The CLEAR Trial: Results of a Large Community-Based Study of Metronidazole Gel in Rosacea

John E. Wolf, Jr, MD; James Q. Del Rosso, DO

A phase 4, open-label, multicenter, community-based study was conducted in subjects with mild to moderately severe papulopustular rosacea of various etiologies and locations to identify subgroups particularly responsive to twice-daily application of metronidazole topical gel 0.75% to the affected areas of the face. A total of 582 subjects were randomized. Evaluations were conducted at baseline and at weeks 4, 8, and 12. At each evaluation, investigator global assessment (IGA) scores, mean papule and pustule counts, erythema scores, and telangiectasia scores improved significantly (P<.0001), with consistent results across sex and age subgroups. The mean erythema severity score decreased significantly (P<.0001) from baseline by week 4 and continued to decline at all study visits, with a nearly 50% reduction by week 12. At study end, subjects indicated a 25% improvement in itching, pain, soreness, or stinging; a 53% improvement in embarrassment or self-consciousness; and a 31% improvement in rosacea's effect on social or leisure activities. Metronidazole topical gel 0.75% was associated with a very low incidence of side effects in this trial, similar to previous clinical trials. The most common treatment-related adverse event (AE) reported in this study was mild application-site discomfort. The gel formulation was well-tolerated and effective in all subject subgroups and in a variety of climates. The findings of this study expand the collected data on the efficacy and safety of metronidazole topical gel 0.75% beyond that demonstrated in controlled clinical trials and confirm the utility of this therapy in the community setting.

Cutis. 2007;79:73-80.

Accepted for publication May 23, 2006.

Dr. Wolf is from the Department of Dermatology, Baylor College of Medicine, Houston, Texas. Dr. Del Rosso is from the Department of Dermatology, University of Nevada School of Medicine, Las Vegas.
This study was supported by an educational grant from Galderma Laboratories, LP, and monitored by Dimensional HealthCare. The study was an open-label, prospective, community-based trial of patients with rosacea in routine clinical practice. The authors had full access to the study data, thoroughly reviewed the analysis, and had complete editorial control of the information included in this manuscript. Dr. Wolf is a consultant and speaker and has conducted clinical research for Galderma Laboratories, LP. Dr. Del Rosso is an advisory board member, consultant, researcher, and speaker for CollaGenex Pharmaceuticals Inc; Doak Dermatologics, a subsidiary of Bradley Pharmaceuticals, Inc; Galderma Laboratories, LP; Intendis, Inc; Medicis Pharmaceutical Corporation; and Stiefel Laboratories, Inc. Reprints not available from the authors.

Rosacea is a common chronic facial skin disease that is estimated to affect approximately 13 to 14 million Americans.[1,2] The prevalence appears to be increasing, possibly because of the aging of the US population.[3] Rosacea most commonly affects individuals aged 30 to 50 years, with fair skin, and of northern European origin, though individuals of all races and ages can be affected.[3,4] Women are approximately 2 to 3 times more likely than men to have rosacea.[3] The etiology and pathogenesis of the disease are not well understood, but several environmental and genetic risk factors have been identified.[2,5] The manifestations of rosacea vary among individuals; however, the typical clinical signs are facial flushing and erythema.[3] Telangiectases and inflammatory lesions (papules and pustules) frequently are associated with rosacea,[6] and ocular complications and rhinophyma may occur in some patients.[3,7] Rosacea has been classified into 4 subtypes: erythematotelangiectactic, papulopustular, phymatous, and ocular, based on the predominant patterns of signs and symptoms.[4] The disease

has a significant effect on patients' quality of life (QOL), causing embarrassment, anxiety, low self-esteem, and avoidance of social situations.[3] Left untreated, rosacea can cause facial disfigurement and ocular complications.[1]

Metronidazole was first reported in 1976 for the treatment of rosacea,[8] and in 1989, it became the first topical therapy for rosacea to receive approval in the United States.[2,9] Since then, metronidazole has become a mainstay of rosacea therapy and is available in 0.75% concentrations in gel, lotion, and cream formulations, as well as a 1% concentration of gel and cream formulations. The efficacy and tolerability of topical metronidazole has been demonstrated in 10 randomized controlled trials in which more than 500 subjects received topical metronidazole therapy.[9] Of these, 110 subjects were treated with metronidazole topical gel 0.75%.[6,9-11] These trials have demonstrated reductions in inflammatory lesion counts and erythema, with little or no effect on reducing the number of established telangiectases.[2,6,10] The mechanism of action of metronidazole in reducing inflammatory lesions and erythema is not known but is believed to be related to the agent's anti-inflammatory effects rather than its antimicrobial activity.[2,12]

Although metronidazole has been in clinical use for decades, no phase 4 trials have evaluated its efficacy, tolerability, or safety in clinical practice. The **C**ommunity-Based Tria**l** of M**e**troGel® in the Tre**a**tment of **R**osacea (CLEAR) investigated the use of metronidazole topical gel 0.75% in this setting for subjects with mild to moderately severe papulopustular rosacea. The trial served to expand the patient base evaluated in clinical trials and allowed study of specific patient subgroups in community-based dermatology practice. Gels are commonly perceived to be drying, and some physicians tend to reserve this formulation for men or patients with greasy skin. Thus, a secondary goal of CLEAR was to determine the acceptance and tolerability of metronidazole topical gel 0.75%, especially among women, in patients with dry or sensitive skin, and in patients living in a variety of climates.

Methods

Study Design—CLEAR was a phase 4, open-label, multicenter, community-based study of the efficacy, tolerability, and safety of metronidazole topical gel 0.75% for the treatment of mild to moderately severe papulopustular rosacea.

Study Population—To be eligible for study enrollment, subjects were required to be aged 18 years or older and in good general health. Subjects were required to have mild to moderately severe papulopustular rosacea, defined as the presence of 8 to 30 inflammatory lesions (papules and/or pustules), and persistent mild to moderate erythema, defined as slight pinkness to bright pinkness with mild edema. Erythema was required to have been present for at least one month prior to enrollment. The presence and assessment of facial erythema was to encompass background erythema and was not limited to perilesional erythema. Presence of telangiectases was allowed but not required.

Subjects were excluded if they had used any topical antiacne, antibiotic, or corticosteroid medications on the face within a 2-week washout period, or if they had used topical retinoids or systemic corticosteroids, rosacea medications, or antibiotics within 4 weeks, or systemic isotretinoin within 6 months. Subjects also were excluded if they had ocular rosacea, another facial skin condition, or a condition or treatment regimen that might interfere with the study.

Treatment—A thin layer of metronidazole topical gel 0.75% was applied twice daily to the affected areas of the face. Subjects were instructed to wash the facial area with a gentle skin cleanser before applying the metronidazole gel; they were allowed to use a mild skin moisturizer as needed. The treatment duration was 12 weeks, with follow-up visits at weeks 4, 8, and 12. Compliance was monitored by a review of the subject's treatment diary at each visit.

Evaluations—The clinical state of the disease was evaluated at baseline and at each follow-up visit by assessing the following characteristics: the score of an investigator global assessment (IGA) of improvement scale, number of papules and pustules, severity of erythema, and severity of telangiectases. The IGA ratings were based on a 7-point scale: (1=worse, 2=no change, 3=slight improvement (1%−24%), 4=moderate improvement (25%–49%), 5=marked improvement (50%–74%), 6=almost clear (75%−99%), 7=clear). The severity of facial erythema and telangiectases was rated on a scale of 0 (no redness for erythema, no telangiectases) to 4 (severe) for 5 individual areas: chin, nose, forehead, left cheek, and right cheek. Ratings for each area were summed to give a total score ranging from 0 to 20. Subject QOL was evaluated at baseline and on study termination using the Dermatology Life Quality Index.[13] Adverse events (AEs) observed by the investigator or reported by the subject were recorded at each visit.

Ethics—The study was conducted in accordance with the ethical principles of the Declaration of

Helsinki, good clinical practice guidelines, and local regulatory requirements. The protocol was reviewed and approved by a national institutional review board and a panel of dermatologist consultants. All subjects gave written informed consent prior to enrollment.

Statistical Methods—Analysis of variance was used to evaluate efficacy variables. Averages were used to describe other data.

Results

A total of 612 subjects from 133 sites were enrolled in the CLEAR study. Of these, 582 subjects were evaluable, and 441 completed the study; 141 discontinued prematurely. Compliance was 95% to 96% at each treatment visit among subjects who had not discontinued. Baseline disease severity is summarized in Table 1. Men had more severe disease at baseline than women, but the trend was not appreciably different.

The efficacy of metronidazole topical gel 0.75% was determined by examining the IGA score, lesion counts, assessment of erythema, telangiectasia index score, QOL score, tolerability, and safety.

IGA Score—The IGA scores showed marked improvement at the first follow-up visit and continued to improve throughout the trial, as shown in Table 2 and Figure 1. The improvement in the IGA scores was greater in subjects who were compliant than in subjects who were noncompliant (mean change from baseline, 0.9 vs 0.3; $P=.0317$). In addition, 42% of subjects were rated clear or almost clear according to the IGA score at study end. Improvement was consistent

Table 1.

Disease Severity Measures at Baseline for All Facial Areas Combined

	Papule Count	Pustule Count	Erythema Score*	Telangiectasia Score*
All, mean±SD (range)	11.9±8.49 (0−95)	3.7±4.98 (0−44)	8.2±3.45 (0−20)	6.6±3.99 (0−20)
Women, mean±SD (range)	11.6±7.74 (0−63)	3.5±4.75 (0−44)	7.9±3.37 (0−20)	6.2±3.79 (0−20)
Men, mean±SD (range)	12.8±10.41 (0−95)	4.3±5.56 (0−31)	9.0±3.57 (2−15)	7.6±4.41 (0−20)

*Rated on a scale of 0 (no redness for erythema, no telangiectases) to 4 (severe) for 5 individual areas: chin, nose, forehead, left cheek, and right cheek. Ratings for each area were summed to give a total score ranging from 0 to 20.

Table 2.

Mean Investigator Global Assessment (IGA) of Improvement Score at Each Visit

	Week 4	Week 8		Week 12	
	Mean IGA* (N=520)	Mean IGA* (N=468)	Change in IGA From Baseline (N=463)	Mean IGA* (N=446)	Change in IGA From Baseline (N=439)
All subjects, mean±SD	3.5±1.16	3.9±1.29	0.3±1.36†	4.4±1.51	0.9±1.52†

*IGA ratings were based on the following scale: 1=worse, 2=no change, 3=slight improvement (1%−24%), 4=moderate improvement (25%−49%), 5=marked improvement (50%−74%), 6=almost clear (75%−99%), 7=clear.
†$P<.0001$ vs baseline.

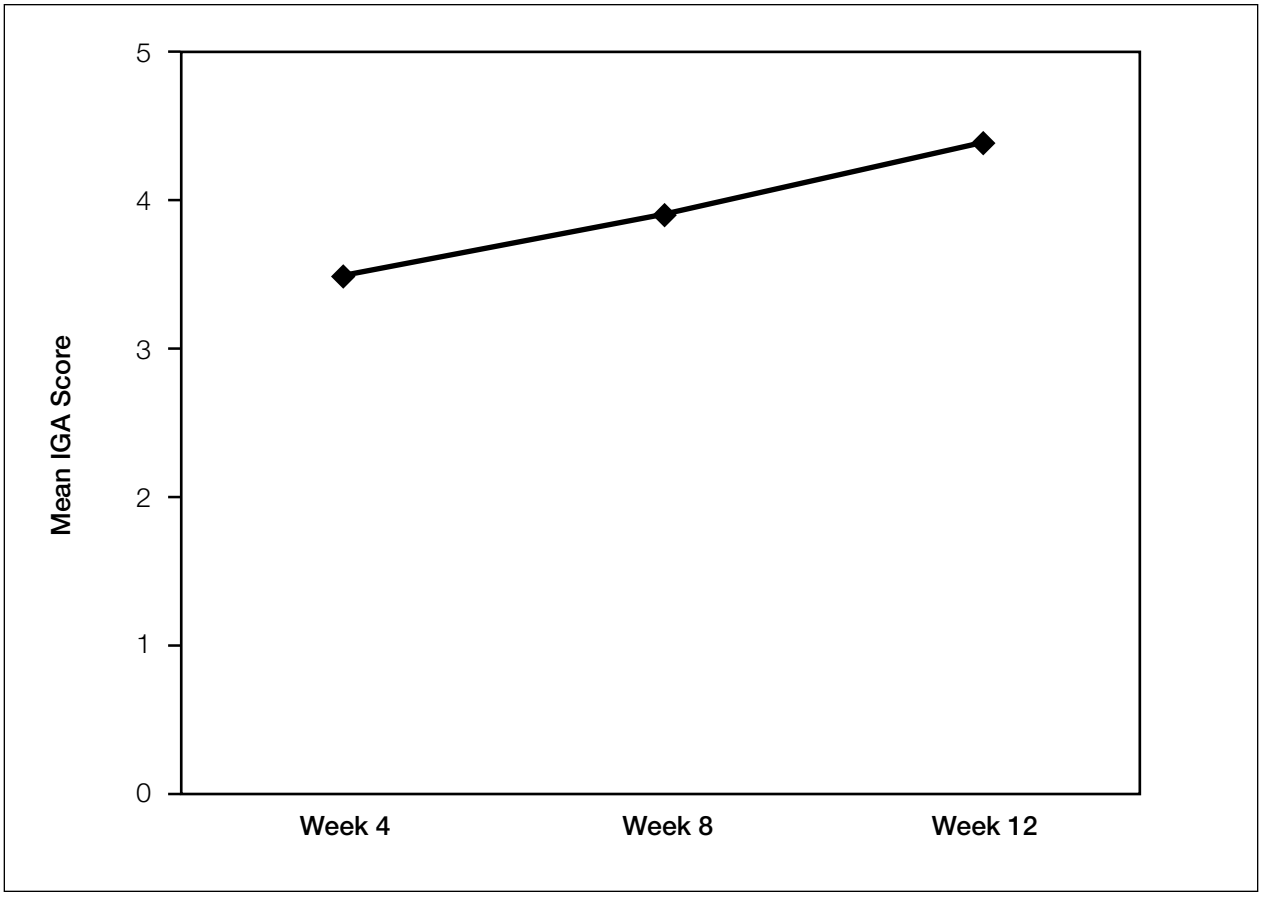

Figure 1. Mean investigator global assessment (IGA) of improvement score for each follow-up visit. Scores ranged from 1 (worse) to 7 (clear). Asterisk indicates $P<.0001$ vs baseline for all follow-up visits.

across subject subgroups based on sex, baseline disease severity, and age.

Lesion Counts—Subjects experienced a significant ($P<.0001$) decrease in papule and pustule counts at each follow-up visit, with reductions in mean inflammatory lesion counts of 44% at week 4, 61% at week 8, and 71% at week 12. Table 3 and Figure 2 detail the changes in lesion counts for papules and pustules among men and women. Lesion count reductions were consistent across sex and age subgroups and increased as baseline rosacea severity worsened.

Erythema—Assessment of erythema included both the overall background erythema and perilesional erythema noted on the chin, nose, forehead, and cheeks. The mean facial erythema severity score improved consistently at all 3 follow-up visits, with a mean percentage decrease of 22% at 4 weeks, 35% at 8 weeks, and 45% at 12 weeks. These decreases were significant ($P<.0001$) at all time points for men, women, and all subjects. Figure 3 shows the changes in erythema score. Notably, erythema improved regardless of its location on the face, and the degree of improvement was most marked in subjects with moderate erythema and in subjects with moderately severe rosacea at baseline.

Telangiectasia Index Score—Telangiectasia severity was assessed using index scores based on overall appearance and not through counting of individual dilated blood vessels. Telangiectasia index scores improved throughout the duration of the trial. The decrease was small (0.7 on the 0 to 4 scale) but represented an approximate 50% reduction ($P<.0001$).

QOL Score—Subjects reported significant ($P<.0001$) improvements over the duration of the trial in 3 important areas: itching, pain, soreness, or stinging; embarrassment or self-consciousness; and effect on social or leisure activities. Table 4 details the mean scores in these areas. Statistically significant improvements also occurred in other areas, such as home activities, clothing selection, sports activities, and relations with partners or close friends ($P<.0001$). There were no significant changes in the difficulty of work or study activities and no problems with skin treatment.

Table 3.

Mean Combined Lesion Counts at Each Visit

		Baseline	Week 4	Week 8	Week 12
All subjects	N	582	520	468	446
	Combined papule count Mean±SD	11.9±8.49	6.9±7.86	4.8±6.52	3.6±6.15
	Decrease from baseline, mean (%)		5 (42)	7.1 (60)	8.3 (70)
	Combined pustule count Mean±SD	3.7±4.98	1.9±3.43	1.3±2.93	0.9±2.43
	Decrease from baseline, mean (%)		1.8 (49)	2.4 (65)	2.8 (76)
Women	n	437	392	348	330
	Combined papule count Mean±SD	11.6±7.74	6.8±7.56	4.7±5.64	3.6±4.83
	Decrease from baseline, mean (%)		4.8 (41)	6.9 (59)	8.0 (69)
	Combined pustule count Mean±SD	3.5±4.75	1.9±3.44	1.3±2.52	0.9±2.18
	Decrease from baseline, mean (%)		1.6 (46)	2.2 (63)	2.6 (74)
Men	n	145	128	120	116
	Combined papule count Mean±SD	12.8±10.4	7.0±8.74	5.2±8.59	3.8±8.92
	Decrease from baseline, mean (%)		5.8 (45)	7.6 (59)	9.0 (70)
	Combined pustule count Mean±SD	4.3±5.56	2.1±3.40	1.6±3.89	1.0±3.05
	Decrease from baseline, mean (%)		2.2 (51)	2.7 (63)	3.3 (77)

Tolerability and Safety—The percentage of subjects reporting AEs was 5.5% at week 4, 2.7% at week 8, and 1.4% at week 12, with a total of 67 AEs reported by 56 subjects. Of the 67 AEs, 17 (25%) were judged to be probably or highly probably related to the trial medication. The most common treatment-related AEs were application-site dermatitis and application-site irritation. Application-site–related events were most common at the beginning of treatment, with 23 (12 treatment related) reported at week 4, 3 (2 treatment related) at week 8, and 2 (1 treatment related) at week 12. No treatment-related serious AEs were reported.

Comment

The CLEAR study investigated the use of metronidazole topical gel 0.75% in the treatment of rosacea in the dermatology office practice setting. Earlier trials reported decreases in lesion counts of 48% to 65% at weeks 7 through 9 and clinically significant improvements in IGA scores and erythema. The results of CLEAR are highly consistent with these results, with a 61% decrease in lesion count at 8 weeks (with continued reductions through week 12), as well as improvements in IGA scores and erythema. The telangiectasia severity index also improved by approximately 50% by trial end.

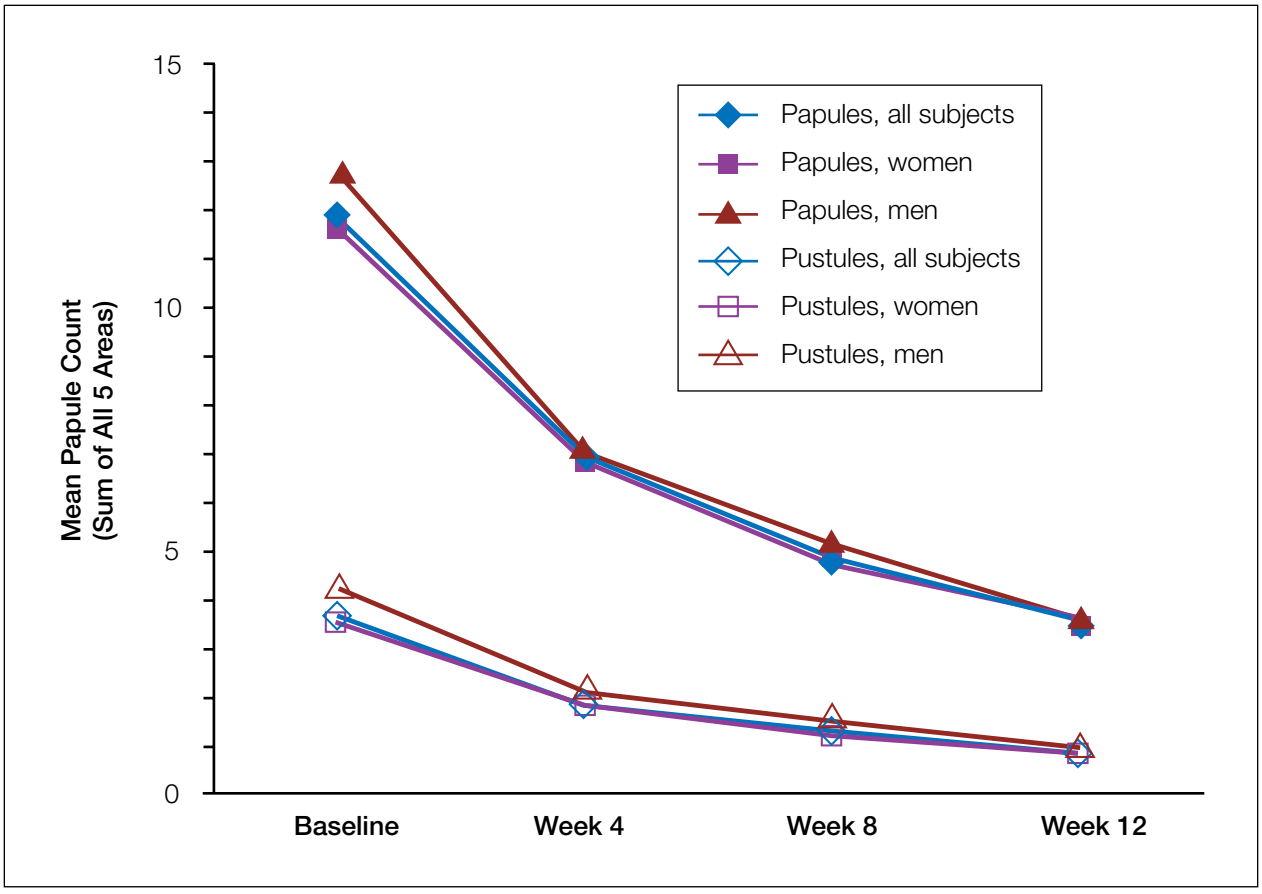

Figure 2. Mean total papule and pustule count at baseline and at each follow-up visit for men, women, and all subjects. $P<.0001$ vs baseline for all follow-up visits.

The tolerance and safety profiles found in CLEAR also are similar to those from earlier randomized controlled trials, with application-site–related events being the most common AEs and few serious events judged to be treatment-related.[6,11] The CLEAR results also are consistent with results for other formulations of topical metronidazole (lotion and cream).[9] Thus, CLEAR confirms that the efficacy and safety of metronidazole determined by earlier studies is maintained in the clinical practice setting, including practices located in diverse climates across the United States. The trial also demonstrates significant QOL improvements in its subject population ($P<.0001$).

Although there is no evidence that medical therapies for rosacea, including topical metronidazole, reduce the number of telangiectatic vessels, the use of a telangiectasia severity index in CLEAR allowed for assessment of the overall severity of facial telangiectasia both pretreatment and posttreatment. In this trial, topical metronidazole did decrease the overall visual appearance of facial telangiectatic vessels based on IGA. However, this finding is not consistent with results from previous trials involving metronidazole.

Because of its large study population, this trial allowed a comparison of the efficacy of metronidazole topical gel 0.75% between men and women. This comparison is interesting because many physicians treat men with a gel and use lotions or creams for women. The results of CLEAR show that the gel can effectively improve the symptoms of rosacea in both men and women, with good cosmetic acceptability and excellent tolerability across a diverse range of climates.

Conclusion

This trial confirms the efficacy and safety of twice-daily metronidazole topical gel 0.75% in the treatment of mild to moderately severe papulopustular rosacea. The gel is effective in reducing inflammatory lesion counts, erythema, and telangiectases. The efficacy in reducing lesion counts is equivalent for men and women. Tolerability, safety, and cosmetic acceptability all are highly favorable with metronidazole topical gel 0.75%.

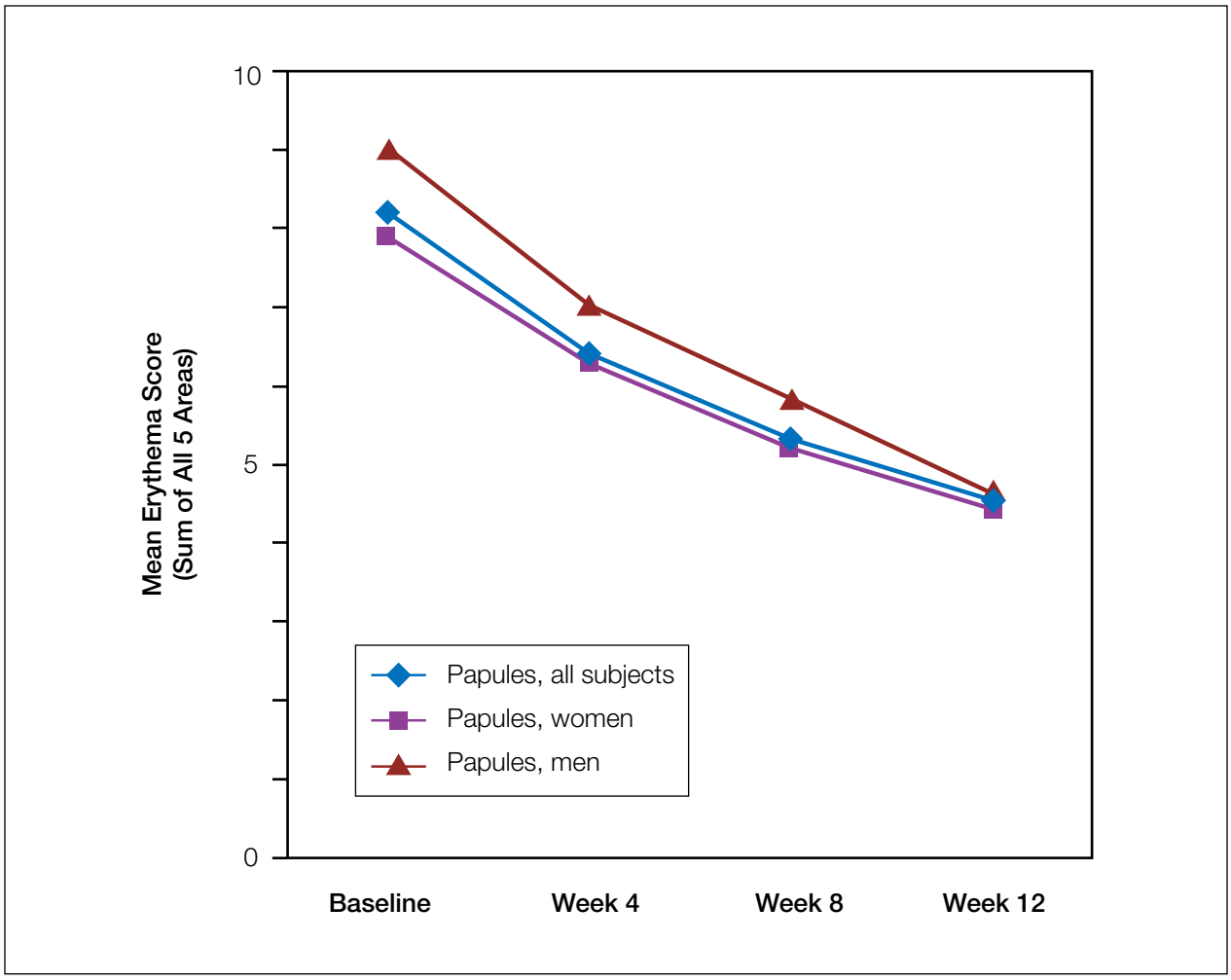

Figure 3. Mean erythema score at baseline and at each follow-up visit for men, women, and all subjects (sum of erythema scores [0=no redness for erythema, 4=severe] for 5 facial areas [chin, nose, forehead, left cheek, right cheek], with a range of 0 to 20 in all 5 areas). $P<.0001$ vs baseline for all follow-up visits.

Table 4.

Summary of Quality-of-Life Changes at Week 12

Quality-of-Life Measure	Baseline N	Baseline Score, Mean±SD	Week 12 N	Week 12 Score, Mean±SD	Mean Change From Baseline	Change From Baseline, %
Itching, pain, soreness, or stinging	581	3.1±0.78	449	3.6±0.61	0.5*	25
Embarrassment or self-consciousness	581	2.6±0.90	449	3.5±0.68	0.9*	53
Effect on social or leisure activities	512	3.4±0.81	388	4.0±0.60	0.6*	31

*$P<.0001$ vs baseline.

REFERENCES

1. Frampton JE, Wagstaff AJ. Azelaic acid 15% gel in the treatment of papulopustular rosacea. *Am J Clin Dermatol*. 2004;5:57-64.
2. Del Rosso JQ. A status report on the medical management of rosacea: focus on topical therapies. *Cutis*. 2002;70:271-275.
3. Blount BW, Pelletier AL. Rosacea: a common, yet commonly overlooked, condition. *Am Fam Physician*. 2002;66:435-440.
4. Wilkin J, Dahl M, Detmar M, et al. Standard classification of rosacea: report of the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea. *J Am Acad Dermatol*. 2002;46:584-587.
5. Buechner SA. Rosacea: an update. *Dermatology*. 2005;210:100-108.
6. Aronson IK, Rumsfield JA, West DP, et al. Evaluation of topical metronidazole gel in acne rosacea. *Drug Intell Clin Pharm*. 1987;21:346-351.
7. Rebora A. The management of rosacea. *Am J Clin Dermatol*. 2002;3:489-496.
8. Pye RJ, Burton JL. Treatment of rosacea by metronidazole. *Lancet*. 1976;1:1211-1212.
9. Wolf JE Jr. The role of topical metronidazole in the treatment of rosacea. *Cutis*. 2004;73(suppl 1):19-28.
10. Bleicher PA, Charles JH, Sober AJ. Topical metronidazole therapy for rosacea. *Arch Dermatol*. 1987;123:609-614.
11. Espagne E, Guillaume JC, Archimbaud A, et al. Double-blind study versus excipient of 0.75% metronidazole gel in the treatment of rosacea [in French]. *Ann Dermatol Venereol*. 1993;120:129-133.
12. Gupta AK, Chaudhry M. Topical metronidazole for rosacea. *Skin Therapy Lett*. Jan 2002;7:1-3, 6.
13. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use. *Clin Exp Dermatol*. 1994;19:210-216.