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Acne Results (CLEAR) Trial Study Group

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A multicenter, investigator-masked, randomized, parallel-group study was performed in 440 patients with mild-to-moderate facial acne vulgaris to compare the efficacy and tolerability of tazarotene monotherapy with 3 combination regimens—tazarotene plus benzoyl peroxide gel, tazarotene plus erythromycin/benzoyl peroxide gel, and tazarotene plus clindamycin phosphate lotion. An additional treatment group—monotherapy with clindamycin phosphate lotion—also was included as a reference arm. The only combination therapy to achieve a significantly greater global improvement than tazarotene monotherapy was tazarotene plus clindamycin. For reducing noninflammatory lesions specifically, none of the combination regimens offered significant benefit over tazarotene monotherapy (though tazarotene plus clindamycin and tazarotene plus erythromycin/benzoyl peroxide were significantly more efficacious than clindamycin monotherapy). For reducing inflammatory lesions, tazarotene plus erythromycin/benzoyl peroxide was significantly more efficacious than all the other regimens. Although tazarotene plus clindamycin and tazarotene plus benzoyl peroxide reduced the incidence of adverse effects compared with tazarotene monotherapy, the difference did not achieve statistical significance.

Topical retinoids form the core of antiacne therapy because they reduce and prevent the development of microcomedos (the precursors of both noninflammatory and inflammatory lesions). Several well-controlled studies have compared different topical retinoids in monotherapy regimens, and

the results of these indicate that none of the topical retinoids currently available are more effective than tazarotene in reducing noninflammatory and inflammatory lesions.¹⁻³ However, it is currently unknown whether adjunctive use of other antiacne medications potentially could further enhance the efficacy and/or tolerability of tazarotene.

The adjunctive use of clindamycin phosphate previously has been shown to enhance the efficacy of tretinoin 0.025% gel.⁴ It is useful to know whether any aspects of tazarotene treatment also can be optimized through the use of combination regimens. A multicenter, investigator-masked, randomized, parallel-group study was performed to evaluate whether the adjunctive use of benzoyl peroxide gel, erythromycin/benzoyl peroxide gel, or clindamycin phosphate lotion could further enhance the efficacy and tolerability of tazarotene monotherapy. An additional treatment group—monotherapy with clindamycin phosphate lotion—also was included as a reference arm.

Methods

Patients—Patients were eligible for recruitment into the trial if they were at least 12 years of age, had mild-to-moderate facial acne vulgaris, and had not used any topical antiacne medication in the 14 days preceding study entry, any oral antiacne medication in the 28 days preceding study entry, or any investigational drug or device in the 30 days preceding study entry. They were required to sign a consent form and, if female and of childbearing potential, to have a regular menstrual cycle and a negative urine pregnancy test at the time of study entry.

Patients were ineligible if they fulfilled any of the following exclusion criteria: previous use of an oral retinoid; nodular or cystic lesions; spontaneously improving or rapidly deteriorating facial acne vulgaris; presence or history of other skin conditions that would interfere with the evaluation of the test

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Table 1.

Grading Scales for Efficacy and Tolerability

Score	Global Response to Treatment	Dryness, Erythema, Peeling, Burning, Pruritus, Perception of Oiliness
0	Completely cleared (no signs or symptoms of disease)	None (normal)
1	Almost cleared (approximately 90% improvement, with only traces of disease remaining)	Between none and mild
2	Marked improvement (approximately 75% improvement, with some disease remaining)	Mild (mild evidence)
3	Moderate improvement (approximately 50% improvement)	Between mild and moderate
4	Mild improvement (approximately 25% improvement, with significant disease remaining)	Moderate (noticeable evidence)
5	No change	Between moderate and marked
6	Exacerbation (worsening of signs or symptoms of disease)	Marked (distinctive evidence)
7	—	Between marked and severe
8	—	Severe (very distinctive evidence)

medications; known sensitivity to any ingredient in the test medications; pregnancy, nursing, or planning a pregnancy; not using a reliable contraceptive; or uncontrolled systemic disease.

Treatment Regimen—Patients were randomized to receive 1 of the following 5 treatment regimens for 12 weeks: once-daily tazarotene 0.1% gel, twice-daily clindamycin phosphate lotion, once-daily tazarotene 0.1% gel plus twice-daily benzoyl peroxide 4% gel, once-daily tazarotene 0.1% gel plus twice-daily erythromycin 3%/benzoyl peroxide 5% gel, or once-daily tazarotene 0.1% gel plus twice-daily clindamycin phosphate lotion.

Randomization and Masking Procedures—Subject medication kits containing sufficient study medication for the 12-week duration of the study were prepared using an electronic randomization scheme. Two sealed and coded kits for each of the 5 study regimens were sent to each study site (a total of 10 kits per site). Each patient was assessed by the

investigator and then assigned a sealed kit by the study nurse. The kits were assigned chronologically in order of study entry. The nurse checked the contents of the kit and, if the assigned treatment regimen included erythromycin/benzoyl peroxide, the nurse mixed the formulation before dispensing it to the patient.

Patient Evaluations—At the baseline visit, the investigators recorded demographic information and made an overall evaluation of the patient's acne. At baseline and at weeks 4, 8, and 12, the investigators evaluated the patients for noninflammatory lesion count (open and closed comedos on the right side of the face only, excluding the nose); inflammatory lesion count (papules plus pustules on the right side of the face only, excluding the nose); levels of dryness, erythema, peeling, burning, and pruritus; and perception of oiliness (Table 1). At weeks 4, 8, and 12, patients also were evaluated for global improvement from baseline. In addition,

Table 2.
Patient Demographics at Baseline

	Tazarotene Monotherapy (n=89)	Cilindamycin Monotherapy (n=85)	Tazarotene + Benzoyl Peroxide (n=89)	Tazarotene + Erythromycin/Benzoyl Peroxide (n=90)	Tazarotene + Clindamycin (n=87)	Between-Group Significant Difference
Age, mean±SD, y	20±9	21±9	21±9	22±10	22±9	—
Female	53%	61%	57%	53%	55%	—
White, n (%)	74 (83)	69 (81)	74 (83)	74 (82)	69 (79)	—
Overall evaluation of facial acne vulgaris score,* mean±SD	3.3±0.9	3.0±0.9	3.3±0.9	3.3±0.8	3.4±0.9	†
Duration of acne, n (%)		‡		§		—
<1 y	10 (11)	8 (10)	11 (12)	9 (10)	13 (15)	
1-2 y	34 (38)	28 (33)	29 (33)	29 (33)	30 (34)	
3-5 y	24 (27)	26 (31)	27 (30)	24 (27)	28 (32)	
6-10 y	11 (12)	13 (15)	15 (17)	11 (12)	8 (9)	
>10 y	10 (11)	9 (11)	7 (8)	16 (18)	8 (9)	
Open and closed comedos, mean±SD	23±27	15±14	21±20	21±22	22±20	
Papules plus pustules, mean±SD	9±8	9±9	9±8	10±10	10±11	—

*Grading scale: 0=none (normal), 2=mild (slightly noticeable), 4=moderate (noticeable), 6=severe (very distinctive).
 †Clindamycin monotherapy significantly lower than tazarotene monotherapy (P≤.02), tazarotene plus benzoyl peroxide (P≤.05), tazarotene plus erythromycin/benzoyl peroxide (P≤.03), and tazarotene plus clindamycin (P≤.02), using the Fisher exact test to compare pairs of treatments.
 ‡n=84 because of missing data.
 §n=89 because of missing data.
 ||On right side of the face only, excluding the nose.
 ||Clindamycin monotherapy significantly lower than tazarotene monotherapy (P≤.01) and tazarotene plus clindamycin (P≤.03), using the Fisher exact test to compare pairs of treatments.

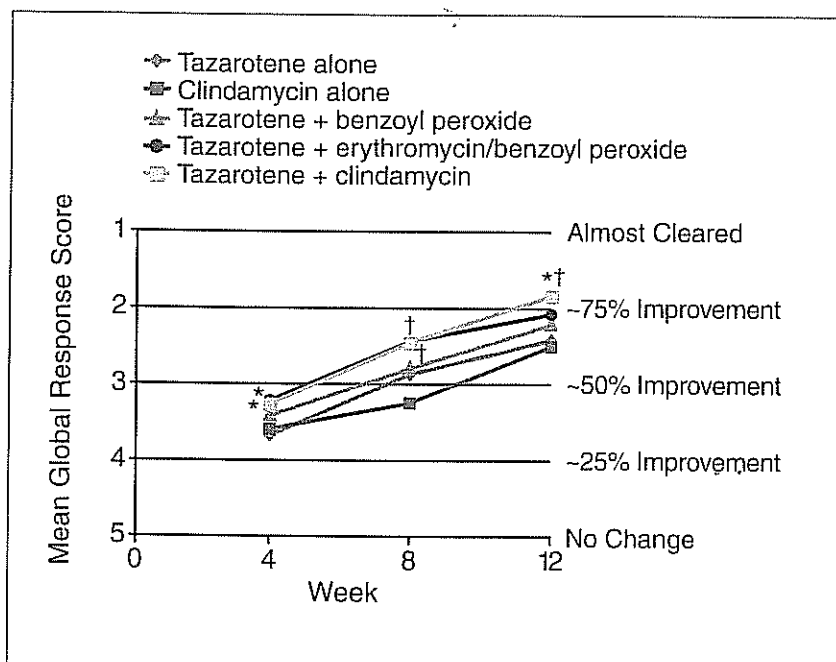


Figure 1. Global response to treatment. Asterisk indicates $P < .05$ vs tazarotene monotherapy; dagger, $P < .05$ vs clindamycin monotherapy. For clarity, figure does not depict any significant differences that may or may not be present between any 2 of the combination regimens.

patients rated their study medication for overall impression (using ratings of highly favorable, favorable, neutral, unfavorable, or highly unfavorable) and efficacy compared with other medications used for acne in the past (using ratings of more effective, as effective, or less effective).

Statistical Analysis—Between-group comparisons of baseline demographics were analyzed using the t test for continuous variables and the χ^2 test for categorical variables. Between-group comparisons of the efficacy outcome measures were analyzed using analysis of variance (for global response scores; baseline lesion counts; and baseline scores for dryness, erythema, peeling, burning, pruritus, and perception of oiliness), likelihood ratio χ^2 (for incidence of treatment success), Wilcoxon rank sum test (for postbaseline lesion counts), or analysis of covariance with the baseline value as the covariate (for postbaseline levels of dryness, erythema, peeling, burning, pruritus, and perception of oiliness). Patient assessments (of the effectiveness of the study medication in relation to previously tried treatments and their overall impression of the study medication) and the incidence of adverse effects and discontinuations were analyzed using the Fisher exact test to compare pairs of treatments. All tests were 2 sided, and a P value of $\leq .05$ was considered statistically significant.

Results

Patient Demographics—Of the 440 patients enrolled and evaluated for demographics, 397 (90%) had data beyond the baseline visit and 311 (71%) com-

pleted the week 12 visit. Baseline demographic details showed that the patients had a mean age of 22 years and a mean of 21 noninflammatory lesions and 9 papules plus pustules. The female-male distribution ratio was 56%:44%. Demographic details according to each treatment group are outlined in Table 2. Generally, baseline demographics were comparable among treatment groups, though the evaluation of facial acne vulgaris was significantly lower in the clindamycin monotherapy group than in all of the other groups, and the comedo count was significantly lower in the clindamycin group than in the tazarotene monotherapy and tazarotene plus clindamycin groups.

Efficacy—The greatest levels of global improvement were achieved with tazarotene plus clindamycin and with tazarotene plus erythromycin/benzoyl peroxide (which achieved a mean global improvement of approximately 77% and 73% at the end of treatment, respectively)(Figure 1). Compared with tazarotene monotherapy, tazarotene plus clindamycin resulted in significantly greater global improvement at weeks 4 and 12, and tazarotene plus erythromycin/benzoyl peroxide resulted in significantly greater global improvement at week 4. Both combinations also achieved significantly greater global improvement than clindamycin monotherapy at weeks 8 and/or 12.

The incidence of treatment success—defined as 75% to 100% clearing of facial acne by week 12—was significantly greater with tazarotene plus clindamycin than with any of the other regimens (67% vs 38%–49%; $P < .05$).

Figure 2. Percentage mean reduction in noninflammatory lesion count (open and closed comedos). Asterisk indicates $P < .05$ vs tazarotene monotherapy; dagger, $P < .05$ vs clindamycin monotherapy. For clarity, figure does not depict any significant differences that may or may not be present between any 2 of the combination regimens.

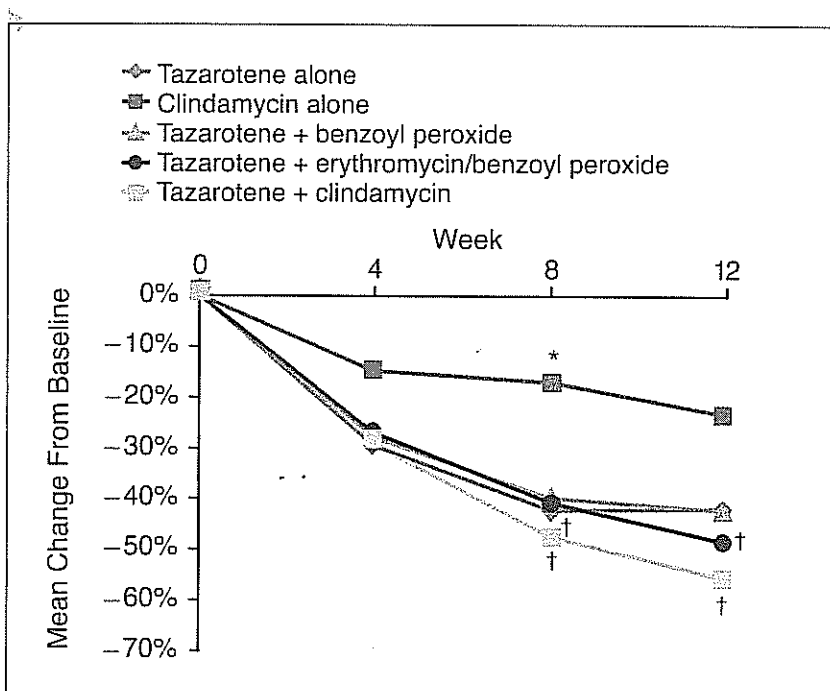
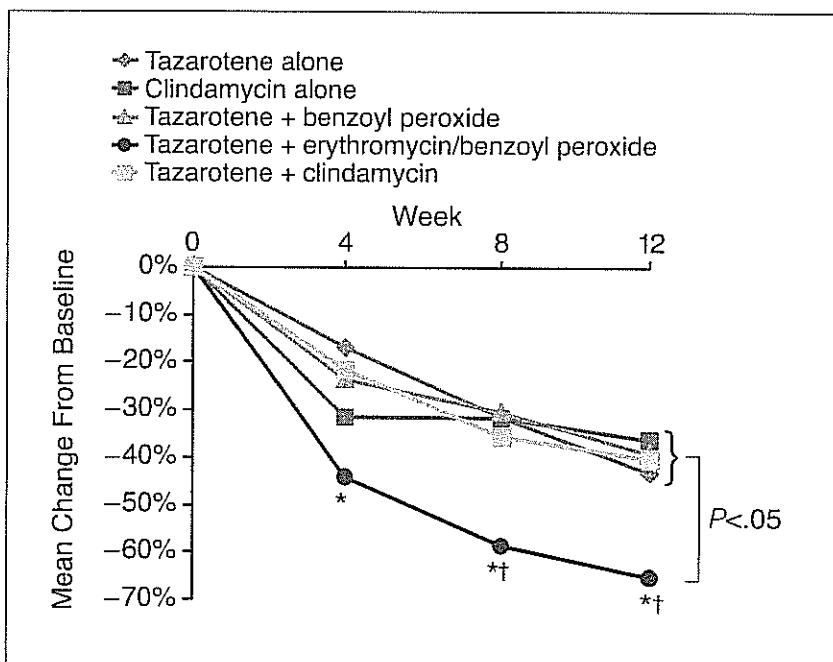


Figure 3. Percentage mean reduction in inflammatory lesion count (papules plus pustules). Asterisk indicates $P < .05$ vs tazarotene monotherapy; dagger, $P < .05$ vs clindamycin monotherapy. For clarity, figure does not depict any significant differences that may or may not be present between any 2 of the combination regimens.



For efficacy against noninflammatory lesions, the most effective regimens were tazarotene plus clindamycin and tazarotene plus erythromycin/benzoyl peroxide, though these were not significantly more efficacious than tazarotene monotherapy (Figure 2). All the tazarotene regimens (including tazarotene monotherapy) appeared to be more effective than clindamycin monotherapy, though significance was achieved only for the

tazarotene plus clindamycin and tazarotene plus erythromycin/benzoyl peroxide regimens at weeks 8 and 12 ($P < .05$). For efficacy against inflammatory lesions, tazarotene plus erythromycin/benzoyl peroxide was significantly more effective than all other regimens ($P \leq .05$, Figure 3).

Patient Evaluations—The highest percentages of patients who had a favorable or highly favorable overall impression of their study medication, and who

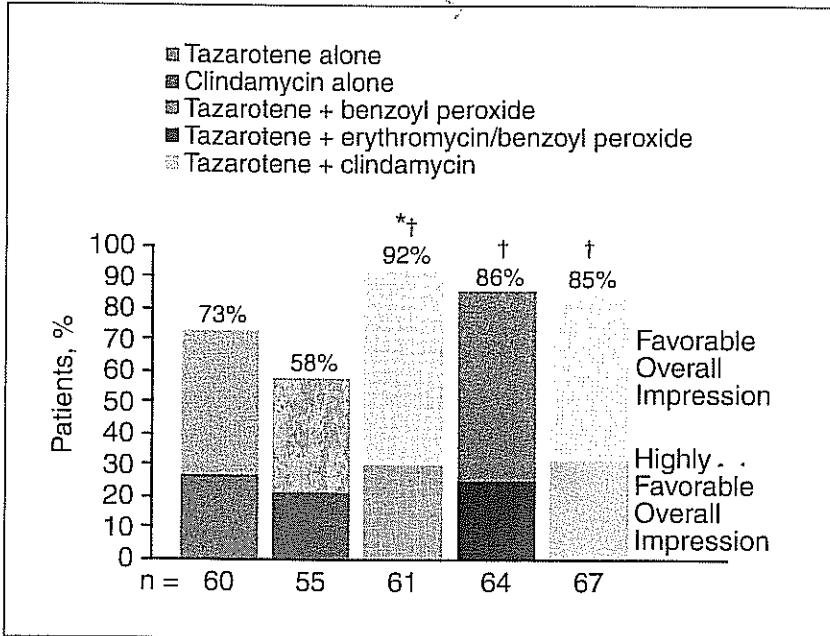


Figure 4. Percentage of patients who had a favorable or highly favorable overall impression of their study medication at the end of the treatment period. Asterisk indicates $P < .05$ vs tazarotene monotherapy; dagger, $P < .05$ vs clindamycin monotherapy. For clarity, figure does not depict any significant differences that may or may not be present between any 2 of the combination regimens.

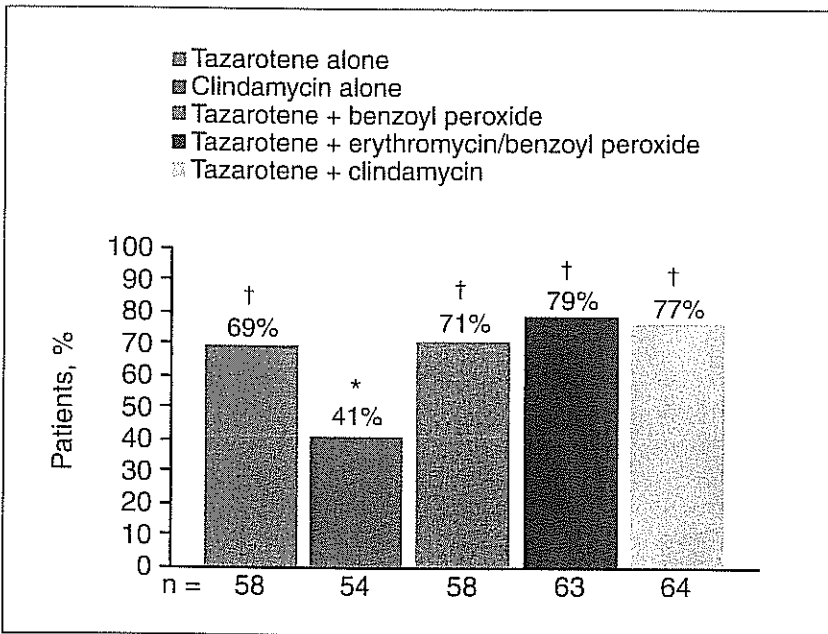


Figure 5. Percentage of patients who considered their study medication to be more effective than other antiacne medications tried previously. Asterisk indicates $P < .05$ vs tazarotene monotherapy; dagger, $P < .05$ vs clindamycin monotherapy. For clarity, figure does not depict any significant differences that may or may not be present between any 2 of the combination regimens.

rated their study medication as more effective than the previous treatments they had tried, occurred with the 3 combination regimens (Figures 4 and 5).

Tolerability—All regimens except clindamycin monotherapy were associated with transient increases in levels of dryness, erythema, peeling, burning, and pruritus (Figure 6, A through E). However, mean maximum levels were generally no worse than mild, and thus, the changes in these parameters were of minimal clinical significance. All regimens resulted in similar reductions in perception of oili-

ness at the end of treatment, with tazarotene plus erythromycin/benzoyl peroxide resulting in a statistically significantly greater reduction than tazarotene monotherapy at week 4 (Figure 6F).

The incidence of adverse effects probably or definitely related to treatment was significantly greater with tazarotene plus erythromycin/benzoyl peroxide and tazarotene monotherapy compared with clindamycin monotherapy (Table 3). There were no other significant between-group differences. Overall, the most common adverse effects were

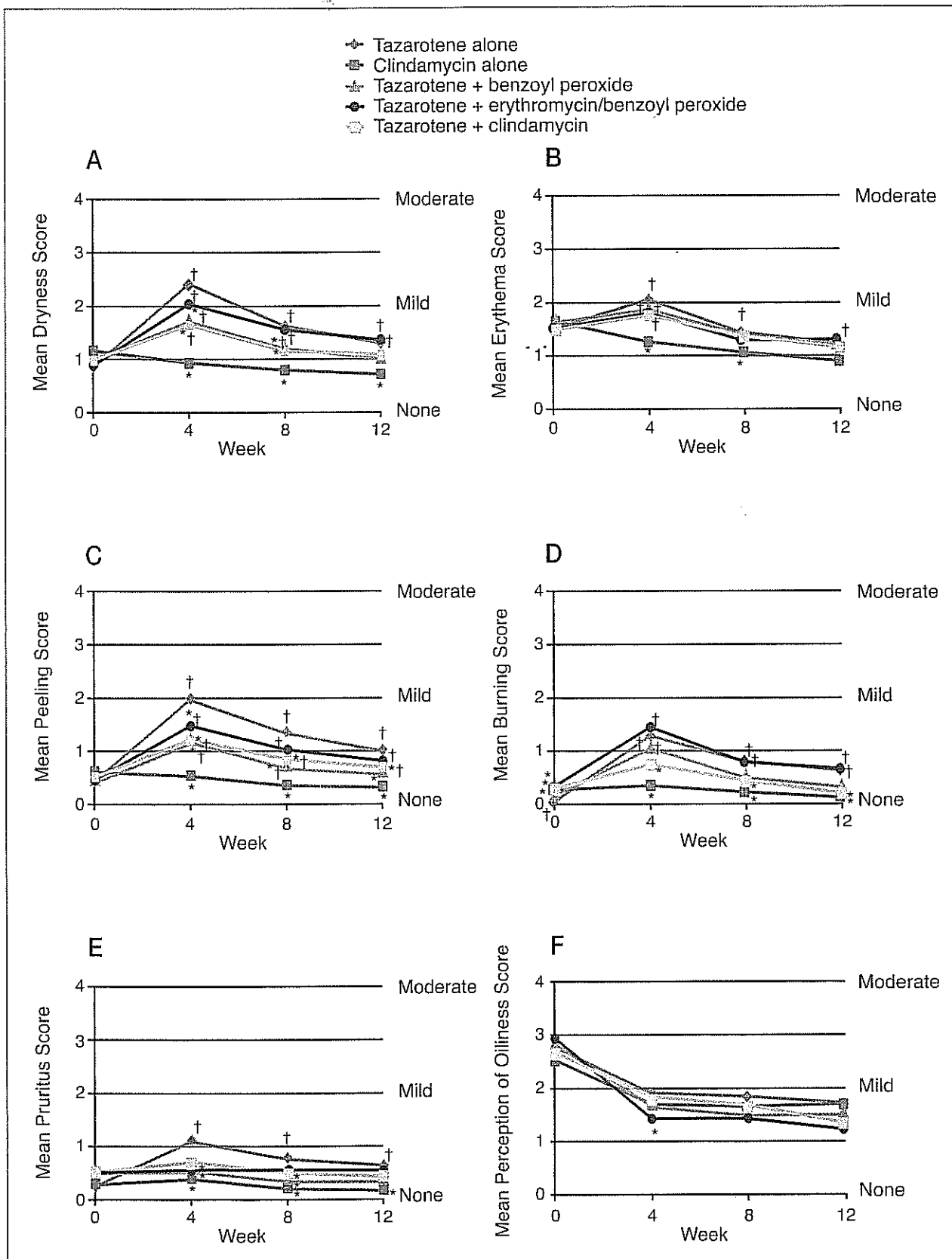


Figure 6. Mean levels of dryness (A), erythema (B), peeling (C), burning (D), pruritus (E), and perception of oiliness (F). Asterisk indicates $P < .05$ vs tazarotene monotherapy; dagger, $P < .05$ vs clindamycin monotherapy. For clarity, figure does not depict any significant differences that may or may not be present between any 2 of the combination regimens.

Table 3.

Incidence of Treatment-Related Adverse Effects and Treatment-Related Patient Discontinuations

Treatment	Incidence of Treatment-Related* Adverse Effects n/N (%)	Incidence of Treatment-Related Discontinuations, n/N† (%)		
		Due to Adverse Effects	Due to Lack of Efficacy	Total (Due to Adverse Effects or Lack of Efficacy)
Tazarotene + erythromycin/benzoyl peroxide	15/90 (17)‡	5/88 (6)	1/88 (1)‡	6/88 (7)
Tazarotene monotherapy	14/89 (16)‡	10/87 (11)	3/87 (3)	13/87 (15)
Tazarotene + clindamycin	9/87 (10)	4/85 (5)	0/85 (0)‡	4/85 (5)
Tazarotene + benzoyl peroxide	8/89 (9)	6/86 (7)	5/86 (6)	11/86 (13)
Clindamycin monotherapy	2/85 (2)	2/83 (2)	7/83 (8)	9/83 (11)

*Probably or definitely treatment related.

†N is less here than in previous column because exit forms were not completed for all patients.

‡ $P \leq 0.05$ vs clindamycin monotherapy, using Fisher exact test to compare pairs of treatments.

erythema (5%), burning (5%), peeling (3%), dryness (3%), irritation (3%), and pruritus (2%).

Patient Discontinuations—The incidence of all treatment-related discontinuations (ie, those due to adverse effects or lack of efficacy) ranged from 5% with tazarotene plus clindamycin to 15% with tazarotene monotherapy (Table 3). The only significant between-group difference was a lower incidence of discontinuation due to lack of efficacy only with tazarotene plus clindamycin and tazarotene plus erythromycin/benzoyl peroxide compared with clindamycin monotherapy.

Comment

All tazarotene regimens (including tazarotene monotherapy) were similarly effective in reducing the noninflammatory lesion count. It is not surprising that the adjunctive use of benzoyl peroxide and/or an antibiotic did not result in any significant enhancement in the reduction of the noninflammatory lesion count, as topical retinoids are considered highly effective in treating noninflammatory acne.

Both benzoyl peroxide and topical antibiotics are antibacterial and more appropriate for the treatment of inflammatory lesions. Indeed, the adjunctive use of erythromycin/benzoyl peroxide with tazarotene was significantly more effective than tazarotene monotherapy. Erythromycin/benzoyl peroxide and tazarotene are both effective against inflammatory lesions, and their different mechanisms of action appear to optimize efficacy when used in conjunction with one another.

Although at baseline the clindamycin monotherapy group showed a significantly lower score for overall evaluation of acne and a significantly lower noninflammatory lesion count compared with some of the other groups, presentation of the efficacy results as a percentage change from baseline (as has been done here) should negate any possible influence this may have had on the results. Overall, clindamycin was the least efficacious regimen but also the best tolerated. Mean levels of dryness, erythema, peeling, burning, and pruritus tended to be greatest with tazarotene monotherapy

Table 4.

Optimizing the Use of Tazarotene in Facial Acne Vulgaris

Regimens to Optimize Efficacy

For optimal global improvement, tazarotene plus clindamycin

For optimal reduction in noninflammatory acne, any of the tazarotene regimens (monotherapy or combination)

For optimal reduction in inflammatory acne, tazarotene plus erythromycin/benzoyl peroxide

Suggestions to Optimize Tolerability

Cleanse using only a mild nonsoap cleanser

Use a moisturizer as needed

Avoid peeling agents, abrasives, astringents, and other drying agents

Initiate tazarotene treatment with alternate-day dosing

Use tazarotene sparingly (spread pea-sized amount in thin film across face)

or tazarotene plus erythromycin/benzoyl peroxide but were lower when clindamycin was used in conjunction with tazarotene, and lowest of all with clindamycin monotherapy (Figure 6). Although the levels of these parameters were of minimal clinical significance (as mean maximum levels were generally no more severe than mild), the incidences of treatment-related adverse effects showed a similar ranking of the regimens for tolerability. The highest incidence was seen with tazarotene plus erythromycin/benzoyl peroxide (17%), followed by tazarotene monotherapy (16%), tazarotene plus clindamycin (10%), tazarotene plus benzoyl peroxide (9%), and clindamycin monotherapy (2%)(Table 3). Again, the adjunctive use of clindamycin reduced the incidence of treatment-related adverse effects compared with tazarotene monotherapy.

Overall, the results of this study suggest that the adjunctive use of tazarotene plus clindamycin can achieve a significantly greater global improvement than tazarotene monotherapy, that erythromycin/benzoyl peroxide can enhance the efficacy of tazarotene against inflammatory lesions, and that the adjunctive use of benzoyl peroxide with tazarotene does not appear to offer any efficacy advantage.

It may take some degree of experimentation with different combinations of agents at different dosages to determine the optimal regimen for an

individual patient. The tolerability of tazarotene can be optimized in all patients not only through combination therapy but also through a variety of treatment management approaches (Table 4). For example, a gentle skin care regimen is important to minimize dryness and irritation. Thus, the face should be cleansed gently using only a mild nonsoap cleanser, and a moisturizer should be used as needed. Peeling agents, abrasives, astringents, and other drying agents should be avoided. Equally important, particularly when initiating tazarotene treatment in patients with sensitive skin, is to apply the medication on alternate days for the first few days before introducing once-daily treatment, as tolerated. Finally, the medication should be used sparingly—a pea-sized amount is sufficient and can be spread in a thin film across the entire face. By following these recommendations to optimize tolerability, it is likely that compliance and therefore efficacy also will be optimal.

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