TAZAROTENE VERSUS TAZAROTENE PLUS CLINDAMYCIN/BENZOYL PEROXIDE IN THE TREATMENT OF ACNE VULGARIS: A MULTICENTER, DOUBLE-BLIND, RANDOMIZED, PARALLEL-GROUP TRIAL

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Abstract

Topical retinoids offer highly effective treatment for both inflammatory and non-inflammatory acne, with tazarotene demonstrating greater efficacy than other topical retinoids. A multicenter, double-blind, randomized, parallel-group trial has been performed to evaluate whether the adjunctive use of clindamycin/benzoyl peroxide could enhance the efficacy of tazarotene still further. Patients with moderate to severe inflammatory acne applied tazarotene 0.1% cream each evening and were randomly assigned to morning applications of vehicle gel or a ready-to-dispense formulation of clindamycin 1%/benzoyl peroxide 5% gel containing 2 emollients. Tazarotene/clindamycin/benzoyl peroxide achieved a significantly greater reduction in comedo count than tazarotene monotherapy and, among patients with a baseline papule plus pustule count of ≥25 (the median value), a significantly greater reduction in inflammatory lesion count. The combination therapy was also at least as well-tolerated as tazarotene monotherapy. The adjunctive use of clindamycin/benzoyl peroxide gel with tazarotene cream promotes greater efficacy and may also enhance tolerability. Any improvements in tolerability could be due to the emollients in the clindamycin/benzoyl gel formulation.

Introduction

Due to their ability to inhibit the development of microcomedos—which are the precursors of all other acne lesions—topical retinoids such as tazarotene are recommended as first-line therapy not only for most cases of comedonal acne but also for mild to moderate inflammatory acne.[1,2] Topical retinoids are thought to act primarily by helping to normalize abnormal desquamation of follicular epithelium in the infrainfundibular portion of the pilosebaceous unit. This facilitates the drainage of not only comedos but also microcomedos—and thus helps to prevent the subsequent development of both inflammatory and non-inflammatory acne lesions. The comedolytic action of topical retinoids also helps to normalize the follicular microenvironment making it less favorable for the proliferation of *Propionibacterium acnes (P. acnes)*. Furthermore, topical retinoids have been reported to have direct immunomodulatory effects that may also contribute to their efficacy against inflammatory acne lesions—including inhibition of the expression of toll-like receptor 2[3] and the stimulation of interleukin-5 release and inhibition of interferon-γ release by superantigen-stimulated human peripheral blood mononuclear cells.[4] Finally, by thinning the stratum corneum, topical retinoids may also enhance the follicular penetration of other agents[1,5]—suggesting that they may even help enhance the efficacy of adjunctive therapies used in combination regimens.

Tazarotene has been shown to offer greater efficacy than other topical retinoids.[6-9] However, it may be possible to enhance its efficacy still further through the adjunctive use of other agents that have different mechanisms of action—for example, antibiotics and benzoyl peroxide. These agents primarily have antibacterial and anti-inflammatory activity and it is thought that their antibacterial action also helps limit the release of comedogenic products from *P. acnes*[5]—benzoyl peroxide in particular has been reported to have comedolytic activity.[1,10,11] As a result, combination antibiotic/benzoyl peroxide products (such as clindamycin/benzoyl peroxide) offer efficacy against both inflammatory and non-inflammatory acne lesions.[12,13] Furthermore, they can also help prevent the development of antibiotic resistance and offer significant clinical improvement among patients who have already developed antibiotic resistance.[11]

With these complementary actions, it might be anticipated that the adjunctive use of clindamycin/benzoyl peroxide with tazarotene treatment could offer greater clinical benefit than tazarotene alone. To investigate this, a multicenter, double-blind, randomized, parallel-group study has been performed.

Methods

Patients

Patients were eligible for enrollment if they were at least 12 years of age and had stable moderate to severe facial inflammatory acne vulgaris (defined as 15-60 papules plus pustules, 10-100 comedos, and no more than 2 nodulocystic lesions with a maximum diameter of 5 mm).

Exclusion criteria included patients with acne known to be resistant to oral antibiotics and females who were pregnant, breastfeeding, or of childbearing potential and not using reliable contraception. In addition, the following washout

periods were required: 2 weeks for topical acne medications, 30 days for systemic antibiotics and investigational drugs, 12 weeks for estrogens/birth control pills if previously used for less than 12 weeks, and 6 months for oral retinoids.

Treatment Regimen

All patients were instructed to apply tazarotene 0.1% cream to their face each evening for 12 weeks. In addition, patients were randomly assigned to adjunctive treatment with either vehicle gel or clindamycin 1%/benzoyl peroxide 5% gel (a ready-to-dispense formulation containing 2 emollients) each morning.

Before applying their study medication patients were requested to wash their face with a non-soap cleanser (Oilatum®-AD, Stiefel Laboratories, Inc., Coral Gables, Florida), to pat it dry with a soft towel and, if needed, to apply a moisturizer (M.D. Forté® Replenish Hydrating Cream, Allergan, Inc., Irvine, California). They were instructed to then apply a pea-sized amount of their study medication in a thin film to cover their entire face—for the morning application this was immediately after washing and for the evening application this was 15-20 minutes after washing. (The medications were applied at different times of the day in order to prevent any possibility of interactions occurring between them.) Patients were not permitted to use any other lotions, creams, medicated powders, or solutions on their face.

Outcome Measures

Investigators evaluated the following outcome measures in each patient every 4 weeks: open plus closed comedo count, papule plus pustule count, global response to treatment, pruritus, peeling, erythema, burning, and dryness. The global response to treatment was rated as one of the following: 100% improvement, ~90% improvement, ~75% improvement, ~50% improvement, ~25% improvement, no change, and worsening. Treatment success was defined as ≥50 % global improvement. Pruritus, peeling, erythema, burning, and dryness were rated on a scale of none, trace, mild, moderate, severe, and very severe. Additional details on the grading definitions of many of these parameters have been published previously.[6]

Patients rated their overall impression of the study medications as highly favorable, favorable, unfavorable, or highly unfavorable.

Statistical Analyses

All statistical tests were 2-sided and interpreted at a 5% significance level. Assuming a power of 80% and a 10% drop-out rate it was calculated that, in order to detect a clinically significant between-group difference of 20% in the incidence of treatment success (ie, ≥50% global improvement), a total sample size of 120 patients (60 in each treatment group) was necessary.

Between-group differences were evaluated by the following tests: patient age by a t-test; race, gender, and the incidence of patients with ≥50%, ≥75%, or ≥90% global improvement by a chi-square test or Fisher's exact test; median percent change from baseline in lesion count by rank analysis of covariance with the baseline value as the covariate; patient's impression of their study medication by the Fisher's exact test; and the incidence of adverse events and the distribution of grades for pruritus, peeling, erythema, burning, and dryness by a chi-square or Fisher's exact test.

Results

Patients

Of 121 patients evaluated, 50/61 (82%) in the tazarotene group and 52/60 (87%) in the tazarotene/clindamycin/benzoyl peroxide group completed. No patients discontinued due to adverse events or lack of efficacy.

Patients had a mean age of 20 years and were predominantly Caucasian (63%) and female (60%). There were no significant between-group differences in the patients' ages, race, or gender.

Efficacy

Both regimens were highly effective (Figures 1 and 2). Treatment with tazarotene plus clindamycin/benzoyl peroxide resulted in a significantly superior reduction in open plus closed comedos relative to tazarotene alone from week 4 onward—a median reduction of 34% versus 18% at week 4 and 70% versus 60% at week 12 ($P \leq .01$; Figure 3).

Tazarotene plus clindamycin/benzoyl peroxide also resulted in a greater reduction in papule plus pustule count than tazarotene alone, with this difference approaching statistical significance from weeks 8 to 12—a median reduction of 30% versus 22% at week 4 and 63% versus 58% at week 12 (Figure 4). A subanalysis of patients whose papule plus pustule count was greater than or equal to the median value (25) showed that tazarotene plus clindamycin/benzoyl peroxide achieved a significantly greater reduction in papule plus pustule count than tazarotene alone (63% vs. 52% at week 12; $P \leq .01$) (Figure 5).

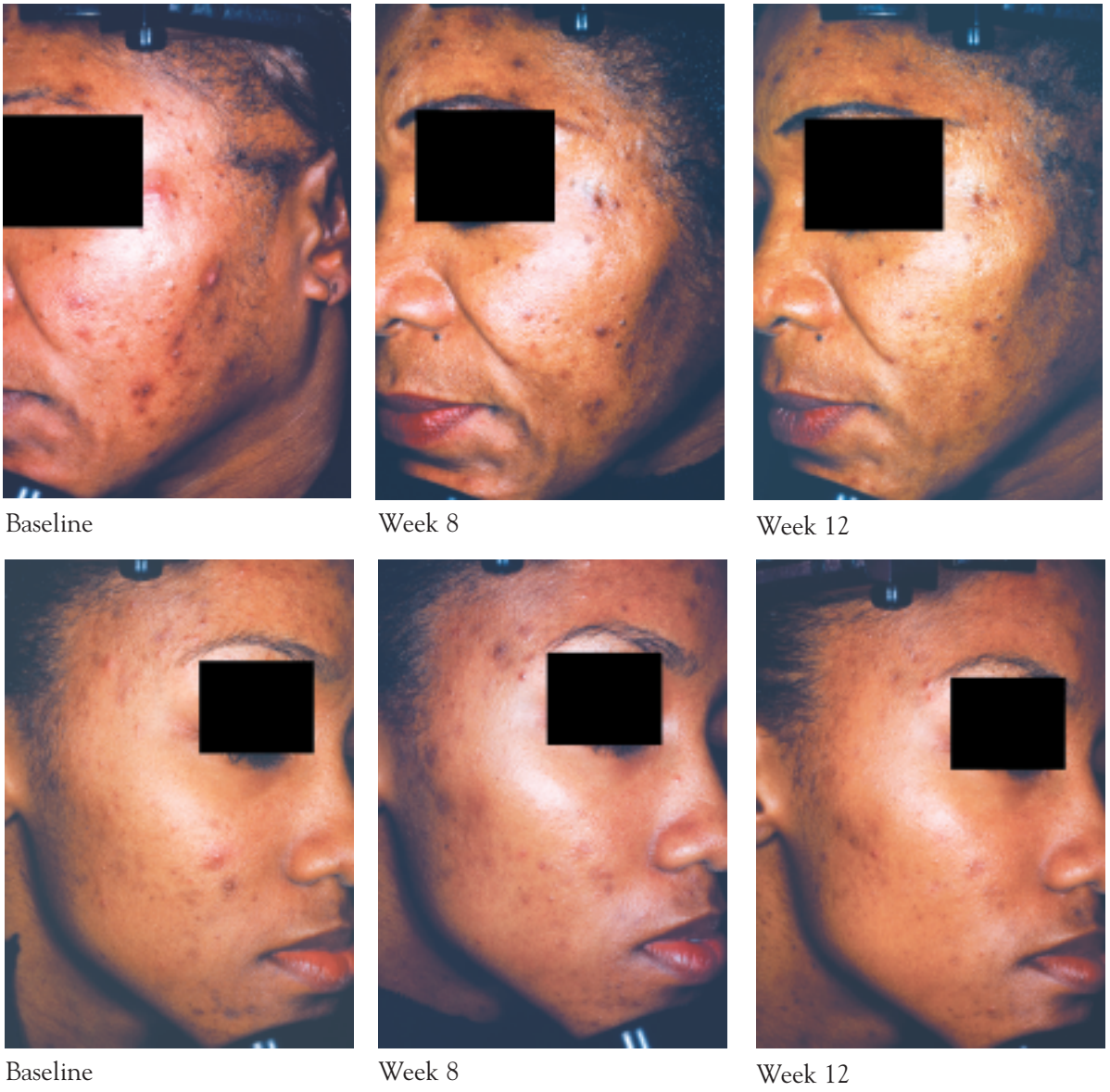
The percentages of patients achieving ≥50% improvement, ≥75% improvement, or ≥90% improvement at week 12 were slightly—though not significantly—higher with combination therapy than with monotherapy (Figure 6). These trends were also evident at earlier time points. For example, at week 8, ≥50% improvement was achieved in 72% of patients on combination therapy versus 63% on monotherapy, ≥75% improvement was achieved in 40% versus 24%, and ≥90% improvement was achieved in 9% versus 6%. At week 4, the trend was evident only in terms of ≥50% improvement (32% on combination therapy versus 24% on monotherapy) with identical incidences of patients achieving ≥75% improvement (9% versus 9%) and ≥90% improvement (0% versus 0%).

Tolerability

Both regimens were well-tolerated, with a lower incidence of peeling and dryness with the combination regimen than with tazarotene cream alone (10% vs. 18% and 8% vs. 12%, respectively; Table 1). However, these differences were not statistically significant.

There were no significant between-group differences in the distribution of grades for pruritus, erythema, burning, or dryness. However, there was a significant between-group

Figure 1. Improvement in Acne within the First Few Weeks of Treatment with Tazarotene Monotherapy.



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difference in the distribution of grades for peeling at week 4, with the combination regimen being associated with milder grades overall—the percentage of patients with a "none" or "trace" grade for peeling at this time point was 57% in the tazarotene group and 67% in the tazarotene plus clindamycin/benzoyl peroxide group.

Overall Impression

The percentage of patients with a favorable or highly favorable overall impression of their study medication at week 12 was comparable in both groups (90% with tazarotene alone and 94% with tazarotene plus clindamycin/benzoyl peroxide).

Discussion

It is already well documented that tazarotene offers efficacy against both non-inflammatory and inflammatory acne lesions. The results of this study confirm this and, in addition, demonstrate that the adjunctive use of a ready-to-dispense formulation of clindamycin/benzoyl peroxide gel containing 2 emollients can further enhance efficacy, and possibly tolerability. Efficacy was significantly enhanced against open plus closed comedos and, in patients with at least the median number of inflammatory lesions at baseline, against papules plus pustules. In addition to increasing efficacy, the combination regimen also promoted more rapid clinical improvement against comedos. Thus, the different mechanisms of action of clindamycin and benzoyl peroxide

Figure 2. Improvement in Acne within the First Few Weeks of Treatment with Tazarotene plus Clindamycin/Benzoyl Peroxide.

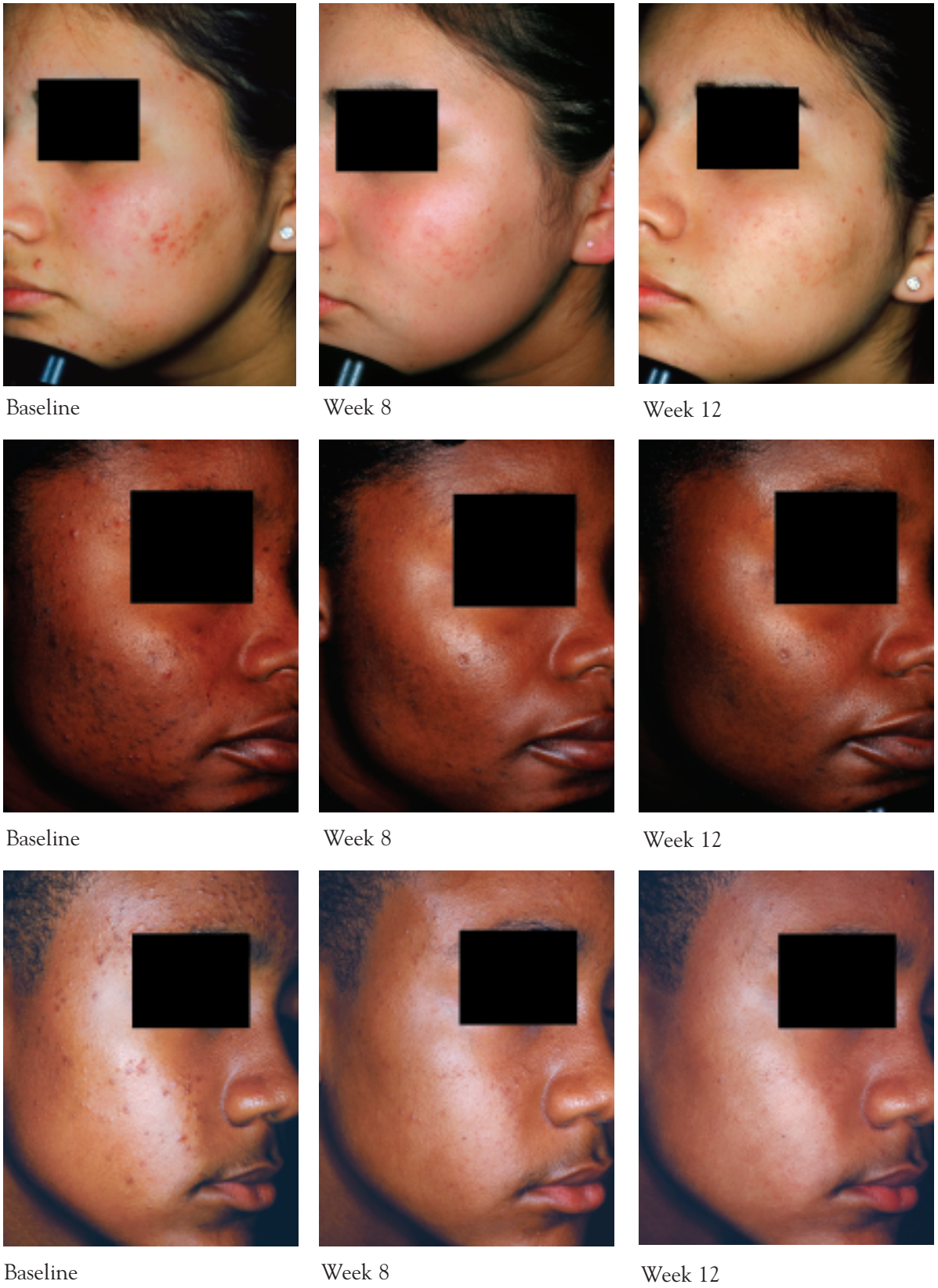

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Figure 3. Median Percentage Reduction in Comedo Count.

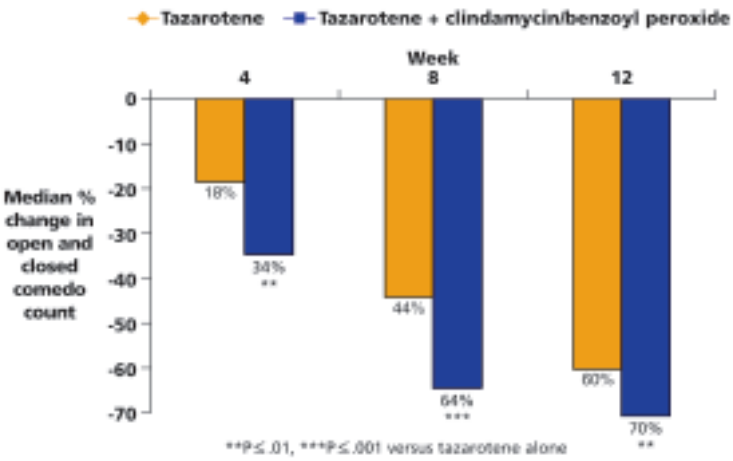


Figure 4. Median Percentage Reduction in Papule plus Pustule Count.

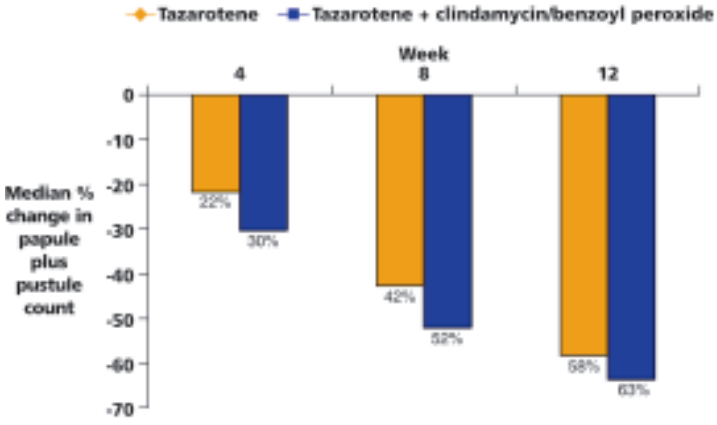


Figure 5. Median Percentage Reduction in Papule plus Pustule Count among Patients whose Baseline Papule plus Pustule Count was Greater than or Equal to the Median Value (25).

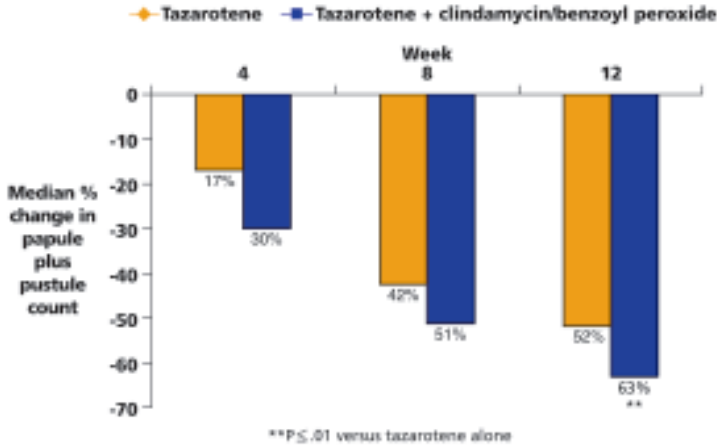
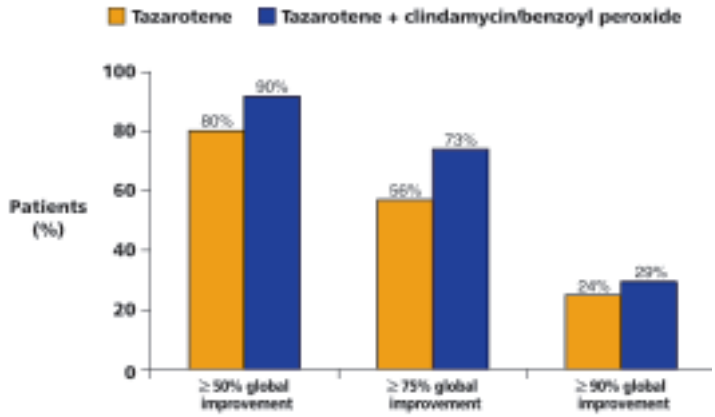


Figure 6. Incidence of Patients with ≥50% Improvement, ≥75% Improvement, or ≥90% Improvement at Week 12.



appear to be complementary to those of tazarotene and result in additional clinical benefit.

The finding that the combination regimen was associated with milder grades of peeling at week 4 than monotherapy is important because the period of retinization (the first few weeks of topical retinoid therapy when the skin is accommodating to the retinoid) is the most likely time for local skin irritation to develop. So, if the potential for peeling can be reduced at this time, patients are presumably more likely to be satisfied with their treatment. Although the differences in the incidence of peeling and dryness were not statistically significant, this study was not designed to detect significant between-group differences in these parameters—as a result, it is possible that significance might be detected in a larger study.

Possible improvements in tolerability have been reported previously when topical retinoids are used in combination therapy rather than as monotherapy. In a study in which erythromycin/benzoyl peroxide was used adjunctively with tazarotene gel, the incidence of discontinuations due to adverse events was lower with tazarotene plus erythromycin/benzoyl peroxide (6%) than with tazarotene gel alone (11%).[14] Less irritation has also been reported when tretinoin is used in conjunction with benzoyl peroxide than when used alone.[15] Nevertheless, the presence of the emollients in the clindamycin/benzoyl peroxide formulation used in this study remains a likely explanation for any improvement in tolerability.

Conclusions

Tazarotene cream plus a ready-to-dispense formulation of clindamycin/benzoyl peroxide gel containing 2 emollients offers significantly greater efficacy than tazarotene cream alone. In addition, the combination regimen promotes more rapid clinical improvement against comedos and may enhance tolerability relative to tazarotene cream alone. It is possible that the emollients in the clindamycin/benzoyl peroxide formulation (dimethicone and glycerin) may help promote good tolerability.

Table 1. Patients with Adverse Events Probably or Definitely Related to Study Treatment.

Adverse events	Tazarotene alone (N = 61)	Tazarotene + clindamycin/benzoyl peroxide (N = 60)	Between-group significance
Peeling	11 (18%)	6 (10%)	NS
Burning	8 (13%)	8 (13%)	NS
Redness/erythema	7 (12%)	8 (13%)	NS
Dryness	7 (12%)	5 (8%)	NS
Facial discomfort	2 (3%)	3 (5%)	NS
Itching/pruritus	2 (3%)	3 (5%)	NS
Oiliness	1 (2%)	1 (2%)	NS
Facial irritation	0 (0%)	1 (2%)	NS

NS = not significant

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