Clinical Evidence for the Role of a Topical Anti-Inflammatory Agent in Comedonal Acne: Findings From a Randomized Study of Dapsone Gel 5% in Combination With Tazarotene Cream 0.1% in Patients With Acne Vulgaris

Emil Tanghetti MD,[a] Sunil Dhawan MD,[b] Lawrence Green MD,[c] Mark Ling MD PhD,[d] Jeanine Downie MD,[e] Marguerite A. Germain MD,[f] J. Scott Kasteler MD,[g] Leon Kircik MD,[h] Michael G. Oefelein MD,[i] Zoe Draelos MD[j]

[a]Center for Dermatology and Laser Surgery, Sacramento, CA
[b]Center for Dermatology, Cosmetic and Laser Surgery, Fremont, CA
[c]Department of Dermatology, George Washington University, Washington, DC
[d]MedaPhase, Inc., Newnan, GA
[e]Image Dermatology PC, Montclair, NJ
[f]Germain Dermatology, Mt. Pleasant, SC
[g]Division of Dermatology, University of Louisville, Louisville, KY
[h]Physicians Skin Care PLLC, Louisville, KY
[i]Allergan, Inc., Irvine, CA
[j]Department of Dermatology, Duke University School of Medicine, Durham, NC

ABSTRACT

Background: Acne pathogenesis is multifactorial and includes inflammation. Combining drugs targeting multiple components of acne pathogenesis is standard practice.

Objective: To assess the safety and efficacy of dapsone gel 5%, an anti-inflammatory agent, in combination with tazarotene cream 0.1% for treatment of acne vulgaris.

Methods: Patients were randomized to receive combination therapy (dapsone gel 5% twice-daily plus tazarotene cream 0.1% daily) or monotherapy (tazarotene cream 0.1% daily). Efficacy and safety data were collected after 1, 2, 4, 8, and 12 weeks of treatment.

Results: Patients in both arms (n=86, dapsone + tazarotene; n=85, tazarotene) showed significant reductions from baseline in inflammatory, noninflammatory and total lesion counts ($P<.001$ for all). At 12 weeks, patients treated with dapsone plus tazarotene showed a greater reduction from baseline in noninflammatory (comedonal) and total lesion counts than tazarotene-treated patients (noninflammatory, 59.7 percent vs. 46.5 percent, $P=.01$; total, 63.3% vs. 53.6%, $P=.02$). The percentage of patients achieving treatment success (an investigator subjective score of 0 [none] or 1 [minimal]) was greater in dapsone plus tazarotene–treated patients (42.2%) than in tazarotene-treated patients (21.8%;$P=.01$). Both treatments were well tolerated.

Conclusion: Combination therapy with dapsone gel 5% plus tazarotene cream 0.1% was more effective than tazarotene monotherapy for treatment of comedonal acne. The results suggest that anti-inflammatory agents such as dapsone can effectively treat early stages of acne (both comedonal and noncomedonal) when used in combination with a retinoid.

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INTRODUCTION

Acne, a common condition that can persist for years beyond adolescence,[1] may result in scarring and post-inflammatory hyperpigmentation (PIH).[2] The pathogenesis of acne is multifactorial and still not fully understood. Current dogma for acne pathogenesis suggests that follicular hyperkeratinization, abnormal epithelial desquamation and sebaceous gland hyperplasia lead to microcomedo formation. Continuous accumulation of sebum and deposition of keratinous material lead to development of lesions (open and closed comedones) traditionally classified as noninflammatory or, with proliferation of *Propionibacterium acnes* and induction of immunomodulatory events, inflammatory lesions.[3,4]

The current model for acne pathogenesis, which focuses on the role of *P. acnes* in inflammatory lesion development, has been brought into question based on accumulating evidence suggesting that inflammation is present throughout the development of acne lesions, even when not clinically apparent, from microcomedones to residual erythematous lesions and PIH.[5,6] The pro-inflammatory cytokines, interleukin (IL)-1α, IL-1β, and tumor necrosis factor (TNF)-α, have been found in open comedones.[7] Moreover, follicular IL-1α and IL-1RTII expression in uninvolved skin of patients with acne was found to be three-fold and thirty-fold higher, respectively, than corresponding levels in normal skin, despite a proliferative and differentiated state of the follicles in uninvolved skin of patients with acne that was histologically comparable to that of follicles in normal skin.[5] Thus, IL-1α from uninvolved follicles in skin of patients with acne has been proposed as an initiating factor for a nonspecific inflammatory response in the skin around the pilosebaceous follicle that occurs prior to, and not as a result of, hyperproliferative or aberrant differentiation events.[5] Early acne inflammation also appears to involve neutrophils, among other inflammatory cells and biochemical mediators of inflammation. Once present at the acne site, neutrophils can recruit additional neutrophils and generate reactive oxygen species that further damage tissue.[8-11] This novel concept raises the possibility that early subclinical inflammation may play a pathogenic role in the formation of not only visible inflammatory lesions, but also in the development of microcomedonal lesions heretofore considered "noninflammatory." This pathogenic model of acne in turn suggests that anti-inflammatory therapies may be suitable for treating both early comedonal as well as later inflammatory lesions in acne.

©Dapsone gel 5% (ACZONE™; Allergan, Inc, Irvine, CA) is a topical anti-acne medication with an anti-inflammatory mechanism of action. In two randomized studies involving more than 3,000 patients, dapsone gel 5% was found to be safe and effective for the treatment of acne vulgaris (both comedonal and noncomedonal acne).[12] With its anti-inflammatory mechanism of action and favorable tolerability profile, dapsone gel 5% seems well suited for use in combination with a retinoid for acne treatment. The purpose of this study was to assess the safety and efficacy of dapsone gel 5% co-administered with tazarotene cream 0.1% in patients with moderate-to-severe inflammatory and comedonal facial acne.

METHODS

Patients

Male or female patients at least 12 years of age with stable, non-rapidly progressing facial acne vulgaris were eligible for inclusion in the study. Facial acne vulgaris was characterized by the presence of 50 to 100 inflammatory lesions (papules, pustules), 25 to 100 facial noninflammatory lesions (open/closed comedones), and no more than three facial nodules and/or cysts of diameter ≥1 cm.

Patients with a skin disease or disorder that might interfere with the diagnosis or evaluation of acne vulgaris or who failed to comply with the protocol-specified wash-out periods for prohibited medications were excluded. Additional exclusion criteria were a history of clinically significant anemia or hemolysis and evidence of recent alcohol or drug abuse. Females of childbearing potential were required to use reliable methods of birth control. Patients with a history of poor cooperation or noncompliance with medical treatment or who failed to comply with specified procedures were also excluded.

Study Design

This was a 12-week, multicenter, single-blinded, randomized, parallel-group study. Patients were assigned 1:1 by computer randomization to receive dapsone gel 5% in the morning and evening plus tazarotene cream 0.1% in the evening, or tazarotene cream 0.1% in the evening alone for 12 weeks. Patients were provided with coded treatment kits and the treatment was self-administered. In the combination treatment arm, the evening application of dapsone gel 5% was applied before tazarotene cream 0.1%. Use of facial moisturizer and cleanser was restricted to those products supplied within the study.

Patient compliance with treatment was assessed verbally at each visit. Patients were asked by study personnnel whether any appliations of study medication were missed since the previous visit and their responses quantified.

Patients attended study visits at baseline and at weeks 1, 2, 4, 8, and 12 during treatment. The primary efficacy variable was the inflammatory lesion count at all time points, defined as the number of papules/pustules on the face only, from the hairline edge to the mandibular line.

Secondary efficacy variables were assessed at all time points and included noninflammatory and total (inflammatory + noninflammatory) lesion counts. In addition, four other investigator-completed assessments were conducted at baseline and at each clinic visit: investigator global assessment (IGA; also referred to as the global assessment of acne severity [GAAS]), overall disease severity, disease signs and symptoms, and PIH. The IGA was conducted using an ordinal scale ranging from zero to 4, where zero indicates no evidence of acne vulgaris, and 4 indicates a significant degree of inflammatory disease, a predominance of papules and pustules, and the possible presence of nodulo-cystic lesions and comedones. Overall disease severity (including size of lesions, overall degree of inflammation, general erythema and skin condition) was quantified using an ordinal rating scale ranging from zero to 6, where zero indicates no disease present (clear, no inflammatory lesions) and 6 indicates severe disease (numerous comedones, papules, and pustules with larger inflamed lesions extending over much of the face, and erythema may be pronounced). Disease signs and

TABLE 1.

Baseline Demographics and Disease Characteristics

	Tazarotene (n = 85)	Dapsone + Tazarotene (n = 86)	All Patients (N = 171)	P
Gender, n (%)				
Male	49 (57.6)	38 (44.2)	87 (50.9)	.0783
Female	36 (42.4)	48 (55.8)	84 (49.1)	
Age, y				
Mean ± SD	19.4 ± 6.5	20.2 ± 6.9	19.8 ± 6.7	.3678
Median (range)	16.7 (12.1-42.9)	17.8 (12.2-45.7)	17.2 (12.1-45.7)	
Race, n (%)				
White	48 (56.5)	52 (60.5)	100 (58.5)	.0649
Black	22 (25.9)	9 (10.5)	31 (18.1)	
Hispanic	3 (3.5)	8 (9.3)	11 (6.4)	
Asian	4 (4.7)	5 (5.8)	9 (5.3)	
Other	8 (9.4)	12 (14.0)	20 (11.7)	
Inflammatory lesions, mean ± SD	40.8 ± 12.9	38.9 ± 11.7	39.9 ± 12.3	.1564
Noninflammatory lesions, mean ± SD	46.5 ± 16.9	46.4 ± 17.4	46.5 ± 17.1	.7316
Total lesions, mean ± SD	87.3 ± 24.2	85.4 ± 22.3	86.3 ± 23.2	.5376
IGA score, mean ± SD	3.04 ± 0.36	2.93 ± 0.37	2.98 ± 0.37	.0619

symptoms relating to the current severity of erythema (disease related and/or related to retinoid use), dryness, peeling and oiliness were rated using an ordinal rating scale ranging from zero (no erythema or dryness, smooth skin, normal oiliness) to 4 (beet red erythema; easily noted dryness with accentuation of skin markings, skin desquamation, and/or fissure formation; extensive peeling and prominent oiliness). In addition, the degree of pruritus and burning was quantified using a numerical scale ranging from zero (normal, no discomfort) to 5 (definite, continuous discomfort interfering with normal daily activities). Distribution and severity of PIH was determined using one scoring system to assess the percentage of the face affected, ranging from zero (none) to 6 (>50%); and a second scale was used to quantify the severity of PIH ranging from zero (absent) to 5 (severe).

The safety of the study medication was assessed throughout the study by recording adverse events at each study visit.

Assessments were performed by investigators blind to the treatment assignment.

Statistical Analyses

It was calculated that 80 patients per treatment group (total sample size 160 patients) were required to yield 80 percent power to detect a difference of 15 percent in the primary outcome parameter, the percentage reduction of inflammatory lesions after 12 weeks of treatment, assuming a standard deviation of 31 percent in both groups and an approximate drop-out rate of 15 percent.

Statistical analyses were conducted on the intent-to-treat population, which included all enrolled subjects. All statistical tests were two-sided and interpreted at a 5% significance level. Descriptive statistics were calculated for all continuous variables, and frequencies for all categorical variables. Where the necessary assumptions for parametric tests were satisfied, comparisons were performed using analysis of covariance with the baseline value as the covariate. The Wilcoxon rank sum test was used if the necessary assumptions for parametric tests were not satisfied. Safety analyses were performed according to the incidence and severity of local tolerability, signs and symptoms, and adverse and/or unexpected events.

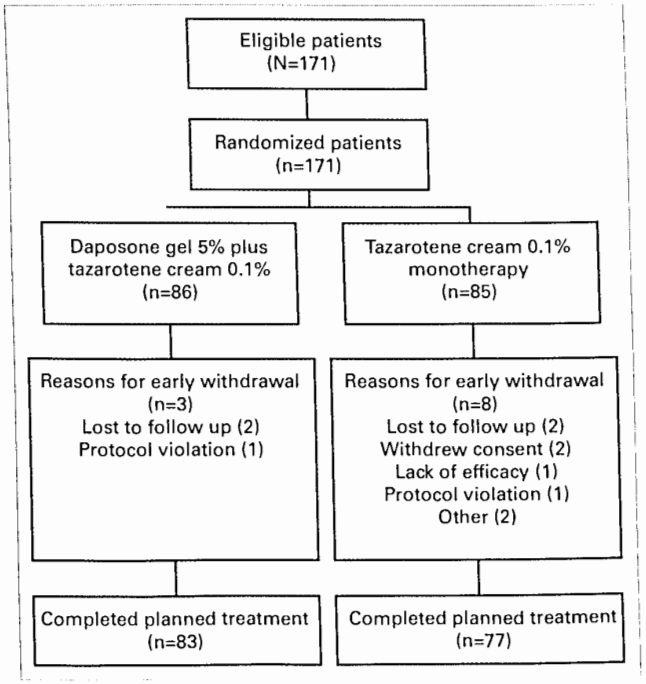
Missing data were imputed by the method of last observation carried forward (LOCF).

RESULTS

Patient Disposition and Demographics

One hundred seventy-one patients were enrolled in the study (Table 1). Treatment groups were generally similar with regard to baseline demographic characteristics; however, the proportion of female patients was higher in the combination arm compared with the monotherapy arm. Baseline lesion counts were similar between treatment arms. Mean baseline inflammatory and noninflammatory lesion counts were 40 and 47 in the overall study population, indicating that study patients had at least moderate acne. The median IGA score was 3.0, also consistent with a moderate acne severity designation.

FIGURE 1. Schematic profile of patient disposition.



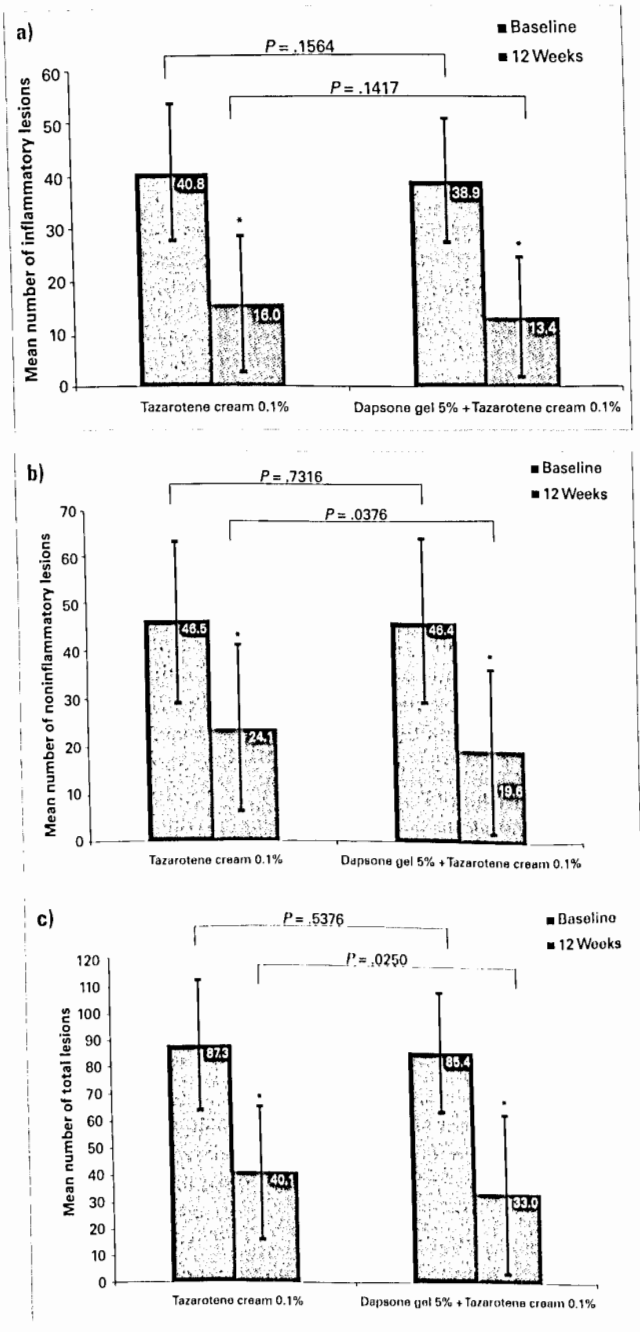
Of the 171 enrolled patients, 160 completed treatment and 11 withdrew early (Figure 1). Three patients receiving dapsone plus tazarotene and eight patients receiving tazarotene monotherapy withdrew prior to completion of the study. None of the withdrawals was due to adverse tolerability.

Inflammatory Lesion Count

There was a significant reduction in inflammatory lesion count compared with baseline in both treatment arms (Figure 2), and at week 12 the mean change from baseline count was −25.77 ± 11.23 lesions in the dapsone plus tazarotene group and −24.82 ± 14.06 lesions in the tazarotene monotherapy group ($P< .0001$ for both treatment groups vs. baseline). However, the magnitude of inflammatory lesion count reduction was not significantly different between the two treatment groups at any time point. At week 12, the mean percentage change from baseline inflammatory lesion count was 66.6 percent for the dapsone plus tazarotene combination therapy group versus 60.9 percent for the tazarotene monotherapy group ($P= 0.17$).

Despite the similarity in magnitude of response at week 12, the onset of effect with combination therapy occurred earlier than with tazarotene monotherapy. At week 2, significantly more patients receiving combination therapy than patients receiving monotherapy achieved a 50 percent reduction in inflammatory

FIGURE 2. Mean number of **a)** inflammatory, **b)** noninflammatory, and total **c)** lesions at baseline and at 12 weeks with tazarotene monotherapy or dapsone plus tazarotene combination therapy. Error bars represent standard deviations.



*$P<.0001$ compared with baseline value. Combination treatment resulted in a significantly greater reduction in noninflammatory ($P=.0376$) and total ($P=.0250$) lesion numbers; however, inflammatory lesions were reduced to a similar extent in both treatment arms ($P>.05$).

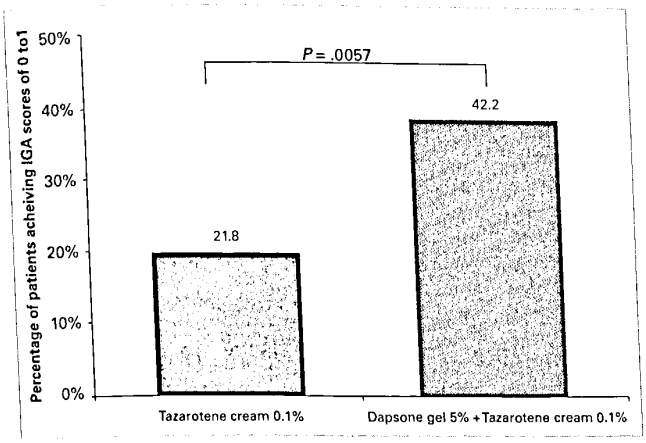
TABLE 2.

Adverse Events Possibly Related to Study Treatment

Adverse Event	Tazarotene (n = 84) No. (%) of Patients	Dapsone + Tazarotene (n = 86) No. (%) of Patients
Dryness	2 (2.4%)	2 (2.3%)
Erythema	4 (4.8%)	2 (2.3%)
Peeling	1 (1.2%)	0 (0.0%)
Pruritus corners of the mouth	1 (1.2%)	0 (0.0%)
Sunburn on face, arms, and shoulders	1 (1.2%)	0 (0.0%)

Note: Patients reporting a particular adverse event more than once are counted only once for that adverse event.

FIGURE 3. Percentage of patients achieving treatment success at week 12 as measured by IGA score of 0 (none) or 1 (minimal).



lesion count (27.4% vs. 12.7%, respectively, $P = 0.02$). Similarly, at weeks 4 and 8, significantly more patients receiving combination therapy than those receiving monotherapy achieved a 75 percent reduction in inflammatory lesion count (week 4, 13.4% vs. 3.8%, $P=.03$; week 8, 22.8% vs. 10.1%, $P=0.03$).

Secondary End Points

Noninflammatory and total lesion counts

After 12 weeks of therapy, there was a significant reduction in noninflammatory lesion count compared with baseline in both treatment arms (Figure 2). Notably, the magnitude of reduction was significantly greater in the combination therapy arm than in the monotherapy arm (59.7% vs. 46.5%, $P=0.01$). Similarly, the decline in total lesion count at week 12 was also significantly greater in the dapsone plus tazarotene combination therapy group compared with the tazarotene monotherapy group (63.3% vs. 53.6%, $P=.02$). Furthermore, the more rapid onset of effect with the combination therapy than with monotherapy was evident as early as week 1 when evaluating total lesion count. At week 1, significantly more patients receiving combination therapy than those receiving monotherapy achieved a 50 percent decline in total lesion count (10.6% vs. 1.2%, $P=.02$), and at weeks 4 and 8, the proportions of patients achieving a 75 percent decline in total lesion count was also significantly greater in the combination arm than in the monotherapy arm (week 4, 9.8% vs. 1.3%, $P=.03$; week 8, 20.3% vs. 3.8%, $P=.002$).

Investigator global assessment score

Mean baseline IGA scores were 2.93 ± 0.37 for patients randomized to dapsone plus tazarotene and 3.04 ± 0.36 for patients receiving tazarotene monotherapy, reflecting moderate acne severity, on average, in both treatment arms. Both treatment groups demonstrated improvement from baseline acne severity at all time points based on the IGA end point. At week 12, the percentage of patients achieving treatment success (defined as achieving a score of 0 [none] or 1 [minimal]) was significantly greater in the dapsone plus tazarotene–treated patients than in the patients treated with tazarotene monotherapy ($P=.006$; Figure 3).

Overall disease severity score

Mean baseline overall disease severity scores were similar between treatment groups (combination dapsone plus tazarotene, 4.03, vs. tazarotene monotherapy, 4.08; $P=.65$), and at week 12, there were significant reductions in scores, indicating improvement in disease severity ($P < 0.0001$) in both treatment arms. However, at week 12, patients treated with combination therapy demonstrated a significantly lower mean disease severity score than did patients treated with monotherapy (2.11 vs. 2.44, $P=.03$).

Disease signs and symptoms

Baseline scores for each of erythema, dryness, peeling, and oiliness were similar between treatment groups. After 12 weeks of therapy, there were significant improvements in the scores for erythema ($P \leq 0.020$) and oiliness ($P < 0.001$) compared with baseline in both treatment arms, but no significant change in dryness or peeling in either treatment arm (Figures 4 and 5). There was no difference between treatment groups in any of the disease signs/symptoms assessed.

Post-inflammatory hyperpigmentation

At baseline, the severity and distribution of PIH were similar between treatment groups (mean severity: 0.84 ± 1.20 and 0.84 ± 1.16; mean distribution: 0.90 ± 1.41 and 0.93 ± 1.40 for combination vs. monotherapy, respectively). At 12 weeks, the mean change in severity from baseline was −0.27 ± 0.84 with dapsone plus tazarotene combination treatment and −0.22 ± 0.71 with tazarotene monotherapy ($P=.01$ and $P=.01$ versus baseline for combination therapy and monotherapy, respectively; $P=.48$ be-

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