margolis D, et al; American Academy of Dermatology Association; Society for Investigative Dermatology. The burden of skin diseases: 2004 a joint project of the American Academy of Dermatology Association and the Society for Investigative Dermatology. *J Am Acad Dermatol*. 2006;55:490-500.
4. Rebora A. The red face: rosacea. *Clin Dermatol*. 1993;11:225-234.
5. Powell FC. Clinical practice. rosacea. *N Engl J Med*. 2005;352:793-803.
6. Yamasaki K, Gallo RL. The molecular pathology of rosacea. *J Dermatol Sci*. 2009;55:77-81.

7. Jansen T, Plewig G. Rosacea: classification and treatment. *J R Soc Med*. 1997;90:144-150.
8. 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.
9. Nizet V, Ohtake T, Lauth X, et al. Innate antimicrobial peptide protects the skin from invasive bacterial infection. *Nature*. 2001;414:454-457.
10. Zanetti M. The role of cathelicidins in the innate host defenses of mammals. *Curr Issues Mol Biol*. 2005;7:179-196.
11. Zanetti M. Cathelicidins, multifunctional peptides of the innate immunity. *J Leukoc Biol*. 2004;75:39-48.
12. Pruzanski W, Greenwald RA, Street IP, et al. Inhibition of enzymatic activity of phospholipases A₂ by minocycline and doxycycline. *Biochem Pharmacol*. 1992;44:1165-1170.
13. Cazalis J, Bodet C, Gagnon G, et al. Doxycycline reduces lipopolysaccharide-induced inflammatory mediator secretion in macrophage and ex vivo human whole blood models. *J Periodontol*. 2008;79:1762-1768.
14. Ueyama Y, Misaki M, Ishihara Y, et al. Effects of antibiotics on human polymorphonuclear leukocyte chemotaxis in vitro. *Br J Oral Maxillofac Surg*. 1994;32:96-99.
15. Raza M, Ballering JG, Hayden JM, et al. Doxycycline decreases monocyte chemoattractant protein-1 in human lung epithelial cells. *Exp Lung Res*. 2006;32:15-26.
16. Hoyt JC, Ballering J, Numanami H, et al. Doxycycline modulates nitric oxide production in murine lung epithelial cells. *J Immunol*. 2006;176:567-572.
17. Akamatsu H, Asada M, Komura J, et al. Effect of doxycycline on the generation of reactive oxygen species: a possible mechanism of action of acne therapy with doxycycline. *Acta Derm Venereol*. 1992;72:178-179.
18. Dan L, Shi-long Y, Miao-li L, et al. Inhibitory effect of oral doxycycline on neovascularization in a rat corneal alkali burn model of angiogenesis. *Curr Eye Res*. 2008;33:653-660.
19. TeKoppele JM, Beekman B, Verzijl N, et al. Doxycycline inhibits collagen synthesis by differentiated articular chondrocytes. *Adv Dent Res*. 1998;12:63-67.
20. Ryan ME, Usman A, Ramamurthy NS, et al. Excessive matrix metalloproteinase activity in diabetes: inhibition by tetracycline analogues with zinc reactivity. *Curr Med Chem*. 2001;8:305-316.
21. Webster GF, Toso SM, Hegemann L. Inhibition of a model of in vitro granuloma formation by tetracyclines and ciprofloxacin. involvement of protein kinase C. *Arch Dermatol*. 1994;130:748-752.
22. Oracea [package insert]. Fort Worth, TX: Galderma Laboratories, LP; 2008 <http://oracea.com/Includes/PDF/PrescribingInformation.pdf>. Accessed April 27, 2010.
23. Sneddon IB. A clinical trial of tetracycline in rosacea. *Br J Dermatol*. 1966;78:649-652.
24. Galderma completes acquisition of CollaGenex [news release]. Lausanne, Switzerland: Galderma Pharma SA; April 11, 2008. <http://www.galdermausa.com/NewsAndMedia/PressRelease25.aspx>. Accessed April 27, 2010.

25. Del Rosso JQ. Effectiveness and safety of doxycycline 40 mg (30-mg immediate-release and 10-mg delayed-release beads) once daily as add-on therapy to existing topical regimens for the treatment of papulopustular rosacea: results from a community-based trial. *Cutis*. 2010;86(suppl 5[i]):16-25.
26. 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.
27. Theobald K, Bradshaw M, Leyden J. Anti-inflammatory dose doxycycline (40 mg controlled-release) confers maximum anti-inflammatory efficacy in rosacea. *Skinmed*. 2007;6:221-226.
28. Del Rosso JQ, Schlessinger J, Werschler P. Comparison of anti-inflammatory dose doxycycline versus doxycycline 100 mg in the treatment of rosacea. *J Drugs Dermatol*. 2008;7:573-576.
29. Kahn JM. Disseminating clinical trial results in critical care. *Crit Care Med*. 2009;37(suppl 1):S147-S153.

Effectiveness and Safety of Doxycycline 40 mg (30-mg Immediate-Release and 10-mg Delayed-Release Beads) Once Daily as Add-on Therapy to Existing Topical Regimens for the Treatment of Papulopustular Rosacea: Results From a Community-Based Trial

James Q. Del Rosso, DO

Rosacea is a prevalent inflammatory skin disorder that affects approximately 16 million individuals in the United States. Although its exact etiology is unknown, basic science, histologic evidence, and clinical evidence suggest that it is inflammatory in nature. In this 12-week, open-label, multicenter, community-based, phase 4 trial, we evaluated the anti-inflammatory effects of once daily subantimicrobial-dose doxycycline 40 mg (30-mg immediate-release and 10-mg delayed-release beads) in participants with papulopustular rosacea (PPR) who were receiving topical therapy (metronidazole, azelaic acid, and/or sodium sulfacetamide-sulfur) at the time of the study entry but whose rosacea symptoms were still present. The primary outcome measure was the change in the investigator global assessment (IGA) score from baseline to end of study (week 12). Secondary outcome measures were changes from

baseline to end of study in the clinician erythema assessment (CEA) score, treatment responders (IGA score of clear, near clear), and safety. After week 12, 75.7% of participants in the per-protocol (PP) population had IGA scores of clear or near clear. In addition, there were significant differences in the distribution of baseline and week 12 IGA scores in the PP group ($P=.0012$). At week 12, most participants (63.6%) had mild CEA scores; the distribution was significantly different from baseline ($P=.0407$). Only 7% of participants had treatment-related adverse events (AEs), mostly mild or moderate in severity. Thus the 40-mg formulation of doxycycline proved to be effective and well-tolerated in a real-world setting in participants with rosacea who were receiving topical therapy but still experiencing symptoms.

Cutis. 2010;86(suppl 5[i]):16-25.

From Valley Hospital Medical Center, Las Vegas, Nevada.

The study described in this report was funded by Galderma Laboratories, LP. Dr. Del Rosso has served as a consultant for, has been a speaker or a member of the speakers bureau for, and has received grants for clinical research from Allergan, Inc; Coria Laboratories, Ltd; Galderma Laboratories, LP; Graceway Pharmaceuticals, LLC; Intendis, Inc; Medcis Pharmaceutical Corporation; Onset Therapeutics; Ortho Dermatologics, a division of Ortho-McNeil-Janssen Pharmaceuticals, Inc; PharmaDerm; Promius Pharma; Ranbaxy Laboratories Ltd; Stiefel, a GSK company; Triax Pharmaceuticals, LLC; Unilever; and Warner Chilcott.

Rosacea is an inflammatory skin condition that affects approximately 16 million individuals in the United States.¹ There are multiple subtypes of rosacea, the most common being erythematotelangiectatic rosacea and papulopustular rosacea (PPR). Erythematotelangiectatic rosacea is characterized by fixed confluent erythema that is predominantly centropacial involving the cheeks, nose, chin, and/or forehead, and an absence of

inflammatory lesions. Papulopustular rosacea also is primarily associated with centropacial erythema; however, inflammatory lesions, primarily papules and pustules, are present.² Erythematotelangiectatic rosacea and PPR are characterized by periods of exacerbation and remission of signs and symptoms.³ In PPR, the frequency of outbreaks varies with time, ranging from once or twice a year to nearly continuous. Management of the inflammatory lesions and erythema associated with PPR warrants adherence with continued therapy, as PPR is a chronic recurrent disorder.

Treatment options for PPR include various topical therapies such as metronidazole, azelaic acid, and sodium sulfacetamide-sulfur. Subantimicrobial-dose doxycycline is a specific capsule formulation of 40 mg of doxycycline incorporating 30-mg immediate-release and 10-mg delayed-release beads administered once daily; it is the first and only oral medication approved for the treatment of PPR.⁴ (To maintain consistency of reference in this article, this specific formulation of anti-inflammatory-dose doxycycline will be referred to as doxycycline 40 mg.) Doxycycline 40 mg once daily has been shown to exhibit anti-inflammatory properties while not exhibiting any antibiotic effect.^{5,6}

Two placebo-controlled pivotal phase 3 trials evaluated the efficacy and safety of doxycycline 40 mg once daily versus placebo in participants with moderate to severe rosacea.⁶ These participants had 10 to 40 papules and pustules and moderate to severe erythema and telangiectasia. Both studies showed marked reductions in the number of inflammatory lesions compared with placebo. Treatment with doxycycline 40 mg significantly reduced the number of lesions from the first follow-up assessment at 3 weeks throughout the entire 16-week study compared with placebo ($P \leq .005$). Doxycycline 40 mg administered once daily resulted in markedly improved investigator global assessment (IGA) scores with erythema scores also reduced in the active treatment groups.⁶

Unlike clinical studies evaluating monotherapy approaches, clinicians sometimes use a combination of topical and oral therapy for patients with PPR, as an increased or additive benefit has been suggested with combination regimens.^{7,8} In some cases, patients with PPR who are treated with topical therapy alone may return for follow-up exhibiting only partial improvement, which warrants consideration of additional therapy. Hence the clinician may prescribe additional therapy in this scenario rather than switching completely to an alternative therapy. The study results described here are part of a trial to evaluate the effectiveness and safety of

doxycycline 40 mg once daily when used as add-on therapy to existing topical regimens. The Oracea[®] for Rosacea: A Community-Based Assessment (ORCA) trial was designed to evaluate the effectiveness and safety of doxycycline 40 mg in a large rosacea population either as monotherapy or add-on therapy. The results of doxycycline 40-mg monotherapy are reported elsewhere in this supplement.⁹ The objective of including the subpopulation of participants treated with doxycycline 40 mg added to their preexisting topical therapy was to fully assess real-world, community-based experience, as it is not uncommon to encounter patients with PPR in clinical practice who are already using topical therapy. Reported here are the effectiveness and safety results of doxycycline 40 mg once daily when added to a preexisting stable regimen of topical therapy in an open-label, community-based trial.

Methods

Study Population—Adult participants with PPR were eligible for enrollment. Severity of rosacea was evaluated using the IGA and clinician erythema assessment (CEA) scales (Tables 1 and 2). Participants were required to have an IGA score of 2 (mild) to 4 (severe) and a CEA score of 2 (moderate) to 4 (severe) for enrollment. Qualifying participants who already were receiving approved topical rosacea therapy (metronidazole, azelaic acid, and/or sodium sulfacetamide 10%-sulfur 5% preparations) were required to have been receiving a stable regimen for at least 4 weeks, to be using this therapy according to the product labeling, and to have demonstrated no evidence of intolerability to this therapy. Candidates were excluded from analysis if they were pregnant or planning to become pregnant during the study; used a topical or systemic acne therapy within 4 months of the baseline visit; used topical or systemic antibiotics within 4 weeks of the baseline visit; had laser or intense pulsed light treatments within 3 months of the baseline visit or anticipated this intervention during the time of the trial; used an investigational drug or device within 90 days of baseline; had a known hypersensitivity to tetracyclines; were receiving treatment for concomitant conditions and were not on a stable dose of medication for at least 3 months; or had any condition that the investigator deemed to place the participant at risk or interfere with the study outcome.

This study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, US Food and Drug Administration Code of Federal Regulations, and local regulatory requirements. The protocol was approved by a central institutional review board or the investigator's local

Table 1.

Investigator Global Assessment Scale

Score	Definition	Guideline
0 (clear)	No signs or symptoms present	Completely clear of inflammatory lesions
1 (near clear)	1 or 2 papules	1–2 small noninflammatory papules
2 (mild)	Some papules and pustules	3–10 papules and pustules
3 (moderate)	Moderate number of papules and pustules	11–19 papules and pustules
4 (severe)	Numerous papules and pustules, nodules	≥20 papules and pustules, nodules

institutional review board for 378 investigative sites. Of the approved sites, 271 enrolled participants. All participants were fully informed about the study and provided written consent prior to participation.

Study Design—The study was a 12-week, open-label, multicenter, community-based, phase 4 trial. At the time of enrollment, participants who were using a stable topical treatment regimen for their rosacea and were thought to potentially benefit from the addition of doxycycline 40 mg to their current regimen were assigned to the add-on therapy arm of the trial. Topical medications allowed for this arm of the trial included metronidazole preparations (MetroGel® 1%, MetroGel 0.75%, MetroCream® 0.75%, MetroLotion® 0.75%, Noritate® Cream 1%, or other generic equivalents); azelaic acid preparations (Azelex® Cream 20%, Finacea® Gel 15%, or other generic equivalents); and sodium sulfacetamide 10%–sulfur 5% preparations (Rosanil® Cleanser, Sulfacet-R® Lotion, or other generic equivalents). It should be noted that although Azelex Cream 20% is not indicated for the treatment of rosacea, it has been used off label for this purpose and was therefore included in the allowable existing therapies.

Participants were instructed to take 1 capsule of doxycycline 40 mg daily in the morning on an empty stomach for 12 weeks. Effectiveness evaluations were conducted at baseline and at weeks 2, 4, 8, and 12 and/or at early termination when applicable. Safety assessments were conducted at weeks 2, 4, 8, and 12. As they may interfere with the metabolism of the study product, participants were cautioned not to use the following drugs for the study duration: long-term use (≥14 days) of a sulfonamide, erythromycin, cephalosporin, or quinolone; tetracycline antibiotics;

Table 2.

Clinician Erythema Assessment Scale

Score	Definition
0 (none)	No redness present
1 (mild)	Slight pinkness
2 (moderate)	Definite redness
3 (significant)	Marked erythema
4 (severe)	Fiery redness

acne treatments including spironolactone, or oral or topical dapsone; penicillin antibiotics; proton pump inhibitors; and niacin at 500 mg or more daily. Iron, antacids, and vitamins containing aluminum, calcium, or magnesium were only permitted if taken at least 1.5 hours before or up to 3 hours after the study medication.

End Points—The primary end point was the change in IGA score from baseline to end of study (week 12). Secondary end points included change in CEA score from baseline to end of study, the proportion of treatment responders at end of study with an IGA score of 0 (clear), and the proportion of treatment responders at end of study with an IGA score of 0 (clear) or 1 (near clear). The change from

baseline in IGA and CEA scores at weeks 2, 4, and 8 also were recorded.

Safety was evaluated at each study visit by recording adverse events (AEs). Clinical laboratory evaluations were conducted if deemed appropriate to fully assess an AE. Adverse events were categorized as mild, moderate, or severe, and their relationship to the study medication was assessed by the investigator.

Statistical Analysis—This study was not powered. A large number of investigators participated in the trial to gather a larger body of evidence regarding the effectiveness and safety of doxycycline 40 mg when used in normal dermatologic practice. Because of the anticipated high dropout rates in a community-based trial, the per-protocol (PP) population was selected a priori for all effectiveness analyses.

The change in IGA and CEA scores from baseline to week 12 were analyzed using the Cochran-Mantel-Haenszel (CMH) test. Significance for all hypotheses testing, except normal distribution, was at $\alpha=.05$. For normal distribution testing, significance was $\alpha=.01$. The proportion of treatment successes (IGA score of 0 [clear]; IGA score of 0 [clear] or 1 [near clear]) at baseline and week 12 were compared using the CMH test. The change from baseline in IGA and CEA scores at weeks 2, 4, and 8 were analyzed using CMH tests. Adverse events were descriptively summarized with incidence rates tabulated using the Medical Dictionary for Regulatory Activities® system organ class and preferred term.

Results

Participant Disposition—The ORCA trial enrolled a total of 1421 participants. Of these, 224 made up the add-on therapy group and were included in the intention-to-treat and safety populations. The PP population included all participants who completed the 12-week trial without major protocol deviations and was used as the primary analysis population. In the add-on therapy group, 140 of 224 participants (62.5%) were included in the PP population for the effectiveness analyses. Major protocol deviations in the add-on therapy group were missed visits (16.1%), switching topical therapies during the study (12.9%), using prohibited therapies during the study (8.9%), and noncompliance with study drug (8.0%). A total of 37 participants from the intention-to-treat population discontinued the trial early. Discontinuations mainly were due to AEs (3.6%), participant request (6.3%), and lost to follow-up (3.6%) (Table 3). All participants who received at least 1 dose of doxycycline 40 mg were included in the safety analysis.

Table 3 summarizes the subgroups within the add-on therapy population based on the participant's

preexisting topical therapy. Most enrolled participants used metronidazole-based therapy ($n=173$), with azelaic acid and sodium sulfacetamide-sulfur subgroups of 48 and 23 participants, respectively. Ten participants included in the add-on subgroup were receiving different regimens and were grouped as other. This subgroup included participants that used adapalene, benzoyl peroxide, calamine 8%–pramoxine hydrochloride 1% lotion, esomeprazole magnesium, lansoprazole, pimecrolimus, salicylic acid, tretinoin, and triamcinolone acetonide. The use of proton pump inhibitors during the study was prohibited and participants who used them were excluded from the PP population. Participants could be included in more than 1 add-on therapy subgroup. Eleven participants received metronidazole and azelaic acid therapies, 9 participants received metronidazole and sodium sulfacetamide-sulfur, and 4 participants received metronidazole plus other therapies. One participant received metronidazole, azelaic acid, and sodium sulfacetamide-sulfur therapies. Three participants received azelaic acid and sodium sulfacetamide-sulfur therapies. The numbers in each of the add-on therapy subgroups were too small to complete any valid statistical analyses; therefore, all analyses were performed for the entire add-on therapy PP and safety populations.

The mean age of participants was 52.7 years (Table 4). Female participants made up most of this population (66.4%). In addition, most of the participants were white (94.3%) with Fitzpatrick skin type II (43.6%) or III (26.4%), and normal (27.9%) or combination skin (41.4%).

IGA Effectiveness Assessment—For the overall PP add-on therapy group, most participants had mild (57.1%) or moderate (32.1%) IGA scores at baseline, with a small group having severe scores (10.7%). At week 12, most participants had clear (38.6%) or near clear (37.1%) IGA scores (Figure 1). The change in distribution of IGA scores between baseline and week 12 was statistically significant ($P=.0012$).

CEA Effectiveness Assessment—At baseline, CEA scores showed that most participants had moderate (62.1%) or significant (33.6%) erythema (Figure 2). At week 12, most participants had mild CEA scores (63.6%). The change in distribution of CEA scores between baseline and week 12 was statistically significant ($P=.0407$). Additionally, CEA scores were significantly improved from baseline at all intermediate study visits ($P\leq.0252$).

Proportion of Treatment Responders—Treatment success was defined as achieving an IGA score of clear or near clear. Treatment success was achieved in 75.7% of the add-on therapy group ($P<.0001$)

Table 3.

Study Populations and Disposition by Add-on Therapy Treatment Subgroup^a

	Metronidazole	Azelaic Acid	Sodium Sulfacetamide–Sulfur	Other ^b	Overall
Total participants enrolled, n	173	48	23	10	224
ITT population, n (%)	173 (100)	48 (100)	23 (100)	10 (100)	224 (100)
Safety population, n (%)	173 (100)	48 (100)	23 (100)	10 (100)	224 (100)
PP population, n (%)	104 (60.1)	35 (72.9)	13 (56.5)	0 (0)	140 (62.5)
Total participants discontinued, ^c n (%)	28 (16.2)	6 (12.5)	4 (17.4)	3 (30.0)	37 (16.5)
AEs	7 (4.0)	0 (0)	1 (4.3)	1 (10.0)	8 (3.6)
Participant request	11 (6.4)	1 (2.1)	3 (13.0)	1 (10.0)	14 (6.3)
Protocol violation	1 (0.6)	1 (2.1)	0 (0)	1 (10.0)	2 (0.9)
Lost to follow-up	5 (2.9)	3 (6.3)	0 (0)	0 (0)	8 (3.6)
Pregnancy	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Other	4 (2.3)	1 (2.1)	0 (0)	0 (0)	5 (2.2)

Abbreviations: ITT, intention to treat; PP, per protocol; AE, adverse event.

^aSome participants were included in more than 1 add-on therapy subgroup.

^bParticipants who were receiving adapalene, benzoyl peroxide, calamine 8%–pramoxine hydrochloride 1% lotion, esomeprazole magnesium, lansoprazole, pimecrolimus, salicylic acid, tretinoin, and triamcinolone acetonide.

^cDiscontinuation from PP population.

(Figure 3). Of those who achieved treatment success, 54 of 140 participants (38.6%) achieved a score of clear. The proportion of treatment responders was significantly different from baseline at weeks 2, 4, 8, and 12 ($P < .0001$).

Safety Assessments—Fifty-seven AEs were reported in 39 of 224 participants (17.4%)(Table 5). Of these, 16 AEs were considered to be treatment related. No serious AEs were reported in the add-on therapy group. Eight participants (3.6%) permanently discontinued the trial because of an AE. Most AEs

were mild to moderate in severity. The most common AEs were diarrhea (2.7%), nausea (1.8%), and rash (1.3%). Other gastrointestinal tract AEs included abdominal discomfort (3 participants) and constipation (2 participants). Vaginal candidiasis was reported in 1 participant. There were no reports of photosensitivity reactions or other fungal infections.

Comment

This community-based study is an analysis of the effectiveness of treating PPR with once daily

Table 4.

Demographics by Add-on Therapy Treatment Subgroup^a

	Metronidazole	Azelaic Acid	Sodium Sulfacetamide–Sulfur	Overall
Total participants enrolled, n	173	48	23	224
Mean age (SD), y	53.3 (12.7)	50.3 (11.3)	49.5 (9.5)	52.7 (12.3)
Female, n (%) ^b	67 (64.4)	26 (74.3)	9 (69.2)	93 (66.4)
Mean rosacea duration (SD), y	6.5 (6.8)	5.7 (6.3)	9.0 (7.4)	6.5 (6.7)

Abbreviation: SD, standard deviation.

^aSome participants were included in more than 1 add-on therapy subgroup.

^bBased on per-protocol population: metronidazole (n=104), azelaic acid (n=35), sodium sulfacetamide–sulfur (n=13), overall (N=140).

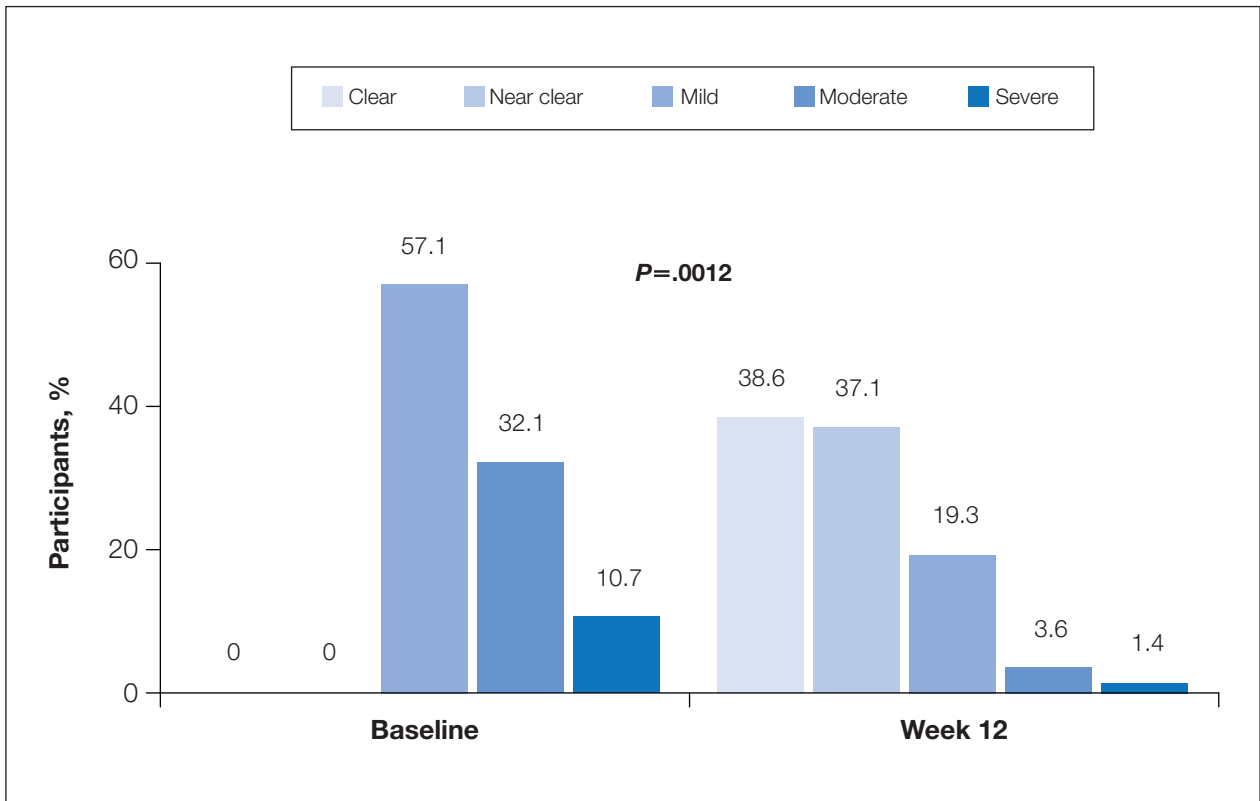


Figure 1. Distribution of investigator global assessment (IGA) scores at baseline and week 12 in the add-on therapy per-protocol population (n=140). *P* value was calculated (Cochran-Mantel-Haenszel test) comparing the distribution of baseline IGA scores with the distribution of week 12 IGA scores. The change in distribution of IGA scores between baseline and week 12 was statistically significant (*P*=.0012).

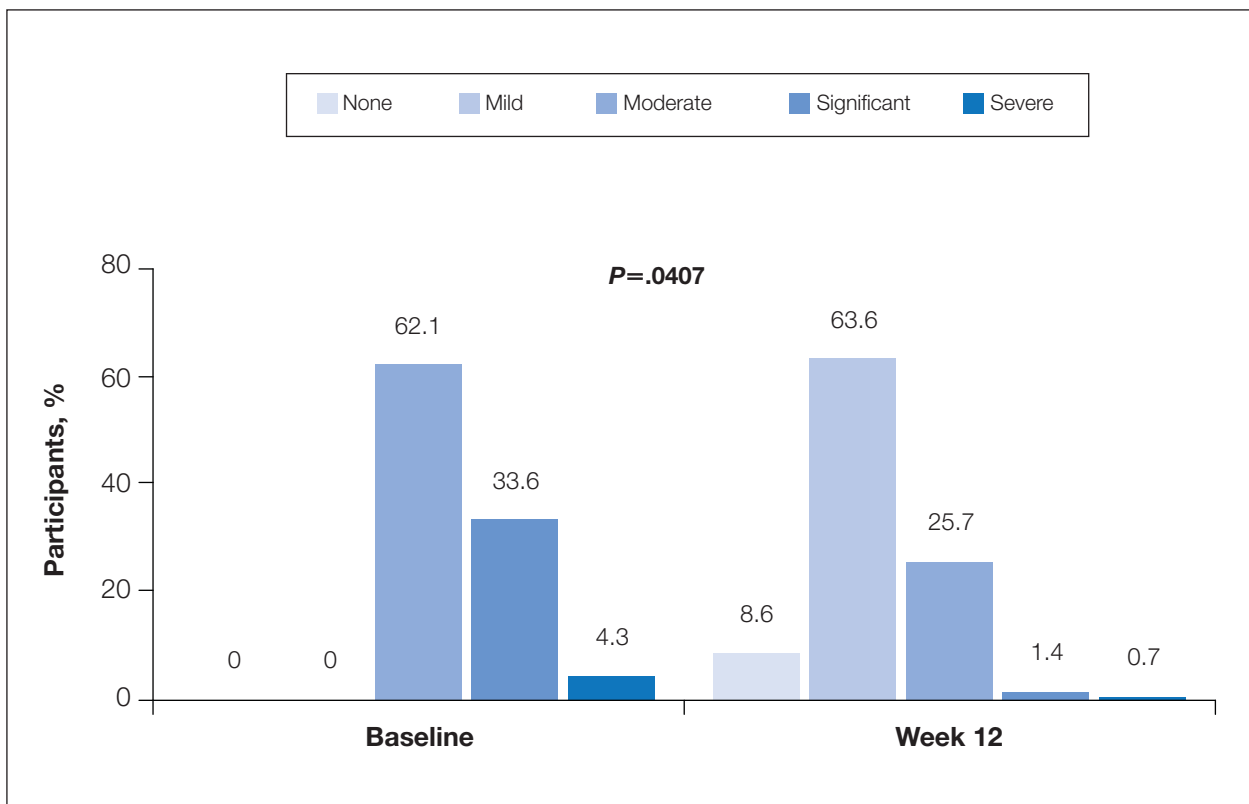


Figure 2. Distribution of clinician erythema assessment (CEA) scores at baseline and week 12 in the add-on therapy per-protocol population (n=140). *P* value was calculated (Cochran-Mantel-Haenszel test) comparing the distribution of baseline CEA scores with the distribution of week 12 CEA scores. The change in distribution of CEA scores between baseline and week 12 was statistically significant (*P*=.0407).

doxycycline 40 mg in the setting of practicing clinical dermatologists. The add-on therapy arm of the ORCA trial represents a subgroup of participants commonly seen in dermatology offices on a regular basis, participants who have had PPR for a number of years and have tried topical therapy regimens but remain inadequately controlled. As many cases of PPR warrant add-on therapy due to only partial response to topical therapy, an oral agent would be given to these participants while they were maintained on a topical regimen. The results reported in the add-on therapy group of the ORCA trial provide data based on an approach that is often used in everyday clinical practice.

Treatment with doxycycline 40 mg significantly improved IGA scores after 12 weeks of treatment (*P*=.0012) in the add-on therapy group, with the majority of participants achieving clear (38.6%) or near clear (37.1%) IGA scores. The distribution of baseline and week 12 IGA scores was significantly different (*P*=.0012). Similar improvements in IGA scores also were seen in a randomized, double-blind, comparative trial of doxycycline 40 mg once daily versus doxycycline 100 mg once daily in participants

who were concurrently treated with metronidazole gel 1% once daily.⁵ Although comparisons between studies must be assessed with caution and definitive interstudy conclusions cannot be made, both studies included participants with PPR and the consistency of results is noteworthy. In the comparative-dose trial, no significant difference was seen in the IGA scores between the two doses of doxycycline across the 16-week trial, suggesting that no additional efficacy is gained with a higher dose of doxycycline.

Erythema associated with PPR, primarily reflective of perilesional inflammatory erythema, also was improved with doxycycline 40 mg when used as add-on therapy to a preexisting stable topical regimen. Most participants in the add-on therapy arm had mild (63.6%) CEA scores at week 12 compared with the baseline assessment in which 62.1% of participants presented with moderate erythema and 37.9% of participants presented with significant or severe erythema. At week 12, 8.6% of participants were completely clear of erythema in this add-on therapy group. The distribution of baseline and week 12 CEA scores was significantly different (*P*=.0407). These reductions in erythema

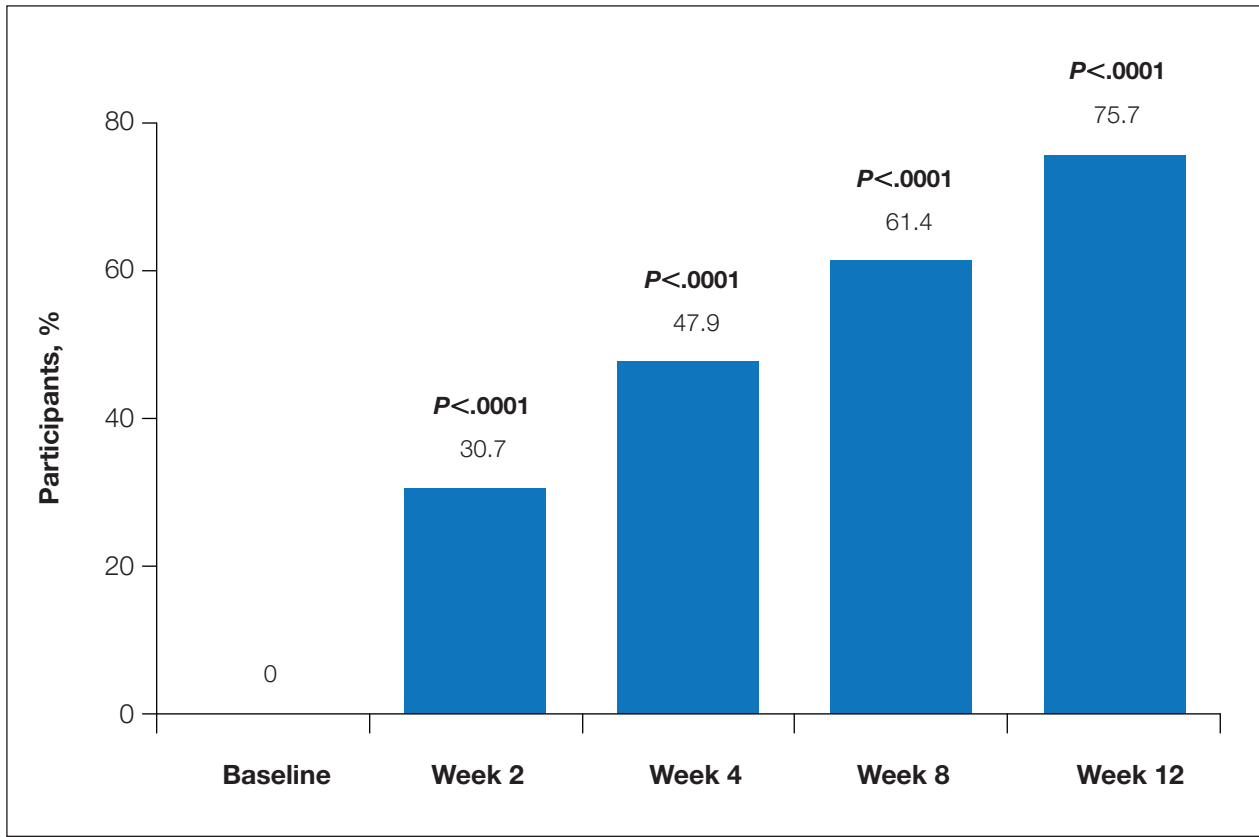


Figure 3. Percentage of participants with clear or near clear investigator global assessment scores at each visit in the add-on therapy per-protocol population (n=140). There was a significant difference between baseline and all postbaseline scores ($P < .0001$) (Cochran-Mantel-Haenszel test). This study was not designed to make comparisons between the monotherapy and add-on therapy groups. Treatment response was evaluated from baseline to 12 weeks.

associated with PPR also were seen in the 2 pivotal trials with doxycycline 40 mg once daily⁶ as well as in the comparative-dose trial of doxycycline 40 mg once daily versus doxycycline 100 mg once daily in which metronidazole gel 1% was used concurrently once daily.⁵

The full monotherapy results are reported elsewhere in this supplement.⁹ However, the ORCA study was not designed for statistical comparisons between groups, with this article discussing only the add-on therapy arm. In this trial, the add-on therapy group included participants who were receiving topical therapy but still met the inclusion criteria of mild to severe rosacea based on IGA score and moderate to severe perilesional erythema based on the CEA scale, which would suggest that these participants were not adequately or fully responsive to their topical regimen and would potentially benefit from the addition of oral therapy to their current regimen. Participants who were effectively treated by or fully pleased with their topical regimen would not likely be enrolled if their topical regimen was deemed satisfactory. This rationale would especially

apply to those participants presenting with moderate or severe PPR at baseline, which represented 42.8% of the add-on therapy group. The basis for partial or inadequate response to topical therapy that led to enrollment in this trial was not explored. Potential reasons included noncompliance, inadequate efficacy of the topical regimen, or participant desire for a greater degree of efficacy versus what was achieved with topical therapy alone. In clinical practice, noncompliance may be an issue with topical medications, as some patients may prefer an oral medication once daily rather than apply a topical medication.¹⁰

Overall, doxycycline 40 mg once daily was well-tolerated in the add-on therapy group. Fifty-seven AEs were reported in 39 of 224 participants (17.4%) with no serious AEs reported. Adverse events were mainly mild or moderate in severity. Eight participants (3.6%) permanently discontinued the trial because of an AE. The most commonly reported AEs were diarrhea, nausea, and rash. No new safety signals emerged regarding the frequency or nature of AEs associated with the use of doxycycline 40 mg

Table 5.

Summary of Adverse Events (AEs)^a

	Add-on Therapy Group (n=224)
Participants with any AEs, n (%)	39 (17.4)
Total no. of AEs	57
Gastrointestinal tract disorders, n (%)	16 (7.1)
Diarrhea, n (%)	6 (2.7)
Nausea, n (%)	4 (1.8)
Skin and subcutaneous tissue disorders, n (%)	7 (3.1)
Rash, n (%)	3 (1.3)
Nervous system disorders, n (%)	4 (1.8)

^aAEs were descriptively summarized by system organ class and preferred term; occurred in >1% of participants by safety population.

once daily, including comparison with AE profiles reported in prior studies.^{5,6,8,9}

This study was a large open-label trial involving 271 investigational sites across the United States. As a community-based trial involving several investigators and study centers, there were more deviations in the protocol primarily related to requirements with allowed concomitant or study medication use and/or incomplete follow-up requirements. Hence a higher attrition rate was fully anticipated compared with what would have typically been seen in a controlled trial completed at 1 or a few study centers. Conversely, this study was designed with the intent to capture the experience of several investigators in a more formal fashion, reflective of results that are consistent with what practitioners observe in community-based practice. Deviations in protocol were handled responsibly, and only the PP population was used for effectiveness analysis to provide data on doxycycline 40 mg once daily when used in normal dermatologic practice.

Conclusion

Doxycycline 40 mg once daily, also referred to as anti-inflammatory-dose doxycycline, has been shown to be efficacious and safe for the treatment of PPR in controlled clinical trials^{5,6,8} and is the only US Food and Drug Administration–approved oral medication for the treatment of PPR.⁴ In a comparative-dose study completed in participants who were concurrently treated with metronidazole gel 1% once daily,

doxycycline 40 mg once daily demonstrated efficacy equivalent with doxycycline 100 mg once daily with fewer AEs, particularly those related to the gastrointestinal tract.⁵ In this large community-based trial, it has been demonstrated that doxycycline 40 mg once daily is effective and well-tolerated when added to a stable topical regimen for PPR, providing significant reductions in both inflammatory lesions and perilesional erythema based on the IGA and CEA ($P=.0012$ and $P=.0407$, respectively). Doxycycline 40 mg once daily appears to be a rational and therapeutically viable option in patients with PPR who are only partially or inadequately responsive to a topical therapy regimen.

Acknowledgments—The ORCA steering committee assisted in the design of the study and participated in its monitoring; James Q. Del Rosso, DO; Hilary E. Baldwin, MD; Guy F. Webster, MD, PhD; John E. Wolf Jr, MD; and James J. Leyden, MD.

The study described in this report was funded by Galderma Laboratories, LP. The authors thank Jodie Macoun, PhD, of Evince Communications for her support in the preparation of this article. Her work was funded by Galderma Laboratories, LP. The authors also would like to acknowledge Luz E. Colon and Kelley Collins-Winters for their significant effort in the conduct of this study, and Norman J. Preston, PhD, for assistance with statistical analyses. Revisions of the manuscript for important intellectual content were performed by each of the listed authors.

REFERENCES

1. Rosacea riddle now threatens more than 16 million Americans [news release]. Chicago, IL: National Rosacea Society; April 1, 2010. <http://www.rosacea.org/press/archive/20100401.php>. Accessed April 27, 2010.
2. Wilkin J, Dahl M, Detmar M, et al; National Rosacea Society Expert Committee. Standard grading system for rosacea: report of the National Rosacea Society Expert Committee on the classification and staging of rosacea. *J Am Acad Dermatol*. 2004;50:907-912.
3. Webster GF. Acne and rosacea. *Med Clin North Am*. 1998;82:1145-1154.
4. Oracea [package insert]. Fort Worth, TX: Galderma Laboratories, LP; 2008. <http://oracea.com/Includes/PDF/PrescribingInformation.pdf>. Accessed April 27, 2010.
5. Del Rosso JQ, Schlessinger J, Werschler P. Comparison of anti-inflammatory dose doxycycline versus doxycycline 100 mg in the treatment of rosacea. *J Drugs Dermatol*. 2008;7:573-576.
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. Kennedy Carney C, Cantrell W, Elewski BE. Rosacea: a review of current topical, systemic and light-based therapies. *G Ital Dermatol Venereol*. 2009;144:673-688.
8. Fowler JF Jr. Combined effect of anti-inflammatory dose doxycycline (40-mg doxycycline, usp monohydrate controlled-release capsules) and metronidazole topical gel 1% in the treatment of rosacea. *J Drugs Dermatol*. 2007;6:641-645.
9. Webster GF. An open-label, community-based, 12-week assessment of the effectiveness and safety of monotherapy with doxycycline 40 mg (30-mg immediate-release and 10-mg delayed-release beads). *Cutis*. 2010;86(suppl 5[i]):7-15.
10. Gupta G, Mallefet P, Kress DW, et al. Adherence to topical dermatological therapy: lessons from oral drug treatment. *Br J Dermatol*. 2009;161:221-227.

A Community-Based Study of the Effectiveness of Doxycycline 40 mg (30-mg Immediate-Release and 10-mg Delayed-Release Beads) on Quality of Life and Satisfaction With Treatment in Participants With Rosacea

Hilary E. Baldwin, MD

Changes to the skin of the face in patients with rosacea have the potential to substantially impair multiple domains of quality of life (QOL); however, the number of publications providing evidence for this topic is limited. This 12-week, open-label, community-based, phase 4 trial of 1421 participants is the largest study of the disease to date. It explores the effects of mild to severe rosacea and its treatment on QOL. Participants were treated with doxycycline 40 mg (30-mg immediate-release and 10-mg delayed-release beads) as monotherapy or add-on treatment to existing topical therapy. This article examines QOL issues in the primary analysis population consisting of 966 participants who completed the trial without a major protocol violation. Quality of life was assessed at baseline and study end (week 12) with the RosaQoL™, a validated 21-question instrument. Participant and investigator satisfaction with treatment also were evaluated. In the monotherapy group, the mean RosaQoL score was 3.3 at baseline and 2.8 at end of study. In the add-on therapy group, the mean RosaQoL score was 3.2 at baseline and 2.8 at end of study. The improvement in QOL was both clinically and statistically significant ($P < .0001$) and was similar in both monotherapy and add-on therapy

groups. Most participants expressed satisfaction with treatment and approximately 90% of the community-based investigators reported that they were likely or very likely to continue prescribing this formulation. The study demonstrates that the impaired QOL in patients with rosacea can be substantially improved during a 3-month period by once-daily treatment with the anti-inflammatory activity of subantimicrobial-dose doxycycline.

Cutis. 2010;86(suppl 5[j]):26-36.

Rosacea is a chronic inflammatory skin disease with prevalence in adults as high as 10%.¹ The National Rosacea Society estimates that as many as 16 million individuals in the United States are affected.² Onset typically occurs between 30 and 50 years of age, some of the most productive years of human life. Although rosacea can occur in all racial and ethnic groups, it most commonly affects white individuals of Celtic origin.¹ Rosacea has been subclassified into 4 types: erythematotelangiectatic, papulopustular (PPR), phymatous, and ocular.^{1,3} Patients with erythematotelangiectatic rosacea present with facial flushing resembling a prolonged blush. Papules, pustules, cysts, and nodules on the face of patients with PPR may mimic changes of acne vulgaris. The sebaceous and connective tissue hyperplasia of phymatous rosacea can be disfiguring and unfairly stigmatizing to the patient. Patients with ocular rosacea

From the State University of New York Medical Center, Brooklyn. The study described in this report was funded by Galderma Laboratories, LP. Dr. Baldwin is an advisory board member, consultant, and speaker for Galderma Laboratories, LP.

experience ocular signs and symptoms that can remarkably impact their lives.

It has been said that a dermatologist's work would be incomplete if he/she did not examine the whole patient, not only the skin, nails, and mucosa but the patient's psyche as well.⁴ This evaluation is reasonable because disease-associated alterations in appearance plus associated psychosocial and emotional issues may impact multiple domains of a patient's life. It seems clear that all subtypes of rosacea have the potential to substantially impair an individual's quality of life (QOL).⁵ Rosacea has been grouped with psoriasis and acne vulgaris as dermatologic disorders associated with a high incidence of psychoemotional factors.⁴ In an assessment of the burden of skin diseases in the United States, the intangible cost of dermatosis was estimated to be approximately 4-fold greater than its total direct and indirect costs because of the effects of the disease on QOL.⁶ The National Rosacea Society has standardized a system for grading the severity of rosacea⁷; however, because the correlation between signs and QOL is poor, most clinicians underestimate the effects of rosacea on patient's lives.⁸ The RosaQoL™ is a validated instrument specifically created to assess the effects of rosacea and its treatment on QOL.⁹

Although rosacea has been recognized since ancient times, a PubMed search in May 2010 of articles indexed for MEDLINE using the terms *rosacea* and *quality of life* only retrieved 3 treatment-related English-language publications with both terms in the title; 2 address QOL issues with pulsed dye laser treatment and 1 evaluates QOL in patients treated with azelaic acid or standard care.¹⁰⁻¹² Doxycycline 40 mg (30-mg immediate-release and 10-mg delayed-release beads) (hereinafter referred to as doxycycline 40 mg) is the only oral medication approved by the US Food and Drug Administration for the treatment of adults with PPR. Although the drug formulation is a subantimicrobial dose, it retains the anti-inflammatory properties of doxycycline. This article expands the existing evidence base by describing the results of the Oracea® for Rosacea: A Community-Based Assessment (ORCA) trial, a 12-week, open-label, phase 4 trial of the effects of this doxycycline formulation on QOL measured by the rosacea-specific QOL instrument (RosaQoL) as well as participant and investigator satisfaction with the 12-week regimen. Because topical treatments also are commonly employed in patients with the disease, the effects of the intervention were evaluated as monotherapy as well as add-on therapy for the subpopulation of participants who

entered the trial while already receiving 1 of several commonly used topical preparations.

Methods

This 12-week, open-label, multicenter, community-based trial evaluated doxycycline 40 mg in participants with mild to severe PPR rosacea with moderate to severe perilesional erythema. The drug was administered as either monotherapy or add-on therapy to the participant's existing topical treatment regimen. Among its many evaluation parameters, this trial was designed to evaluate the effects of the proprietary formulation on QOL as well as participant satisfaction in those who would have otherwise been treated with 100-mg antimicrobial-dose doxycycline, and to assess the treating investigator's satisfaction with the treatment. This study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, US Food and Drug Administration Code of Federal Regulations, and local regulatory requirements. A central institutional review board or the investigator's local institutional review board approved the protocol for all investigative sites. All participants were fully informed about the study and provided written consent prior to participation.

Study Population—Adults 18 years and older were eligible for the study if they had a diagnosis of mild to severe rosacea as defined by the investigator global assessment with moderate to severe perilesional erythema as determined by the clinician erythema assessment. (See the Del Rosso¹³ and Webster¹⁴ articles in this supplement.) Both disease parameters were assessed on 5-point scales, with higher numbers reflecting more severe manifestations. Qualifying participants who already were receiving approved topical rosacea therapy (metronidazole, azelaic acid, and/or sodium sulfacetamide 10%–sulfur 5% preparations) were allowed to continue their therapy as long as the dosage had been stable for at least 4 weeks prior to enrollment and remained stable for the duration of the trial, the drug was used according to the product labeling, and there was no evidence of intolerability. Participants were excluded if they had contraindications to treatment and/or comorbidities or active and/or recent therapy that may interfere with completion of the study or interpretation of the results. (For more detailed exclusion criteria, see the Del Rosso¹³ and Webster¹⁴ articles in this supplement.)

End Points—Outcome measures were changes in the results of the 21-question rosacea-specific RosaQoL survey between baseline and study end (week 12) or at the time of early termination (Figure 1). Participant satisfaction with therapy also was assessed

- | | |
|--|--|
| 1. I worry that my rosacea may be serious. | 13. I try to cover up my rosacea (with makeup). |
| 2. My rosacea burns or stings. | 14. I am bothered by persistence/reoccurrence of my rosacea. |
| 3. I worry about getting scars from my rosacea. | 15. I avoid certain foods or drinks because of my rosacea. |
| 4. I worry that my rosacea may get worse. | 16. My skin feels bumpy (eg, uneven, not smooth, irregular). |
| 5. I worry about side effects from rosacea medications. | 17. My skin flushes. |
| 6. My rosacea is irritated. | 18. My skin gets irritated easily (eg, cosmetics, aftershaves, cleansers). |
| 7. I am embarrassed by my rosacea. | 19. My eyes bother me (feel dry or gritty). |
| 8. I am frustrated by my rosacea. | 20. I think about my rosacea. |
| 9. My rosacea makes my skin sensitive. | 21. I avoid certain environments (eg, heat, humidity, cold) because of my rosacea. |
| 10. I am annoyed by my rosacea. | |
| 11. I am bothered by the appearance of my skin (eg, redness, blotchiness). | |
| 12. My rosacea makes me feel self-conscious. | |

Figure 1. Rosacea-specific quality of life (RosaQoL™) survey questions. Participants selected the appropriate response to each statement, which was assigned a value on a 5-point scale (1=never; 2=rarely; 3=sometimes; 4=often; 5=all the time). Overall score was calculated as the average of responses to all questions. This figure lists the questions from the survey but does not consist of the entire instrument. Reprinted from Nicholson et al,⁹ Copyright 2007, with permission from the American Academy of Dermatology.

at week 12 or at the time of early termination with a 10-item questionnaire (Figure 2). Investigator satisfaction with treatment was assessed with a 5-item survey done after all participants had completed the trial (Figure 3). Effectiveness and safety end points are reported elsewhere. (See the Del Rosso¹³ and Webster¹⁴ articles in this supplement.)

Statistical Analysis—The per-protocol (PP) population was selected a priori as the primary analysis population because of the anticipated high dropout rates in a community-based trial. The baseline RosaQoL score was compared with the end of treatment RosaQoL score using a paired *t* test or Wilcoxon signed rank test, depending on the normal distribution of the data. The critical value for all statistical analyses in this study was $\alpha = .05$.

Results

Participant Disposition—The intention-to-treat (ITT) population consisted of 1421 participants from 271 investigational sites. The PP population was selected a priori as the primary analysis population. Of the ITT population, 966 participants (68.0%) completed the trial without a major protocol violation and were included in the PP analyses (826 participants

received doxycycline 40 mg as monotherapy and 140 participants received the medication as add-on therapy to their existing topical treatment). Most PP participants were women (70.8%) ranging in age from 18 to 87 years; the mean age of the population was 50.6 years. More than 90% of the participants were white and were not of Hispanic or Latino ethnicity. Overall, the mean duration of disease was 5.2 years. Participant satisfaction surveys were received from 962 of 966 participants in the PP population (99.6%). Of the 271 investigators, 259 (95.6%) completed satisfaction surveys.

Quality of Life—In the monotherapy group, the mean RosaQoL score was 3.3 at baseline and 2.8 at end of study ($P < .0001$) (Figure 4A). In the add-on therapy group, the mean RosaQoL score was 3.2 at baseline and 2.8 at end of study ($P < .0001$). The significant decrease in RosaQoL scores indicates an improvement in the participants' QOL from baseline to end of study in both treatment groups ($P < .0001$) (Figure 4B). There also was a significant difference between baseline and end of study RosaQoL scores for the metronidazole and azelaic acid add-on therapy subgroups ($P < .0001$), indicating an improvement in the QOL in these subgroups at the end of the study. *P* values were not calculated

1. Before the study, how frequently did you experience a rosacea flare-up?
 - a. Every few days
 - b. Once a week
 - c. Once a month
 - d. Every few months
 - e. Once a year
 - f. Other
2. Before the study, how long did your rosacea flare-ups usually last?
 - a. Less than a day
 - b. More than a day
 - c. More than a week
 - d. Several weeks
 - e. More than a month
 - f. Other
3. In the past, has medication been effective in controlling your rosacea?
 - a. Yes
 - b. Somewhat
 - c. No
4. Before the study, how did you manage your rosacea? (Select all that apply.)
 - a. Avoid triggers such as sun exposure or spicy foods
 - b. Over-the-counter topical treatment
 - c. Prescription topical treatment
 - d. Prescription oral antibiotic treatment
 - e. Light therapy
 - f. Laser therapy
 - g. No prior treatments
5. In the past, did avoiding factors that aggravate your rosacea work for you in controlling your flare-ups?
 - a. Yes
 - b. Somewhat
 - c. No
6. In the past, how satisfied were you with your previously prescribed treatments for rosacea?
 - a. Very satisfied
 - b. Satisfied
 - c. No opinion
 - d. Dissatisfied
 - e. Very dissatisfied
 - f. None of the above
7. During the study, how satisfied were you with your Oracea® treatment?
 - a. Very satisfied
 - b. Satisfied
 - c. No opinion
 - d. Dissatisfied
 - e. Very dissatisfied
8. Which of the following statements would keep you from continuing the Oracea treatment you used during the study? (Select all that apply.)
 - a. I forget to take my medicine
 - b. I don't like taking pills
 - c. I was bothered by the side effects
 - d. I still experience some flare-ups with the treatment
 - e. I may not be able to afford the treatment
 - f. The treatment interferes with my lifestyle
 - g. None of the above
9. Which concerns you most about the Oracea treatment you received during the study? (Select all that apply.)
 - a. My treatment has to be taken orally
 - b. My treatment has to be taken once a day
 - c. My treatment may cause unwanted side effects
 - d. None of the above
10. How likely are you to continue Oracea treatment?
 - a. Very likely
 - b. Likely
 - c. Don't know/not sure
 - d. Unlikely
 - e. Very unlikely

Figure 2. Participant satisfaction survey. The participant satisfaction survey was completed at week 12 or at early termination by each participant. Oracea® is the study drug (doxycycline capsules 40 mg [30-mg immediate-release and 10-mg delayed-release beads]).

1. Was this your first experience using Oracea® to treat patients in your practice with rosacea?
 - a. Yes
 - b. No
2. How satisfied were you with the overall results of the Oracea treatment you observed in your patients?
 - a. Very satisfied
 - b. Satisfied
 - c. No opinion
 - d. Dissatisfied
 - e. Very dissatisfied
3. How likely are you to continue prescribing Oracea in the future?
 - a. Very likely
 - b. Likely
 - c. Don't know
 - d. Unlikely
 - e. Very unlikely
4. If you plan to prescribe Oracea in the future, would you? (Select all that apply.)
 - a. Prescribe Oracea as monotherapy
 - b. Prescribe Oracea in combination with a topical medication
 - c. Prescribe Oracea in an ongoing fashion to decrease the inflammatory lesions of rosacea
5. What would be the reason(s) for you not to prescribe Oracea in the future? (Select all that apply.)
 - a. There is another product on the market with better effectiveness
 - b. There is another product on the market with equivalent effectiveness
 - c. I am concerned with long-term side effects of oral medications in general
 - d. My patients may not be able to afford the medication
 - e. Other reasons

Figure 3. Investigator satisfaction survey. At the end of each investigator's participation in the study, he/she was asked to complete a satisfaction survey after all participants had completed the trial. Oracea® is the study drug (doxycycline capsules 40 mg [30-mg immediate-release and 10-mg delayed-release beads]).

for the sodium sulfacetamide–sulfur add-on therapy subgroup because of the small sample size.

Participant Satisfaction—Disease characteristics from the participant satisfaction survey indicate that approximately two-thirds of participants experience frequent rosacea flare-ups that typically range in duration from 1 day to more than a week and are poorly controlled by trigger avoidance (Figures 5A–5C). Prior to study entry, the 3 most common disease management approaches reported by participants in the monotherapy group were prescription topical agents (26.6%), trigger avoidance (18.8%), and over-the-counter topical agents (18.0%) (Figure 5D). For the add-on therapy group, the 3 most common disease management approaches were prescription topical agents (45.5%), trigger avoidance (18.7%), and prescription oral antibiotic treatment (15.6%). Fewer than 18% of participants in both groups reported that the medications they received before enrollment were effective in controlling their rosacea (Figure 5E), and 80% or more of participants in both groups reported that the prior medication was somewhat or not effective.

Following treatment with the study drug, approximately 80% of participants in both groups responded

that they were either very satisfied or satisfied with doxycycline 40 mg (Figure 6A). Most participants in both groups reported that they were very likely or likely to continue the study drug (Figure 6B). In response to the question about factors that would keep the participant from continuing treatment with the study drug, the most commonly identified issues in the monotherapy and add-on therapy groups were may not be able to afford the treatment (32.1% and 31.3%, respectively) and may still experience some flare-ups with the treatment (21.7% and 24.2%, respectively). Approximately 23% of participants in both groups responded that none of the issues listed in the questionnaire would keep them from continuing treatment with the study drug. The survey responses for a particular question were statistically different from each other for the monotherapy and add-on therapy groups for all survey questions (Rao-Scott χ^2 test, $P < .0001$).

Investigator Satisfaction—Most of the 259 investigators who submitted survey responses reported that this was not their first experience using doxycycline 40 mg to treat participants (83.4%) and they were very satisfied (39.1%) or satisfied (49.8%) with the overall results (Figure 7A). Investigators also

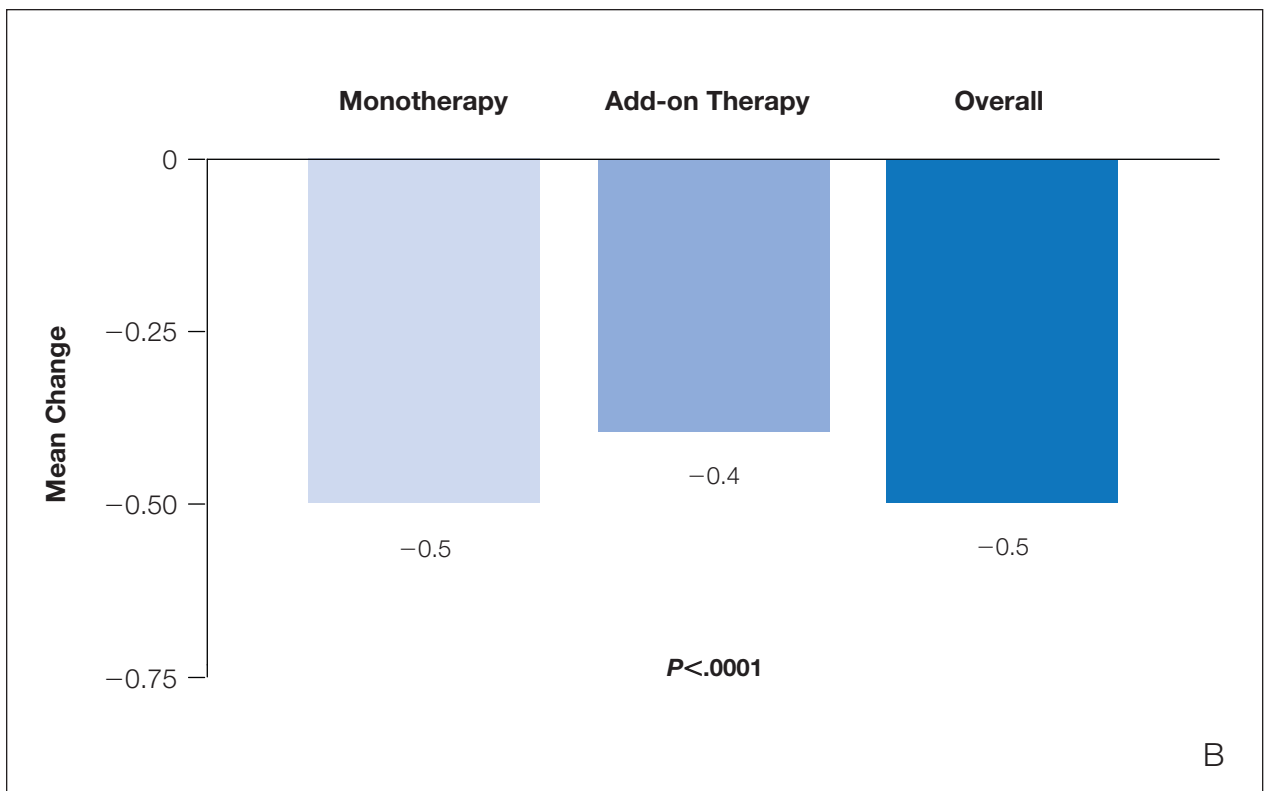
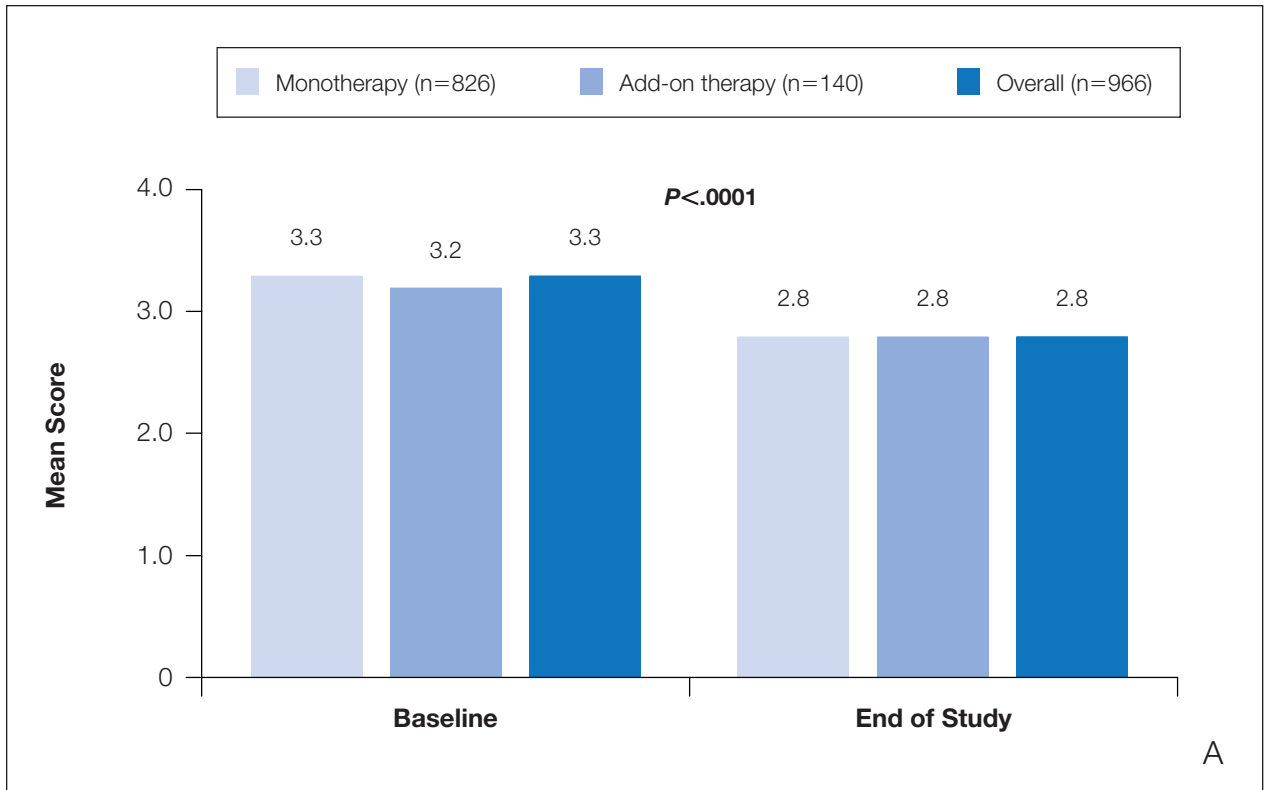


Figure 4. Rosacea-specific quality of life instrument (RosaQoL™) scores at baseline and end of study (week 12) for the monotherapy group, add-on therapy group, and overall (A). The mean change in RosaQoL from baseline to end of study (per-protocol population; N=966) also was evaluated (B). The mean score at baseline versus end of study was significant as well as the mean change ($P < .0001$ for both).

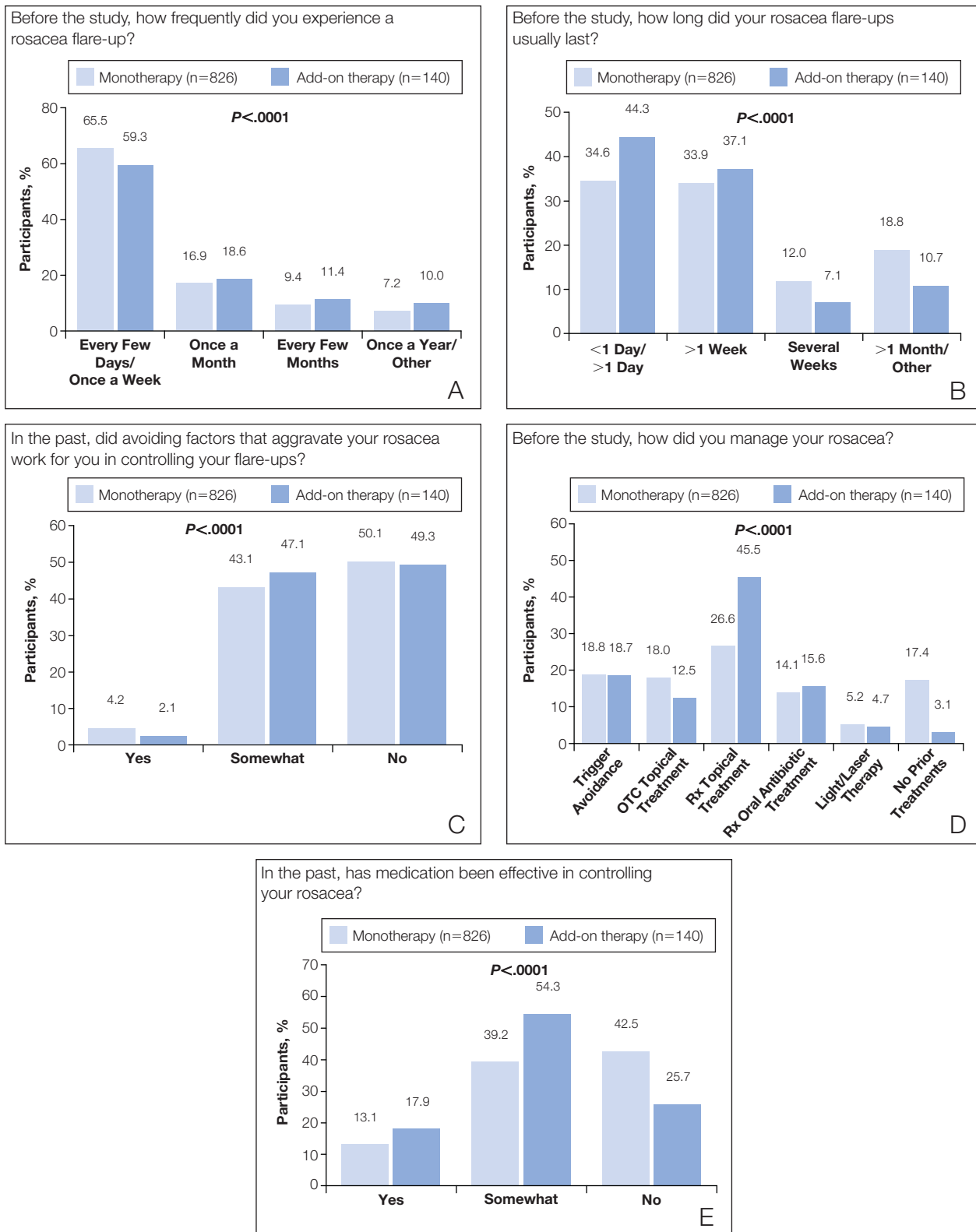


Figure 5. Results of the participant satisfaction survey (per-protocol population; N=966) for frequency of rosacea flare-ups (A), duration of rosacea flare-ups prior to study entry (B), effectiveness of trigger avoidance to control rosacea flare-ups (C), treatment choice for rosacea flare-ups (D), and effectiveness of medication for rosacea prior to enrollment (E). The survey responses for a particular question were all statistically different from each other ($P<.0001$). Percentages are based on the total number of responses. OTC indicates over-the-counter; Rx, prescription.

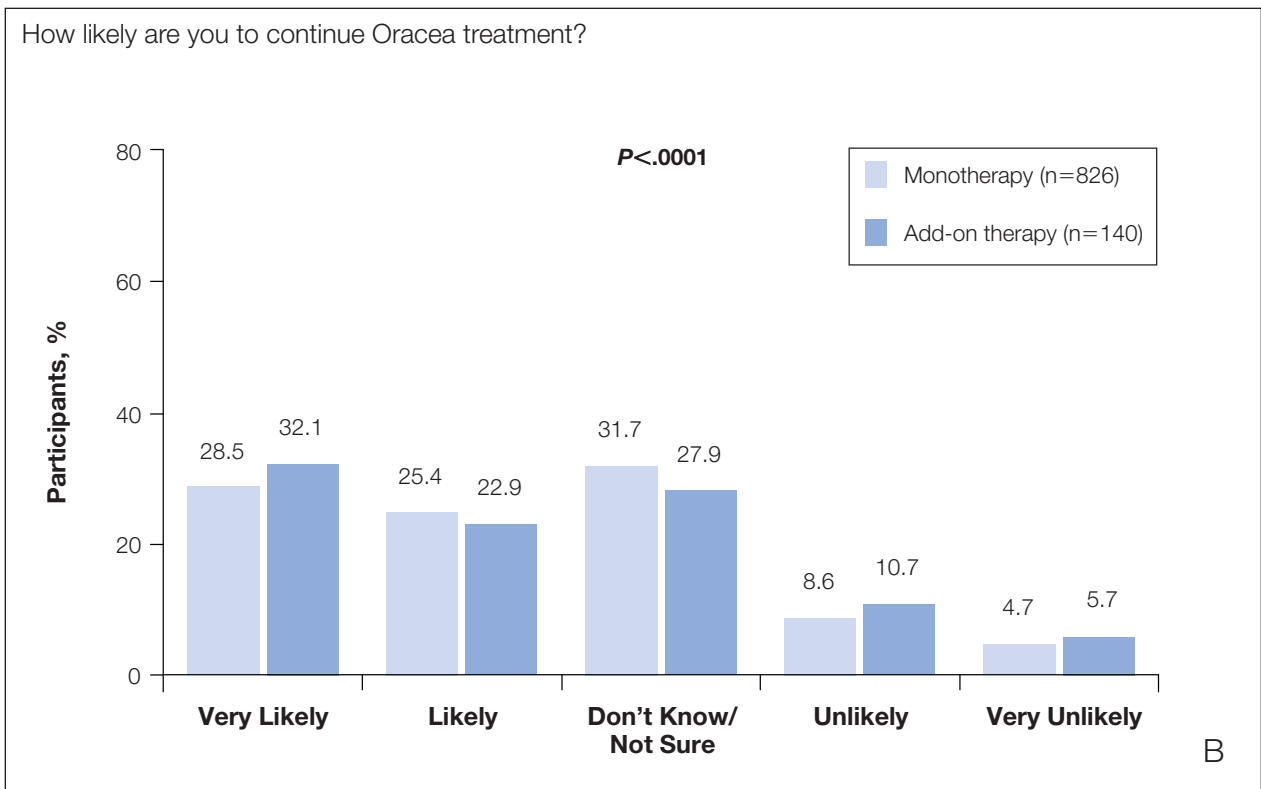
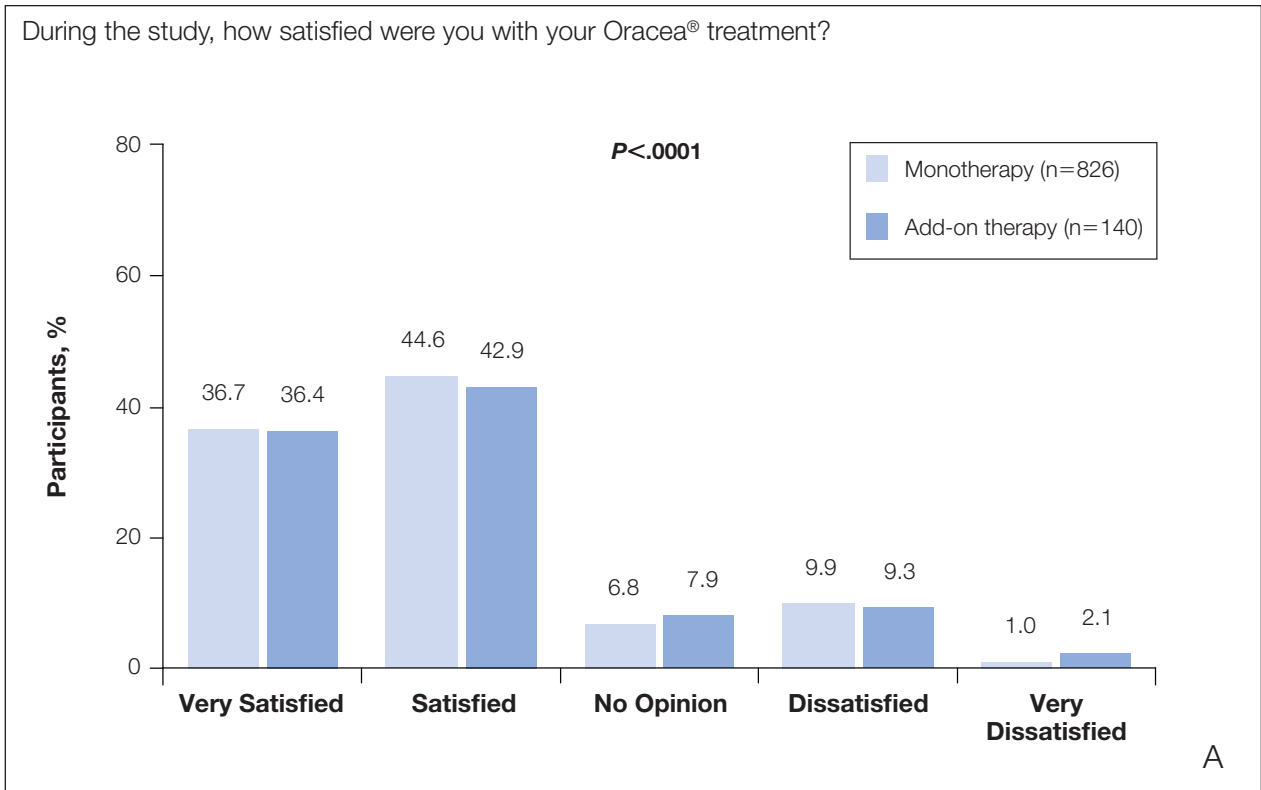


Figure 6. Results of the participant satisfaction survey (per-protocol population; N=966) for participant satisfaction with doxycycline 40 mg (A) and likelihood that the participant will continue doxycycline 40 mg (B). The survey responses for a particular question were all statistically different from each other ($P<.0001$). Percentages are based on the total number of responses.

reported that they were very likely (61.6%) or likely (28.8%) to continue to prescribe the study drug in the future (Figure 7B). The investigators answered that they would prescribe doxycycline 40 mg as monotherapy (46.6%), in combination with a topical medication (24.6%), or in an ongoing fashion to decrease the inflammatory lesions of rosacea (28.8%). The survey responses for a particular question were statistically different from each other for all survey questions (Rao-Scott χ^2 test, $P < .0001$).

Comment

The ORCA trial is the largest rosacea trial conducted to date. It used the validated RosaQoL instrument to assess the impact of the anti-inflammatory activity of doxycycline 40 mg on rosacea-associated impairments in QOL. The RosaQoL is a 21-item instrument specifically designed to assess the effects of rosacea on symptoms, functioning, and emotions of participants with the disease and their change across time.⁹ As designed and used in the trial, each participant selected never, rarely, sometimes, often, or all the time to each of the 21 questions (Figure 1). Each response was assigned a value on a 5-point scale from 1 (never) to 5 (all the time). Thus lower values for each response indicated perceptions of better QOL for the individual items versus higher scores. The overall RosaQoL score was calculated as an average of responses to all questions and improvement identified by a decrease from the baseline score. Lower values represented better self-reported disease-associated QOL. During its validation, the RosaQoL was found to be reliable, reproducible, and responsive to changes in disease across time and relatively more sensitive to changes in QOL in participants with rosacea than the Skindex-29.⁹

Participants enrolled in the trial had mild to severe rosacea (investigator global assessment score) and moderate to severe perilesional erythema (clinician erythema assessment score). As reported by Del Rosso¹³ and Webster,¹⁴ doxycycline 40-mg treatment produced clinical and statistical reductions in investigator-assessed disease severity and perilesional erythema. At week 12, approximately 75% of participants achieved investigator global assessment scores of clear or near clear and clinician erythema assessment scores of none or mild.¹⁴ As measured by RosaQoL responses, doxycycline 40 mg produced significant improvements in disease-associated QOL compared with baseline in participants with all degrees of disease severity, both as monotherapy and in combination with metronidazole or azelaic acid add-on therapy ($P < .0001$). At baseline, the mean RosaQoL score for the overall PP population was 3.3. This baseline value corresponds with a

self-reported rosacea severity of poor to fair.⁹ In both groups, 12 weeks of treatment decreased RosaQoL scores (monotherapy, 3.3 to 2.8; add-on therapy, 3.2 to 2.8), a 0.5 and 0.4 improvement in score in the monotherapy and add-on therapy groups, respectively. A RosaQoL score of 2.8, as reported in the present trial, was perceived by participants as good rosacea. In addition to the clinical improvement associated with lower RosaQoL scores, the improvement between baseline and week 12 scores was statistically significant for both monotherapy and add-on treatment groups ($P < .0001$).

Given the paucity of literature on this topic, data from the large number of enrollees in this trial make a substantial contribution to the evidence base on QOL in patients with rosacea, indicating that untreated or inadequately treated patients with the disease have impairments in multiple domains of QOL. While studies of pulsed dye laser treatment and azelaic acid have indicated that treatment can improve QOL,¹⁰⁻¹² the ORCA trial is the first to report the effects of oral therapy with doxycycline 40 mg on this important parameter. It also demonstrates that doxycycline 40 mg administered for 3 months can significantly improve QOL ($P < .0001$), irrespective of concurrent use of a topical therapy. As a community-based trial, the outcomes achieved in the ORCA trial can be obtained in real-world settings.

The use of the PP population rather than the ITT population for primary analysis is a potential limitation. Although an a priori decision made by the trial designers ensured that the maximum amount of information on the effects of treatment on QOL could be obtained, not all participants take all of their medicines for all of the time that they are prescribed.^{15,16} Thus results from the PP population would be expected to report better effectiveness than the ITT population and potentially overreport participant satisfaction because nonresponders may be more likely to drop out of the trial. Although the RosaQoL has been validated, responsiveness of the instrument has been assessed only in participants who were improved or unchanged at baseline, and the instrument has yet to be studied in a community setting or in some participant subgroups.⁹

Results of the participant and investigator satisfaction surveys offer practical insight into the disease-specific features, state of treatment of the disease, and approaches to therapy for the disease in the community setting. The results of the participant survey indicate that most participants had flare-ups that occurred every few days or weekly and lasted days to weeks. In general, the participants reported that a strategy of avoiding triggers did not control their disease. As may be expected, the disease

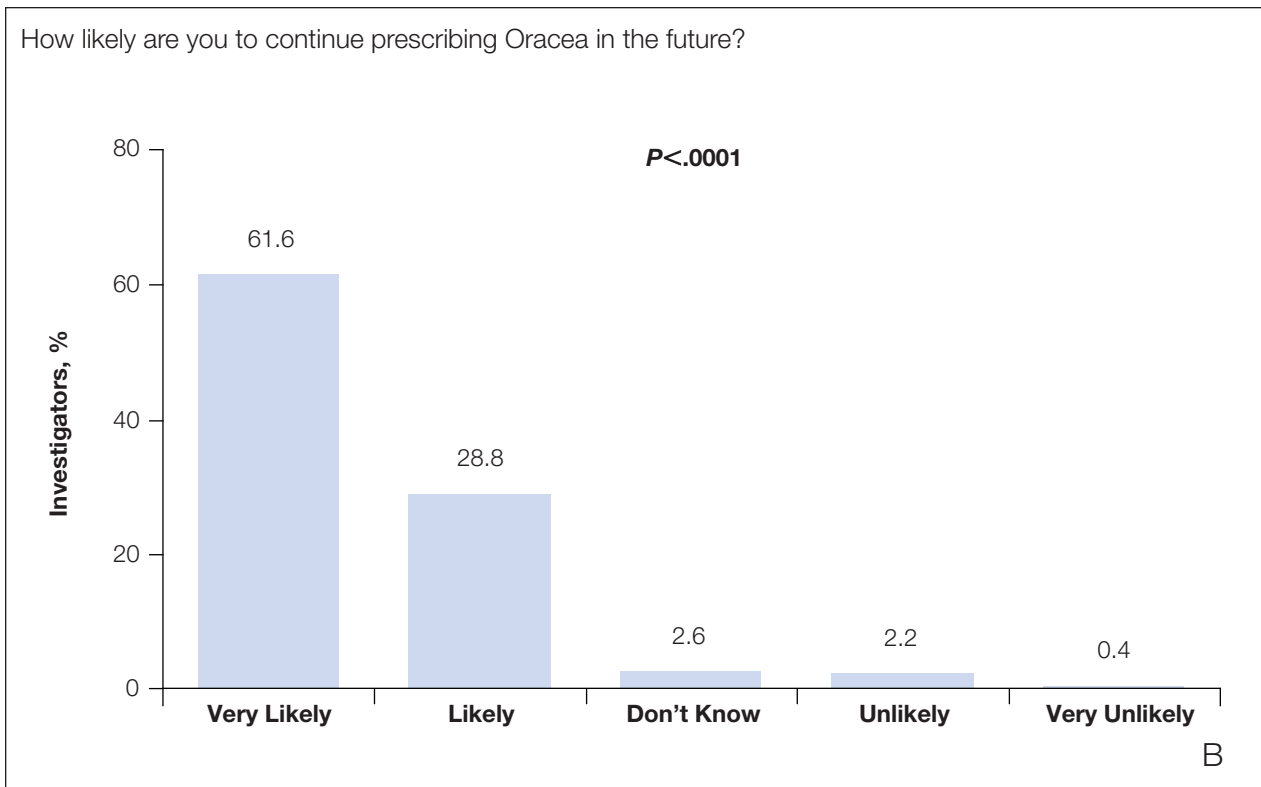
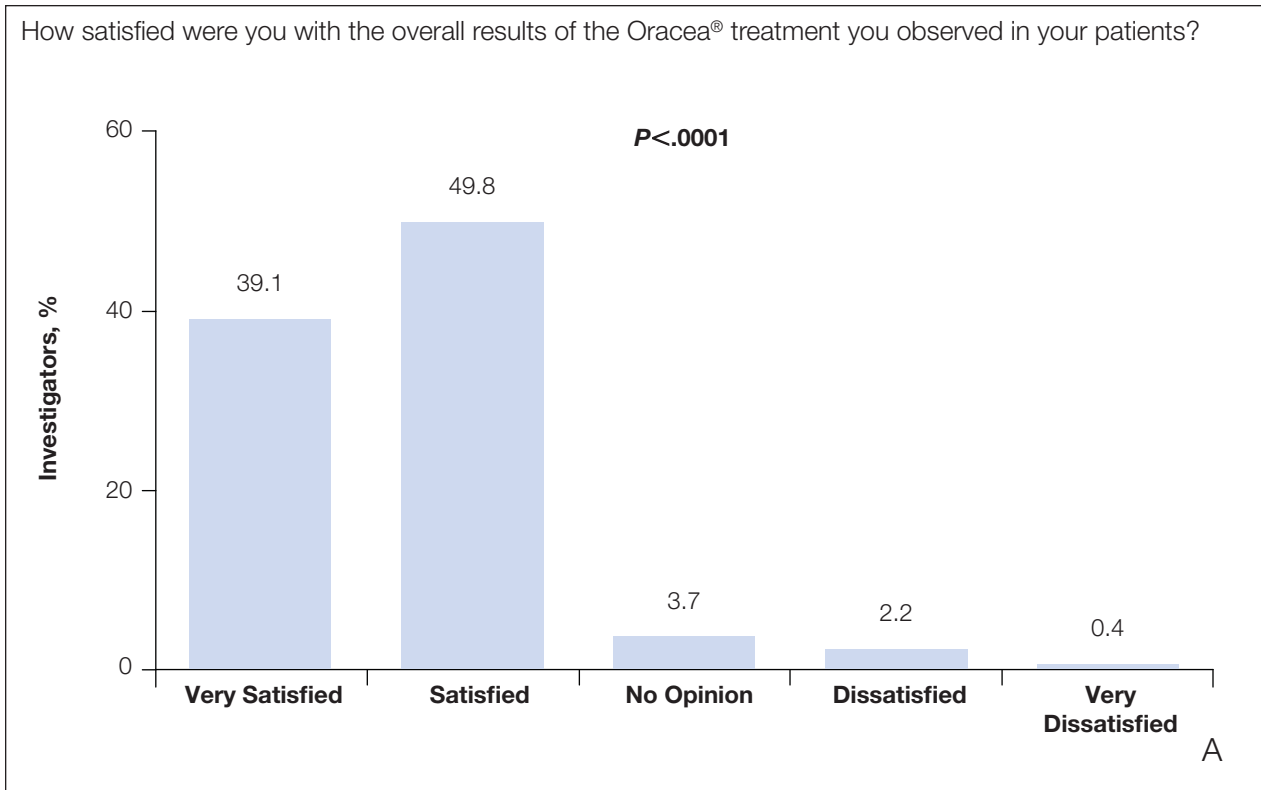


Figure 7. Results of the investigator satisfaction survey (259 responses received from 271 investigators) for investigator satisfaction with doxycycline 40 mg (A) and likelihood that the investigator will continue to prescribe doxycycline 40 mg in the future (B). The survey responses for a particular question were all statistically different from each other ($P < .0001$). Percentages are based on the total number of responses.

requires specific interventions such as over-the-counter or prescription topical medications or oral antibiotics, or some form of phototherapy. The unmet needs in the study population were emphasized by the responses that indicated that only approximately one-third of the respondents were satisfied with a previous therapy, a number that increased to approximately 80% after completion of a 12-week course of doxycycline 40 mg. Most of the investigators had prior experience with anti-inflammatory-dose doxycycline, with approximately 90% reporting that they were satisfied with treatment during the trial and would prescribe the drug in the future. In combination with the objective improvements in QOL from treatment, surveys of both the participants and investigators support the benefits of treatment with doxycycline 40 mg and point to its role as a first-line agent in patients with mild to severe PPR with moderate to severe perilesional erythema.

Conclusion

In this large community-based trial of participants with PPR, a disease-specific, validated QOL instrument showed that participants with PPR have significant impairments in QOL ($P < .0001$). Oral treatment with doxycycline 40 mg significantly improved QOL while decreasing the severity of PPR disease and associated perilesional erythema ($P < .0001$). The study indicates that treatment with the anti-inflammatory 40-mg formulation of doxycycline improves rosacea-associated QOL in participants treated in community-based settings. Survey responses from participants and investigators reported that both groups were satisfied with treatment and that most intended to continue to manage the disease with oral therapy.

Acknowledgments—The ORCA steering committee assisted in the design of the study and participated in its monitoring: James Q. Del Rosso, DO; Hilary E. Baldwin, MD; Guy F. Webster, MD, PhD; John E. Wolf Jr, MD; and James J. Leyden, MD.

The study described in this report was funded by Galderma Laboratories, LP. The authors thank Jodie Macoun, PhD, of Evince Communications for her support in the preparation of this article. Her work was funded by Galderma Laboratories, LP. The authors also would like to acknowledge Luz E. Colon and Kelley Collins-Winters for their significant effort in the conduct of this study, and Norman J. Preston, PhD, for assistance with statistical analyses. Revisions of the manuscript for important intellectual content were performed by each of the listed authors.

REFERENCES

1. Powell FC. Clinical practice. rosacea. *N Engl J Med*. 2005;352:793-803.

2. Rosacea riddle now threatens more than 16 million Americans [news release]. Chicago, IL: National Rosacea Society; April 1, 2010. <http://www.rosacea.org/press/archive/20100401.php>. Accessed April 27, 2010.
3. Crawford GH, Pelle MT, James WD. Rosacea: I. etiology, pathogenesis, and subtype classification. *J Am Acad Dermatol*. 2004;51:327-341.
4. Panconesi E. Psychosomatic factors in dermatology: special perspectives for application in clinical practice. *Dermatol Clin*. 2005;23:629-633.
5. Panconesi E. Psychosomatic dermatology. *Clin Dermatol*. 1984;2:94-179.
6. Bickers DR, Lim HW, Margolis D, et al; American Academy of Dermatology Association; Society for Investigative Dermatology. The burden of skin diseases: 2004 a joint project of the American Academy of Dermatology Association and the Society for Investigative Dermatology. *J Am Acad Dermatol*. 2006;55:490-500.
7. Wilkin J, Dahl M, Detmar M, et al; National Rosacea Society Expert Committee. Standard grading system for rosacea: report of the National Rosacea Society Expert Committee on the classification and staging of rosacea. *J Am Acad Dermatol*. 2004;50:907-912.
8. Chren MM, Lasek RJ, Quinn LM, et al. Skindex, a quality-of-life measure for patients with skin disease: reliability, validity, and responsiveness. *J Invest Dermatol*. 1996;107:707-713.
9. Nicholson K, Abramova L, Chren MM, et al. A pilot quality-of-life instrument for acne rosacea. *J Am Acad Dermatol*. 2007;57:213-221.
10. Menezes N, Moreira A, Mota G, et al. Quality of life and rosacea: pulsed dye laser impact. *J Cosmet Laser Ther*. 2009;11:139-141.
11. Tan SR, Tope WD. Pulsed dye laser treatment of rosacea improves erythema, symptomatology, and quality of life. *J Am Acad Dermatol*. 2004;51:592-599.
12. Fleischer A, Suephy C. The face and mind evaluation study: an examination of the efficacy of rosacea treatment using physician ratings and patients' self-reported quality of life. *J Drugs Dermatol*. 2005;4:585-590.
13. Del Rosso JQ. Effectiveness and safety of doxycycline 40 mg (30-mg immediate-release and 10-mg delayed-release beads) once daily as add-on therapy to existing topical regimens for the treatment of papulopustular rosacea: results from a community-based trial. *Cutis*. 2010;86(suppl 5[i]):16-25.
14. Webster GF. An open-label, community-based, 12-week assessment of the effectiveness and safety of monotherapy with doxycycline 40 mg (30-mg immediate-release and 10-mg delayed-release beads). *Cutis*. 2010;86(suppl 5[i]):7-15.
15. Zaghoul SS, Goodfield MJ. Objective assessment of compliance with psoriasis treatment. *Arch Dermatol*. 2004;140:408-414.
16. Balkrishnan R, Carroll CL, Camacho FT, et al. Electronic monitoring of medication adherence in skin disease: results of a pilot study. *J Am Acad Dermatol*. 2003;49:651-654.

Cutis®

