Two randomized studies demonstrate the efficacy and safety of dapsone gel, 5% for the treatment of acne vulgaris

Zoe D. Draelos, MD,[a] Eric Carter, MD,[b] J. Michael Maloney, MD,[c] Boni Elewski, MD,[d] Yves Poulin, MD,[e] Charles Lynde, MD,[f] and Steven Garrett, DDS,[g] for the United States/Canada Dapsone Gel Study Group*
High Point, North Carolina; New York, New York; Denver and Fort Collins, Colorado; Birmingham, Alabama; Sainte-Foy, Quebec, and Markham, Ontario, Canada

Background: A new aqueous gel formulation of dapsone has been developed that allows clinically effective doses of dapsone to be administered topically with minimal systemic absorption.

Objectives: The goal of these studies was to evaluate the efficacy and safety of dapsone gel, 5% in the treatment of acne.

Methods: Patients 12 years of age and older with acne vulgaris (N = 3010) participated in two identically designed 12 week, randomized, double blind studies of twice daily monotherapy with dapsone gel, 5%, versus a vehicle gel.

Results: Dapsone gel treated patients achieved superior results in terms of the investigator's global acne assessment ($P < .001$) and the mean percentage reduction in inflammatory, noninflammatory, and total lesion counts (all, $P < .001$) at week 12. Reductions in inflammatory lesion counts favoring dapsone gel over vehicle were apparent as early as 2 weeks and reached statistical significance by 4 weeks. No clinically significant changes in laboratory parameters, including hemoglobin, even among glucose 6 phosphate dehydrogenase deficient patients, were observed. Adverse events were comparable between the treatment groups and rarely led to discontinuation.

Limitations: Adjunctive topical treatments and their impact on acne were not studied in this trial.

Conclusions: Dapsone gel, 5% appears to be an effective, safe, and well tolerated treatment for acne vulgaris, with a rapid onset of action. (J Am Acad Dermatol 2007;56:439.e1 10.)

Acne is experienced almost universally by adolescents and young adults in westernized societies,[1-3] and in the United States it is one of the most common complaints for which individ uals consult dermatologists.[4] For many patients, acne poses a heavy psychosocial burden, negatively impacting mood, self esteem, body image, and perceived levels of social isolation.[5,6] Successful treatment of acne significantly reduces symptoms of anxiety and depression and improves acne patients' quality of life.[7,8]

Dapsone, a sulfone that has both anti inflamma tory and antimicrobial properties, was shown to be an effective treatment for acne, including inflammatory

From Dermatology Consulting Services, High Point[a]; the Department of Dermatology, Columbia University Medical Center, New York[b]; Cherry Creek Research, Inc, Denver[c]; the Department of Dermatology, University of Alabama, Birming ham[d]; Centre of Dermatology Research, Sainte Foy[e]; Lynde Cen ter for Dermatology, Markham[f]; and QLT USA, Inc, Fort Collins.[g]
*Additional members of the United States/Canada Dapsone Gel Study Group are available at www.eblue.org as an online only appendix to this article.
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Reprint requests: Zoe D. Draelos, MD, Dermatology Consulting Services, 2444 N Main St, High Point, NC 27262. E mail: zdraelos@northstate.net.
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Abbreviations used:

GAAS: Global Acne Assessment Score
G6PD: glucose 6 phosphate dehydrogenase
ITT: intent to treat

nodulocystic acne, in the era predating the availability of isotretinoin.[9,10] However, the use of oral dapsone for acne was never widespread because of its potential to cause systemic toxicity, and, until recently, efforts to develop a topical formulation of dapsone were hindered by the poor solubility of dapsone in the aqueous vehicles that are typically used in dermatologic products.

Advances in cutaneous pharmacology have produced an aqueous gel that allows clinically effective doses of dapsone to be administered topically with minimal systemic absorption. The efficacy and safety of a new formulation, dapsone gel, 5% (Aczone; QLT USA, Inc. Fort Collins, Colo), in the treatment of acne vulgaris have been studied in two identically designed, pivotal trials.

METHODS

Study design

Two 12 week, double blind, randomized, parallel group, phase III studies were conducted under identical protocols to evaluate the efficacy and safety of dapsone gel, 5% (dapsone gel), compared with a vehicle gel control in the treatment of acne vulgaris. A total of 103 centers in the United States and Canada participated in the studies between November 2002 and September 2003.

Eligible patients were randomly assigned in a 1:1 ratio to either dapsone gel or vehicle gel according to a fixed block computer generated randomization table. The investigators, patients, and sponsor personnel were blinded to the treatment assignment, and patients were instructed not to bring their medications to the examination room or discuss the appearance of their study medication with the investigator. These procedures were established because the active and vehicle test articles were of a slightly different color. To maintain blinding, personnel who were not involved in efficacy or safety assessments conducted the drug accountability and test article weight assessments.

Patients were instructed to apply a thin layer of dapsone gel or vehicle gel twice daily to acne involved areas of the face. Patients could also treat acne affected areas other than the face; however, these areas were not assessed for efficacy. After washing with a standard noncomedogenic soap free cleanser (Cetaphil; Galderma Laboratories, LP), study drug was applied once in the morning and again at least 1 hour before bedtime to the entire affected area and rubbed in until it completely disappeared.

These studies were conducted in accordance with the ethical principles of the Declaration of Helsinki and in compliance with the Good Clinical Practice Guidelines. The protocols for each study center were reviewed and approved by an institutional review board or ethics committee. Written informed assent and consent was obtained from each patient or his/her parent or guardian, as appropriate, before the start of study procedures.

Patients

Male and female patients 12 years of age or older with a clinical diagnosis of acne vulgaris involving the face were enrolled in these studies. Patients were to have 20 to 50 inflammatory lesions (defined to include papules and pustules) and 20 to 100 noninflammatory lesions (comedones) above the mandibular line at baseline. Individuals with severe cystic acne, acne conglobata, or any active or developing nodules above the mandibular line at baseline were excluded from participation. Other exclusion criteria included concurrent use of topical drugs or treatments that could affect acne, including antibiotics and anti inflammatory agents; use within 4 weeks before baseline of systemic immunosuppressive drugs or systemic medications or therapy known to affect acne or inflammatory responses; use of isotretinoin within 3 months of baseline; or known allergy or hypersensitivity to dapsone, sulfa drugs, or excipients of the dapsone gel product. Women of childbearing potential could not be pregnant or nursing, had to be practicing an effective method of birth control as determined by the enrolling physician, and, if using hormonal contraception, had to have been using a stable dose for a minimum of 3 months. Systemic contraceptives were not to be initiated during the study.

Efficacy and safety assessments

All patients underwent a dermatologic examination at screening/baseline and at weeks 2, 4, 6, 8, and 12. At each of these visits, investigators recorded a Global Acne Assessment Score (GAAS) (Table I) and counted the number of inflammatory and noninflammatory acne lesions present. The total lesion count was the sum of both inflammatory and noninflammatory lesions.

The primary efficacy end points were the proportion of patients achieving success based on the GAAS and the mean percent reduction from baseline in acne lesion counts at week 12. Success for GAAS

on the 5 point static scale was defined as a rating of "none" (0) or "minimal" (1). Success for acne lesion counts was defined as statistically greater mean percent reductions at week 12 in at least two of the three types of lesion counts (inflammatory, noninflammatory, and total) in the dapsone gel treated patients compared with the vehicle gel treated patients. Secondary efficacy end points included mean lesion counts for inflammatory, noninflammatory, and total acne lesions as well as mean reduction from baseline at week 12 for all of these.

Adverse events, local signs and symptoms (adverse reactions of facial oiliness, peeling, dryness, and erythema), physical examination findings (including vital signs), and laboratory analyses were monitored throughout the study. Patients were specifically queried at each study visit, including at baseline, for the presence of local signs or symptoms; a worsening of these symptoms from baseline or the appearance of any other local sign or symptom was reported as an application site adverse event. Blood was drawn for hematology and serum chemistry determinations at baseline and week 12, and all patients were screened for glucose 6 phosphate dehydrogenase (G6PD) deficiency at baseline. Plasma dapsone concentrations were not routinely assessed in these studies; however, investigators were instructed to report any adverse event known to be associated with systemic dapsone exposure, at which time plasma dapsone concentration evaluations would be conducted. All laboratory analyses were performed at a central laboratory (Quintiles Transnational Corp, Smyrna, Ga) and normal ranges for each analyte were provided.

Table I. The Global Acne Assessment Score

	GAAS	Severity	Description
Success	0	None	No evidence of facial acne vulgaris
	1	Minimal	A few noninflammatory lesions (comedones) are present; a few inflammatory lesions (papules/pustules) may be present
Failure	2	Mild	Several to many noninflammatory lesions (comedones) are present; a few inflammatory lesions (papules/pustules) are present
	3	Moderate	Many noninflammatory lesions (comedones) and inflammatory lesions (papules/pustules) are present; no nodulocystic lesions are allowed
	4	Severe	Significant degree of inflammatory disease; papules/pustules are a predominant feature; a few nodulocystic lesions may be present; comedones may be present

GAAS, Global Acne Assessment Score.

Statistical methods

Data from both studies were analyzed individually and combined for the statistical analyses. Efficacy results are presented for the combined analysis of the intent to treat (ITT) population (defined as all enrolled patients to whom study drug was dispensed) with the last observation carried forward. The safety evaluable population includes all patients who applied study drug. The incidence of success based on a GAAS of 0 or 1 at week 12 was analyzed using the Cochran Mantel Haenszel procedure, stratifying by study center. Acne lesion counts were summarized using descriptive statistics (mean, median, range, standard deviation, standard error, minimum, maximum) for continuous data. For the combined analysis reported in this article, an analysis of variance was used to analyze the mean percent reduction in acne lesion counts with treatment, study, treatment by study, and center nested in study as factors. Both primary end points were to be met for the study to be deemed successful. Statistical comparisons of the two treatment groups used a significance level of 0.05. The sample size calculations for these studies are based on estimate success rates of 19.5% for active treatment versus 14% for vehicle treatment. It was determined that a total of 1450 evaluable patients would provide an 80% power to detect this difference.

Adverse events, regardless of relationship to study medication, were tabulated and summarized by incidence as application site or non application site events. Relationship to treatment was determined by the investigator. Common adverse events were defined as being those experienced by at least 2% of all patients. Laboratory evaluations were summarized using descriptive statistics.

RESULTS

Patient disposition and baseline characteristics

A total of 3010 patients were enrolled and were dispensed dapsone gel (n = 1506) or vehicle gel (n = 1504) and made up the ITT population (Fig 1). The safety evaluable population, defined as all enrolled subjects who applied study drug, included 1466

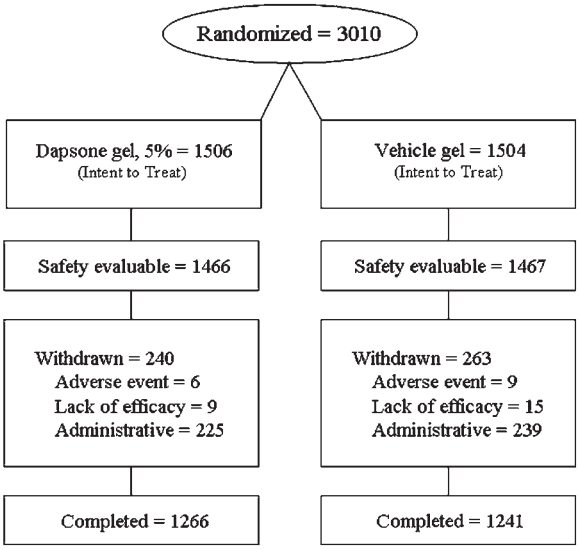

Fig 1. Patient disposition. Administrative reasons for withdrawal include loss to follow up, voluntary withdrawal, protocol violation, and treatment noncompliance.

patients who received dapsone gel and 1467 who received vehicle gel. Approximately equal numbers from each treatment group discontinued treatment prematurely: 15.9% (240/1506) of the dapsone gel treated patients and 17.5% (263/1504) of the vehicle gel treated patients. The vast majority of premature study discontinuations (92.2%, 464/503) were for administrative reasons, including loss to follow up, voluntary withdrawal, protocol violation, and treatment noncompliance (Fig 1). Very few patients treated with dapsone gel discontinued because of lack of efficacy (0.6%; 9/1506) or an adverse event (0.4%; 6/1506).

Baseline characteristics for the ITT population were similar between treatment groups and are summarized in Table II. At baseline, both the acne severity scores and acne lesion counts were similar between treatment groups. Most patients (58.4%; 1759/3010) had moderate acne, whereas 33.8% of patients (1016/3010) had mild acne.

Table II. Patient demographics and baseline characteristics

Demographic parameter	Dapsone gel, 5% (n = 1506)	Vehicle gel (n = 1504)
Sex, No. (%)		
Male	725 (48.1)	698 (46.4)
Female	781 (51.9)	806 (53.6)
Age, y		
Mean [SD]	19.3 [7.5]	19.6 [7.6]
Minimum, maximum	12, 81	11, 59
12-15, No. (%)	578 (38)	547 (36)
≥ 16, No. (%)	928 (62)	957 (64)
Race, No. (%)		
Caucasian	1107 (73.5)	1088 (72.3)
African American	209 (13.9)	211 (14.0)
Hispanic	138 (9.2)	145 (9.6)
Asian	31 (2.1)	35 (2.3)
Other	21 (1.4)	25 (1.7)
GAAS, No. (%)		
0 = None	0 (0.0)	0 (0.0)
1 = Minimal	78 (5.2)	79 (5.3)
2 = Mild	500 (33.2)	516 (34.3)
3 = Moderate	894 (59.4)	865 (57.5)
4 = Severe	34 (2.3)	44 (2.9)
Lesion counts		
Inflammatory		
Mean [SD]	30.8 [10.2]	30.3 [9.9]
Minimum, maximum	11, 114	11, 114
Noninflammatory		
Mean [SD]	48.2 [24.3]	47.8 [23.4]
Minimum, maximum	13, 240	8, 172
Total		
Mean [SD]	79.0 [28.3]	78.1 [27.3]
Minimum, maximum	39, 288	37, 261

GAAS, Global Acne Assessment Score.

Efficacy results

Dapsone gel treated patients were significantly more likely than vehicle gel treated patients to achieve treatment success at week 12 in terms of the investigator's static global assessment (GAAS of none or minimal acne; $P < .001$ in the combined studies, Fig 2). This finding was consistent across the participating centers. Superior GAAS 12 week success rates were achieved with dapsone gel treatment, regardless of whether the baseline acne was, in terms of acne lesion counts, relatively more severe (ie, ≥ 28 inflammatory lesions, ≥ 40 noninflammatory lesions, or ≥ 71 total lesions) or less severe (data not shown).

Dapsone gel treated patients experienced significantly greater reductions from baseline to 12 weeks in noninflammatory and total lesion counts (both $P < .001$, Fig 3, *A* and *B*). However, the greatest reduction occurred in inflammatory lesion counts, which fell by nearly half after 12 weeks of treatment with dapsone gel (47.5% vs 41.8%, $P < .001$, Figs 2 and 3, *C*).

The onset of response to dapsone gel treatment was rapid, particularly in terms of reductions in inflammatory lesion counts. A small difference between active and vehicle was seen as early as 2 weeks and approached statistical significance ($P = .052$) (Fig 3, *C*). At 4 weeks this difference in inflammatory lesion counts was highly statistically significant ($P = .008$). By 8 weeks, statistically significant differences between the treatment groups were clearly apparent

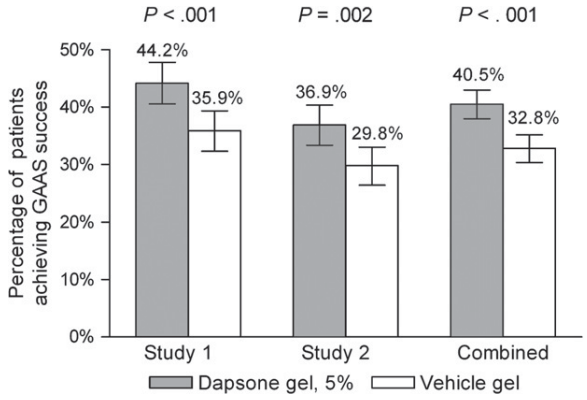

Fig 2. Success rate at week 12. Percentage of patients achieving success by Global Acne Assessment Score of "none" (0) or "minimal" (1). *Error bars* represent 95% confidence intervals.

in the mean percentage changes in counts of all 3 lesion types (inflammatory, $P < .001$, Fig 3, *C*; noninflammatory, $P = .003$, Fig 3, *A*; and total, $P < .001$, Fig 3, *B*). The magnitude of these differences steadily increased through the remaining weeks of the studies.

Statistically significant differences in favor of dapsone gel were noted for each of the secondary efficacy variables, including mean lesion counts at week 12 for inflammatory, noninflammatory, and total acne lesions (all $P < .001$ compared with vehicle gel), and mean change from baseline in lesion counts at week 12 for each of these assessments (all $P < .001$ compared with vehicle gel).

Reduction of acne lesions over time can be seen in facial photographs of patients in the dapsone gel treatment group (Figs 4 and 5). These images are representative of the treatment group as a whole.

Safety results

Overall, patients experienced adverse events at similar rates in the two treatment groups: 58.2% (853/1466) of dapsone gel treated patients and 58.6% (860/1467) of vehicle gel treated patients. Most events were of mild to moderate intensity, resolved during treatment, and did not result in treatment discontinuation.

Patients were asked at each visit about local signs and symptoms, including skin dryness, erythema, oiliness, and peeling. Oiliness and erythema were the most frequent symptoms reported at a level of moderate or greater severity by patients in both treatment groups at baseline and week 12 (Table III). Substantial declines in all of the local signs and symptoms occurred in both treatment groups over the course of the study.

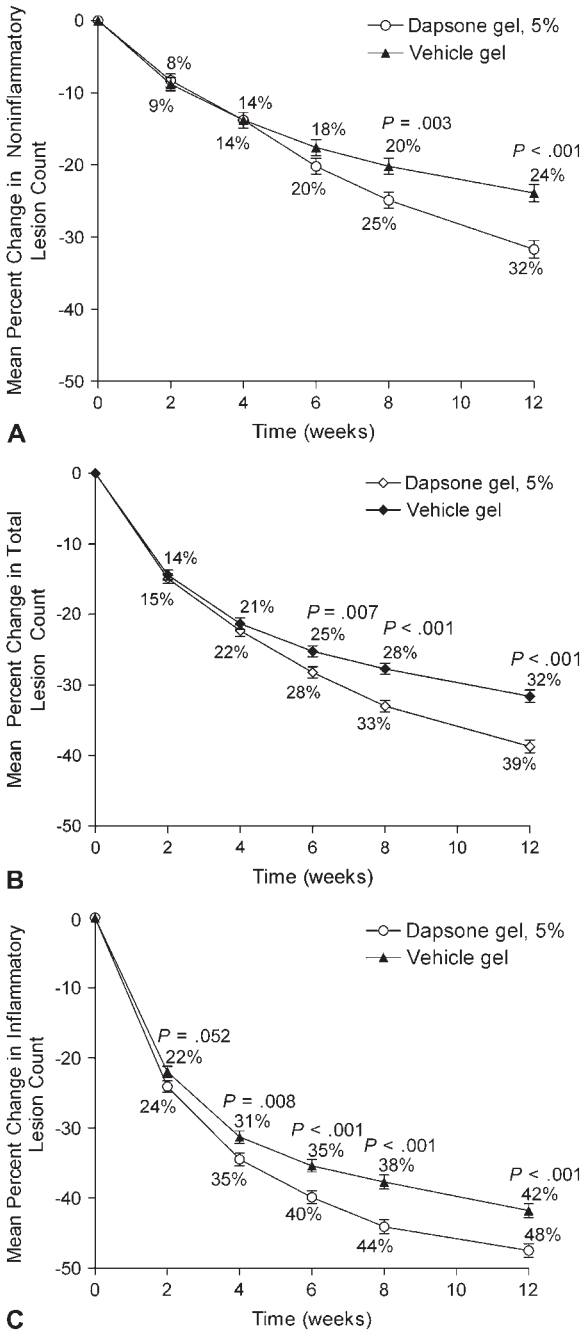

Fig 3. Mean percent reduction in noninflammatory (**A**), total (**B**), and inflammatory (**C**) lesion count over time. *Error bars* represent standard error.

Patients were also monitored for application site adverse events, including any local cutaneous ab normalities that emerged during treatment, irrespec tive of whether the abnormalities were judged by the investigator to be related to the study medication. Comparable numbers of patients in each treatment group experienced application site adverse events

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