The Efficacy and Tolerability of Dapsone 5% Gel in Female vs Male Patients With Facial Acne Vulgaris: Gender as a Clinically Relevant Outcome Variable

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ABSTRACT

Background: Gender differences in skin and acne have been reported.
Objective: To evaluate the effect of gender on the efficacy and tolerability of dapsone 5% gel.
Methods: This was a pooled analysis of data from 2 identical phase 3 randomized, double-blind, and vehicle-controlled trials (DAP0203 and DAP0204) of dapsone 5% gel conducted in the United States and Canada between November 2002 and September 2003. A total of 2,898 patients with acne vulgaris were included in the pooled analysis. Of these, 1,453 patients (753 female, 700 male) received dapsone 5% gel twice daily, and 1,445 patients (767 female, 678 male) received vehicle twice daily. End points included the mean percentage reduction from baseline in acne lesion counts and the proportion of patients achieving clinical success (Global Acne Assessment Scale score of 0, clear skin, or 1, almost clear skin). Assessments were performed at baseline and at weeks 2, 4, 6, 8, and 12.
Results: The mean percentage reduction in acne lesion counts at 12 weeks was significantly greater in females than males in both treatment groups. The mean reduction in total lesion counts in dapsone-treated females and males was, respectively, 46.6% vs 35.8% ($P<.0001$). Reductions in papulopustular and comedonal lesion counts were likewise significantly higher in female than male patients (each $P<.0001$). Significantly more dapsone-treated females than males achieved clinical success (48.6% vs 34.4%; $P=.0003$).
Conclusion: The response to dapsone 5% gel appears to be influenced by gender, with female patients experiencing a significantly greater reduction in acne lesion counts and a significantly higher clinical success rate following 12 weeks of treatment. These data suggest that gender is a novel predictor of outcome that should be considered in acne clinical trial design and analysis.

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INTRODUCTION

Acne is a very common disease that remains prevalent in adults, with more adult women being afflicted than adult men.[1] This raises the intriguing possibility that gender differences in skin may influence acne pathogenesis and response to acne treatment. Indeed, gender differences in skin, both its function and structure, have been the focus of considerable research to understand more about skin disease pathogenesis and response to treatment. For example, gender differences in skin surface pH have been reported, although findings have been inconsistent.[2-7] It has also been shown that males have thicker skin than females,[8] while females have thicker subcutaneous tissues than males.[9] Skin thickness tends to decrease with age, especially in women, suggesting that estrogens play a role in maintaining skin.[10] Estrogens also have been implicated in regulating the composition of stratum corneum sphingolipids[11] and cutaneous protein[5] and in decreasing sebum production.[12,13] In contrast, androgens appear to increase sebum production,[14] possibly by influencing cell proliferation and lipogenesis in the sebaceous gland.[14] Sebum production and sebaceous gland activity are major factors in acne lesion development.

Dapsone is an anti-inflammatory agent that, in the 5% gel formulation, is approved for the topical treatment of acne vulgaris.[15] It has been studied and found to be effective for at least 12 months of treatment[16] and to reduce comedonal as well as papulopustular acne lesions when used as monotherapy[15] or in combination with a retinoid.[17,18] During clinical trials of dapsone 5% gel, some investigators observed a greater acceptance and efficacy of the product in female patients vs in male patients. Given this observation, and previously reported gender differences in skin and acne,[19] we explored whether gender impacts the efficacy and tolerability of dapsone 5% gel.

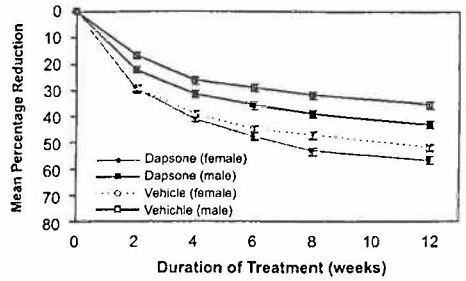
METHODS

Patients, Treatment, and Assessments

The two 12-week, double-blind trials (DAP0203 and DAP0204) enrolled patients 12 years and older with facial acne vulgaris. Patients had 20 to 50 papulopustular lesions and 20 to 100 comedones above the mandibular line at baseline. Other exclusion criteria and study design details are reported in the original study publication.[15] Patients were randomized 1:1 to receive either dapsone 5% gel or vehicle gel. Assessments were performed at baseline and at weeks 2, 4, 6, 8, and 12. The following parameters were analyzed and compared in female vs male patients at all time points: the mean percentage reduction from baseline in acne lesion counts

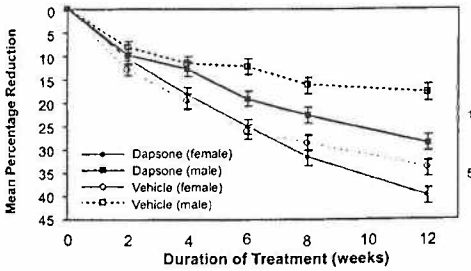
FIGURE 1. Mean percentage reduction in lesion counts from baseline to 12 weeks. NS, not significant.

a) Papulopustular lesions



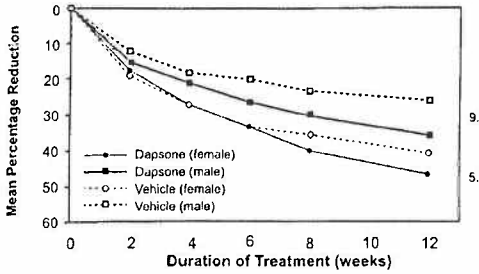
P values (dapsone vs vehicle)					
Female:	NS	NS	NS	.001	.01
Male:	002	.007	.0003	.0003	.0002
P values (male vs female)					
Vehicle:	<.0001	<.0001	<.0001	<.0001	<.0001
Dapsone:	<.0001	<.0001	<.0001	<.0001	<.0001

b) Comedonal lesions



P values (dapsone vs vehicle)					
Female:	NS	NS	NS	NS	.02
Male:	NS	NS	.003	.008	<.0001
P values (male vs female)					
Vehicle:	.0101	.0003	<.0001	<.0001	<.0001
Dapsone:	NS	.0154	.0074	.0002	<.0001

c) Total lesions



P values (dapsone vs vehicle)					
Female:	NS	NS	NS	.01	.003
Male:	.02	.08	.0002	.0001	<.0001
P values (male vs female)					
Vehicle:	.0101	.0003	<.0001	<.0001	<.0001
Dapsone:	NS	.0004	<.0001	<.0001	<.0001

achieving treatment success (Global Acne Assessment Scale [GAAS] score of 0 [none] or 1 [minimal]; Table 1), and the proportion of patients without local signs and symptoms (erythema,

Statistical Analyses

Data from 2,898 patients in both studies were combined for the statistical analyses. One hundred and twelve patients were excluded from the analysis because of an absence of posttreatment efficacy data.

Lesion reduction data were analyzed using a longitudinal mixed-effect repeated-measures analysis of covariance model, which also established the suitability of pooling the data from the 2 clinical trials. Data for GAAS and for local signs and symptoms were analyzed based on a repeated-measures logistic regression model. A modified last observation carried forward (LOCF) approach was used to impute missing data: (i) continuous parameters—for week 2 missing data, the average between baseline and week 4 data were used; for all other weeks of measurement, LOCF was used; (ii) discrete parameters—LOCF was used for all weeks. For all analyses, outcomes were considered significant if $P<.05$.[15]

RESULTS

Patient Disposition and Baseline Characteristics

Of the 2,898 patients included in the pooled analysis, 1,453 (753 female, 700 male) received dapsone 5% gel twice daily, and 1,445 patients (767 female, 678 male) received vehicle twice daily. The treatment groups were similar with respect to the distribution of males and females (Table 2). Males had a higher mean total lesion count at baseline than females (83.00 vs 74.06 in the vehicle gel group, and 84.01 vs 74.25 in the dapsone gel group) and tended to have a higher baseline GAAS score (proportion of patients with GAAS score ≥2: 96.8% vs 92.8% [vehicle] and 95.4% vs 94.3% [dapsone]).

Lesion Counts

The mean percentage reduction in all acne lesion counts from baseline to 12 weeks was significantly greater in females than males in both the dapsone-treatment and vehicle-treatment groups (Figure 1). In dapsone-treated patients, the mean percentage reduction in total lesion counts was 46.6% in females and 35.8% in males ($P<.0001$). Correspondingly, the percentage reduction of papulopustular lesions at 12 weeks was 56.8% in dapsone-treated females and 43.2% in dapsone-treated males ($P<.0001$). Reductions at 12 weeks in comedonal lesions were 39.8% and 28.5% in females vs males, respectively, in the dapsone-treatment group ($P<.0001$).

In female patients at week 12, dapsone 5% gel elicited significantly greater reductions in papulopustular (4.83%, $P=.0138$), comedonal (5.90%, $P=.0154$), and total (5.51%, $P=.0029$) lesion counts than vehicle gel. In male patients at week 12, the treatment differences also favored dapsone, but with greater reductions of 7.56% ($P=.0002$), 10.7% ($P<.0001$), and 9.72% ($P<.0001$) in papulopustular, comedonal, and total lesion

GAAS Incidence of Treatment Success

A significantly greater proportion of female patients achieved treatment success (as indicated by a GAAS score of 0 or 1) compared with male patients in both treatment arms (Figure 2). The treatment success rate in females and males, respectively, was 48.6% vs 34.4% (P=.0003) with dapsone 5% gel and 39.4% vs 28.0% (P=.0013) with vehicle gel.

The within-gender treatment difference (dapsone gel – vehicle gel) in the proportion of patients achieving treatment success was 9.2% in females (P=.0001) and 6.4% in males (P=.0010). The odds ratio for treatment success in dapsone-treated vs vehicle-treated patients was 1.61 in females (95% confidence interval [CI], 1.26-2.06) and 1.56 in males (95% CI, 1.20-2.03).

Tolerability

The proportion of patients with erythema, dryness, peeling, or oiliness was low, regardless of gender or treatment group. Erythema and oiliness decreased from baseline over the 12 weeks of treatment in both treatment groups and for both female and male patients. The occurrence of erythema, dryness, peeling, or oiliness was similar between males and females and did not differ significantly by treatment arm, regardless of time point (P>.05 at 12 weeks) (Figure 3).

DISCUSSION

The findings of this pooled analysis indicate that females with acne responded better than males to dapsone 5% gel. Female patients experienced a significantly greater reduction from baseline in acne lesion counts and a significantly higher clinical success rate at 12 weeks compared with males. For all efficacy outcomes, the vehicle was also found to have a beneficial effect, albeit to a significantly lesser degree than the dapsone 5% gel, again with females being more responsive than males.

The reasons for the gender difference in response observed in this study are not clear, and there have been no previously published reports of gender-based analyses from other acne clinical trials to inform our interpretation of the findings. However, possible reasons for the gender difference in response include differences between men and women with respect to treatment adherence, differences in lesion scoring for men vs women, unknown/uncharacterized dapsone-hormone interactions, differences in male and female physiology, and differences in acne pathology between men and women related to their physiological differences.

Gender has been identified as a potential source of nonadherence with treatment and may explain our current findings.[20] Some evidence suggests that female patients are more compliant with acne treatment than male patients.[20-23] A recent literature review by Lott and colleagues[24] examined medication adherence in teenagers with acne and described a weak association between poorer adherence and male gender.

FIGURE 2. Treatment success rate (assessed by Global Acne Assessment Scale [GAAS]).

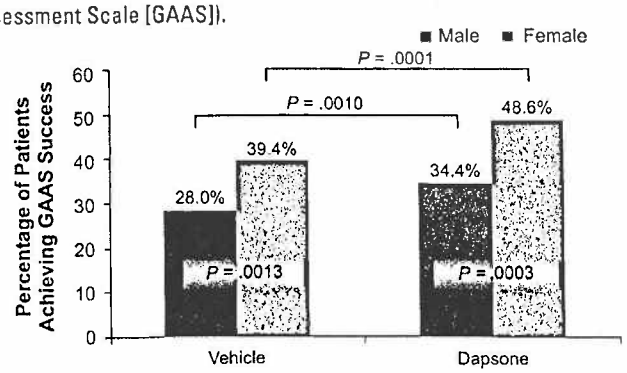


TABLE 1.

The Global Acne Assessment Scale (GAAS) Definitions

Success	0	None	No evidence of facial acne vulgaris
	1	Minimal	A few comedones are present; a few papulopustular lesions may be present
Failure	2	Mild	Several/many comedones are present; a few papulopustular lesions are present
	3	Moderate	Many comedones and papulopustular lesions are present; nodulocystic lesions are allowed
	4	Severe	Significant degree of noncomedonal disease; papules/pustules are a predominant feature; a few nodulocystic lesions may be present; many comedones may be present

Adverse events are another source of nonadherence.[25] Some authors have observed that local side effects of topical therapy, such as cutaneous irritation, erythema, dryness, peeling, and scaling, can lead to poor patient compliance.[26,27] In the present analyses, the tolerability of dapsone 5% gel did not differ between males and females.

Differences in cleansing care practices between males and females also may have contributed to the differential response to treatment. Skin cleansing, perhaps as part of a cosmetic routine, may be more strictly followed by females than males. All patients in this study were required to wash daily with a standard noncomedogenic, soap-free cleanser before application of study medication.

An intriguing alternative explanation for the observed gender difference in response to dapsone 5% gel is the possibility of a difference between males and females in underlying acne

TABLE 2.

Demographics and Baseline Characteristics

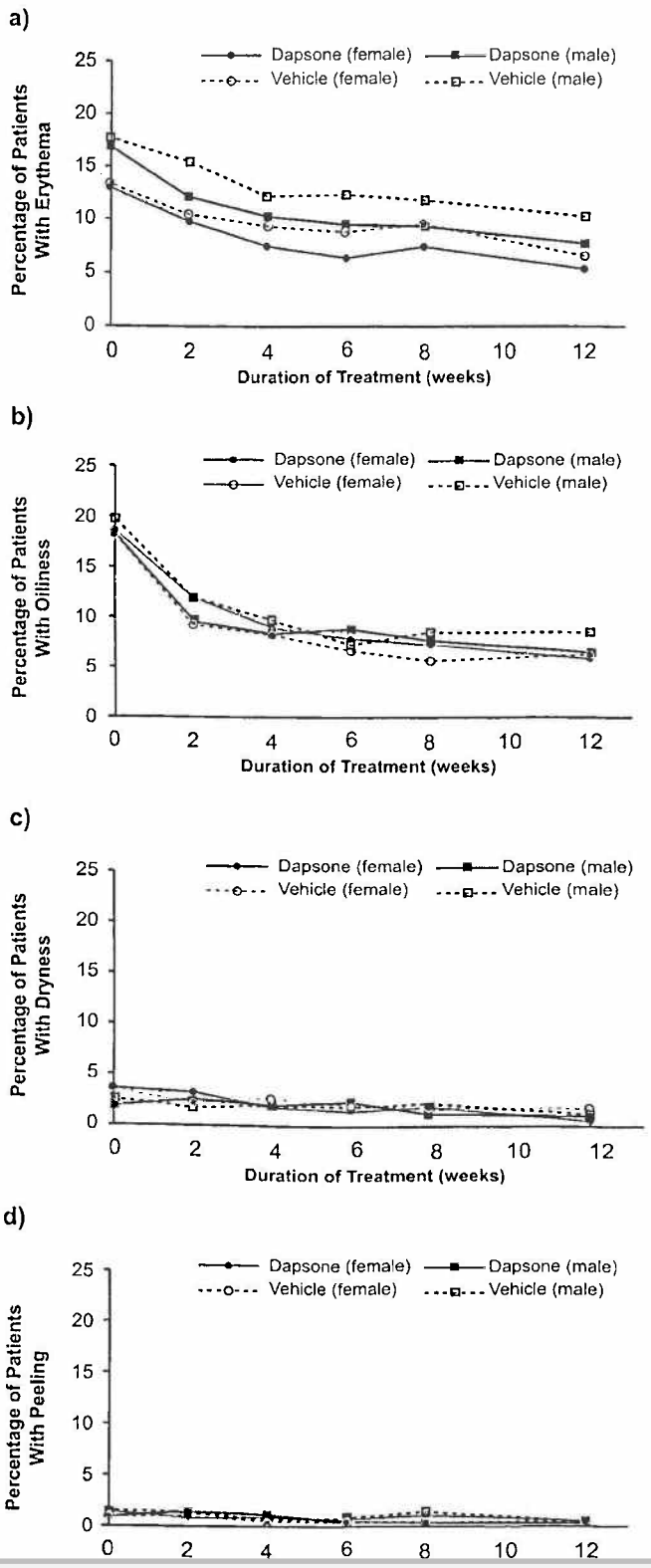
Sex, n (%)		
Female	767 (53.1)	753 (51.8)
Male	678 (46.9)	700 (48.2)
Lesion counts, mean ± SE		
Papulopustular		
Female	28.17 ± 0.30	28.18 ± 0.31
Male	32.95 ± 0.43	33.61 ± 0.41
Comedonal		
Female	45.89 ± 0.81	46.07 ± 0.86
Male	50.06 ± 0.93	50.40 ± 0.94
Total		
Female	74.06 ± 0.92	74.25 ± 0.98
Male	83.00 ± 1.10	84.01 ± 1.08
GAAS scores, n (%)		
0 or 1		
Female	55 (7.2)	43 (5.7)
Male	22 (3.2)	32 (4.6)
≥2		
Female	712 (92.8)	710 (94.3)
Male	656 (96.8)	668 (95.4)

GAAS, Global Acne Assessment Scale; SE, standard error.

pathology. Dao and Kazin[19] suggested that hormonal interactions contribute substantially to the gender differences in acne, notably, sebum production, which plays a key role in the development of acne. It is increased by androgens and decreased by estrogens. Moreover, both components of sebum and their peroxidation products, as well as androgens, have putative immunomodulatory effects,[28-30] which may impact the inflammatory component of acne pathology in males. Increased sebum production and a modified inflammatory response, in turn, may lead to the development of acne in males that is more severe and refractory to treatment. Interestingly, on average, the male patients in this study did present at baseline with more comedonal and papulopustular acne lesions than their female counterparts.

Notably, female patients in this study not only responded better than males to dapsone therapy, but also responded better to the vehicle gel. The reason for this unknown, but the findings suggest an action of the vehicle gel on skin that is more robust in females. The dapsone 5% gel vehicle contains diethylene glycol monoethyl ether (DGME), an organic solvent, which may favorably impact se-

FIGURE 3. Incidence of adverse events at 12 weeks: dapsone 5% gel vs placebo.



increase the water solubility of waxy substances, such as polyoxyethylene-2-stearyl ether.[31] Hypothetically, a similar dissolution of sebum fatty acids in the skin may confer a clinical benefit in acne, the magnitude of which may be greater in females than in males.

The results of this analysis are intriguing but must be considered within the limitations of the analysis. The analysis was post hoc. Moreover, differences were apparent between males and females regarding the magnitude of the drug effect relative to the placebo effect, with a greater mean treatment difference reported for male patients. How these variations in response may have contributed to the findings of this analysis is not known.

"Female patients experienced a significantly better response to dapsone 5% gel than male patients."

In conclusion, female patients experienced a significantly better response to dapsone 5% gel than male patients. Further assessment of skin differences between genders is necessary to more clearly understand varying treatment outcomes between males and females. Nonetheless, these data suggest that patient gender may be a novel predictor of outcome that should be considered in acne clinical trial design as well as analysis.

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DISCLOSURES

Dr. Tanghetti is an investigator and speaker for Allergan and Steifel Laboratories and a consultant and speaker for Galderma Laboratories. Dr. Harper is a consultant, advisor, and speaker for Allergan; an advisor and speaker for Coria Laboratories and Galderma Laboratories; a speaker and investigator for Intendis; an investigator for Medicis; and a consultant and speaker for Steifel Laboratories. Dr. Oefelein is a former employee of Allergan and was an employee at the time the analyses were performed. Third-party medical writing assistance, supported by Allergan, Inc, was used in the preparation of this paper. Allergan also funded the statistical analyses of this substudy. The pivotal trials on which this substudy was based were originally sponsored by Fujisawa Healthcare, Inc, and QLT USA, Inc, Laboratories.

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