Hematologic Safety of Dapsone Gel, 5%, for Topical Treatment of Acne Vulgaris

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Objective: To evaluate the risk of hemolysis in subjects with glucose-6-phosphate dehydrogenase (G6PD) deficiency who were treated for acne vulgaris with either dapsone gel, 5% (dapsone gel), or vehicle gel.

Design: Double-blind, randomized, vehicle-controlled, crossover study.

Setting: Referral centers and private practice.

Participants: Sixty-four subjects 12 years or older with G6PD deficiency and acne vulgaris.

Intervention: Subjects were equally randomized to 1 of 2 sequences of 12-week treatment periods (vehicle followed by dapsone gel or dapsone gel followed by vehicle). The washout period was 2 weeks. Treatments were applied twice daily to the face and to other acne-affected areas of the neck, upper chest, upper back, and shoulders as required.

Main Outcome Measures: Results of clinical chemical analysis and hematology values; plasma dapsone and *N*-acetyl dapsone concentrations; spontaneous reports of adverse events.

Results: A 0.32-g/dL decrease in hemoglobin concentration occurred from baseline to 2 weeks during dapsone gel treatment. This was not accompanied by changes in other laboratory parameters, including reticulocytes, haptoglobin, bilirubin, and lactate dehydrogenase levels, and was not apparent at 12 weeks as treatment continued. The number of subjects with a 1-g/dL drop in hemoglobin concentration was similar between treatment groups at both week 2 and week 12. The largest drops in hemoglobin concentration were 1.7 g/dL in the vehicle gel treatment group and 1.5 g/dL in the dapsone gel treatment group. No clinical signs or symptoms of hemolytic anemia were noted.

Conclusions: After treatment with dapsone gel, 5%, no clinical or laboratory evidence of drug-induced hemolytic anemia was noted in G6PD-deficient subjects with acne vulgaris.

Trial Registration: clinicaltrials.gov Identifier: NCT00243542.

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DAPSONE IS A SULFONE WITH both anti-inflammatory and antimicrobial properties.[1-4] Use of oral dapsone may be associated with hematologic adverse effects, including dose-dependent hemolysis due to

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oxidative damage to red blood cells from its hydroxylamine metabolite.[5,6] Individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency are more sensitive to developing hemolytic anemia after exposure to hemolytic stressors including dapsone.[7] Because the G6PD enzyme is encoded on the X chromosome, the deficiency is more common in male patients. In the United States, a recent study of military personnel reported the prevalence of G6PD deficiency to be 2.5% in men and 1.6% in women.[8] Among racial groups, the prevalence was highest in African American men (12.2%), Asian men (4.3%), and African American women (4.1%), and lowest in white men and women (0.3% and 0%, respectively). An apparent direct linear relationship exists between oral dapsone dose and hemolysis regardless of G6PD deficiency status. However, clinically relevant hemolysis is generally not apparent with oral dapsone doses of 50 mg or less in G6PD-deficient subjects compared with 100 mg or less in normal subjects.[9-11]

A topical formulation of dapsone was recently developed to deliver therapeutic concentrations of dapsone to the skin. Clinical studies have shown that dapsone gel, 5% (Aczone; QLT USA Inc, Fort Collins, Colorado), was effective in the treatment of acne vulgaris[12] with approximately 1% of the systemic exposure that is seen with typical oral dapsone treatment.[13,14] No evidence of hemolytic anemia was found in any of the studies. However, the small number of subjects with G6PD deficiency in those studies precluded definitive conclusions about the hematologic effects of dapsone gel in this patient population. The present study was designed specifically to evaluate the risk of drug-induced hemolytic anemia from dapsone gel used for the topical treatment of acne vulgaris in patients with G6PD deficiency.

METHODS

STUDY DESIGN

This was a double-blind, randomized, vehicle-controlled, crossover, postapproval commitment study. Eighteen study centers in the United States enrolled patients from November 10, 2005, to March 29, 2006, and all treatment and follow-up was completed by October 13, 2006. Subjects were equally randomized into 1 of 2 sequences of treatment according to a computer-generated randomization scheme: dapsone gel followed by vehicle gel or vehicle gel followed by dapsone gel. The vehicle gel consisted of the same inactive ingredients as the dapsone gel. After washing with a standard, nonmedicated cleanser (Cetaphil; Galderma Laboratories LP, Fort Worth, Texas), subjects applied a thin film of the study treatment twice daily (once in the morning and once at night) to the entire face and, as required, to acne-affected areas of the neck, shoulders, upper chest, and upper back. Subjects applied each treatment for a period of 12 weeks, with a 2-week washout period between treatments and a 2-week follow-up period following the last treatment, for a total study duration of 28 weeks.

Study center personnel were blinded to the sequence of study treatment. As a further precaution, subjects were instructed to apply their study treatment at home or away from the study center. Two independent physicians, who were specialists in hematology and also blinded to the treatment sequence, acted as medical safety monitors for the study and reviewed all subjects' laboratory data on an ongoing basis. The medical monitors recommended additional laboratory follow-up tests if and when appropriate.

The study was conducted according to the ethical principles of the Declaration of Helsinki and in compliance with good clinical practice guidelines. The protocol was reviewed and approved by an institutional review board appropriate to each study center. Written informed assent and consent were obtained from each subject and from a parent or guardian if applicable before the start of study procedures.

SUBJECTS

The main eligibility requirements included age 12 years or older, a diagnosis of G6PD deficiency (G6PD enzyme activity below the lower limit of normal according to *Laboratory and Safety Assessments*[15]), and a diagnosis of acne vulgaris (at least 20 inflammatory and/or noninflammatory lesions, 10 or more of which were located on the face). Subjects were excluded if they had severe cystic acne or acne conglobata; had received treatment with isotretinoin within 3 months of baseline; or were using other topical and/or systemic medications for acne at the time of study entry. Subjects were also excluded if they had a predisposition to anemia for other medical reasons such as gastrointestinal tract bleeding or cancer.

LABORATORY AND SAFETY ASSESSMENTS

Adverse events were collected throughout the study with standard interviewing techniques at each study visit. Blood tests were scheduled for the baseline, 2-week, and 12-week points of each treatment period to measure plasma dapsone and *N*-acetyl dapsone concentrations and evaluate clinical chemistry and hematology parameters.

Blood samples from all subjects were tested for G6PD deficiency by a central laboratory (ARUP Laboratories, Salt Lake City, Utah) using a validated spectrophotometric assay performed with a commercially available kit (Trinity Biotech PLC, Bray, Ireland). The laboratory's normal reference range for G6PD activity was 7.0 to 20.5 U/g hemoglobin (Hb). Plasma dapsone and *N*-acetyl dapsone metabolite concentrations were measured by CANTEST BioPharma Services (Burnaby, British Columbia, Canada) using a validated liquid chromatography tandem mass spectrometry method. The lower limit of quantification for this assay was 0.30 ng/mL; levels below the lower limit of quantification were assigned a value of 0 for the summary analyses. All clinical chemistry and hematology tests were analyzed centrally by Quintiles Laboratories (Smyrna, Georgia), which assigned a high or low flag to any values that were determined to be outside of the laboratory normal range.

STATISTICAL METHODS

The planned sample size of approximately 60 subjects was designed to comply with the US Food and Drug Administration's recommended sample size of approximately 50 evaluable subjects. The *intent-to-treat population* was defined as all randomized subjects; the *safety population* was defined as all subjects who applied dapsone gel or vehicle gel at least once; and the *safety-evaluable population* was defined as all subjects who applied at least 50% of the required treatment applications and had the week 2 blood draw in the first treatment period. To assess the risk of hemolysis and hemolytic anemia, the following laboratory parameters were identified as important markers: Hb and bilirubin levels reticulocyte counts, and haptoglobin and lactate dehydrogenase (LDH) levels. For each of these parameters, the values at each time point, changes from baseline at 2 and 12 weeks, and within-subject between-treatment differences in the values and changes from baseline were summarized with descriptive statistics (mean, standard deviation, median, minimum, and maximum). Two-sided 95% confidence intervals were also calculated for the changes from baseline and within-subject between-treatment differences in the change from baseline. In addition, the number and percentage of subjects with any of the following outcomes were determined for the 2-week and 12-week time point of each treatment period: an Hb concentration shift from normal or high to below normal or from low to normal or high; an Hb concentration reduction of 1 g/dL or more; an increase in bilirubin level above the upper limit of normal; an increase in reticulocyte count above the upper limit of normal; a reduction in haptoglobin level below the lower limit of normal; and a reduction of 1 g/dL or more in Hb concentration with concomitant increase in bilirubin level, increase in reticulocyte count, or reduction in haptoglobin level. (To convert Hb to grams per liter, multiply by 10.0.) Unplanned correlation analyses between the changes in Hb concentration and changes in reticulocyte count or bilirubin, haptoglobin, or LDH level were per-
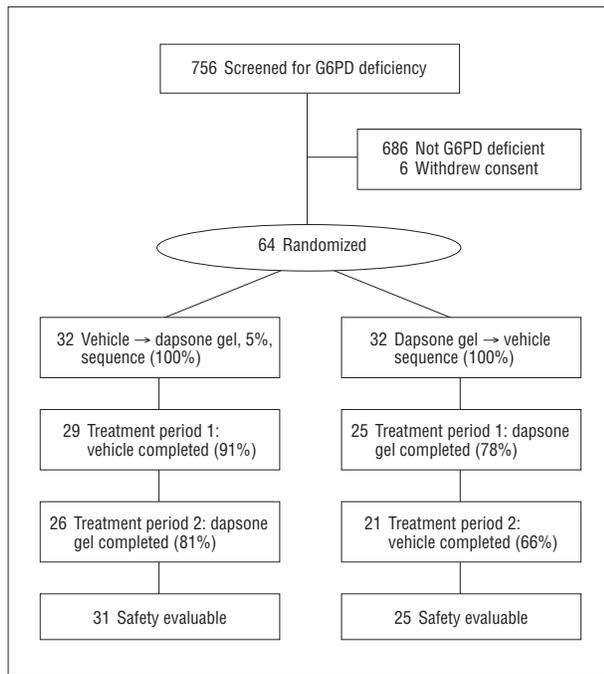
Figure 1. Subject randomization and protocol disposition. G6PD indicates glucose-6-phosphate dehydrogenase.

Table 1. Demographic and Baseline Characteristics of the Intent-to-Treat Population

Characteristic	Value[a]
Total subjects	64 (100)
Age, mean (SD) (range), y	28 (10) (12-61)
Women	35 (55)
Ethnic group	
African American	56 (88)
Asian	4 (6)
Hispanic	1 (2)
Other[b]	3 (5)
G6PD enzyme activity, mean (SD), U/g Hb	3.8 (1.9) (0.7-6.9)
Severely deficient[c]	15 (23)
Deficient[d]	49 (77)
Lesion count, mean (SD) (range), No.	
Inflammatory	16.2 (12.5) (0-50)
Noninflammatory	26.5 (25.4) (0-139)
Total[e]	42.8 (27.8) (10-162)

Abbreviations: G6PD, glucose-6-phosphate dehydrogenase; Hb, hemoglobin.

[a] Unless otherwise indicated, data are reported as number (percentage) of subjects.

[b] The subjects who identified their ethnic group as other were Middle Eastern, mixed race (white black), and Haitian.

[c] *Severely deficient* is defined as 2 U/g of Hb or lower.

[d] *Deficient* is defined as higher than 2 U/g Hb up to the lower limit of normal at 7 U/g Hb.

[e] Total lesion count is the sum of inflammatory and noninflammatory lesion counts.

Table 2. Plasma Concentrations of Dapsone and *N*-Acetyl Dapsone for Subjects Treated With Dapsone Gel, 5% (Safety Population)

Measurement Time	Plasma Concentration, Mean (SD) (Range), ng/mL	
	Dapsone	*N*-Acetyl Dapsone
2 wk	5.63 (6.10)	2.77 (6.75)
(n=58 for both groups)	(0.00-36.85)	(0.00-48.70)
12 wk	5.30 ± 6.66	2.51 ± 4.79
(n=51 for both groups)	(0.00-30.58)	(0.00-26.88)

formed with Pearson correlations. A preplanned subgroup analysis based on the degrees of G6PD deficiency, which were defined as *severely deficient* (≤2 U/g Hb) and *deficient* (>2 U/g Hb up to the lower limit of normal at 7 U/g Hb) was performed for all variables related to the risk of hemolysis.

RESULTS

SUBJECT DISPOSITION AND DEMOGRAPHIC CHARACTERISTICS

A total of 756 subjects were screened for G6PD deficiency for this study; 64 subjects (8.5%) were identified as G6PD deficient and consented to participation (**Figure 1**). Of the 64 subjects in the intent-to-treat population, 63 make up the safety population and 56 make up the safety-evaluable population. Seventeen subjects did not complete the study, primarily for administrative reasons (loss to follow-up, voluntary withdrawal, treatment noncompliance, urticaria [not related to treatment], preexisting anemia [protocol violation], or pregnancy), but 1 of these subjects discontinued owing to an adverse event (mild contact dermatitis). Baseline demographics and characteristics were similar between treatment groups (**Table 1**).

PLASMA DAPSONE AND METABOLITE CONCENTRATIONS

Dapsone and *N*-acetyl dapsone levels reached steady state within 2 weeks of dapsone gel treatment and fell rapidly after the cessation of treatment (**Table 2**). In addition, in subjects who applied dapsone gel in the first treatment period (n=25), dapsone levels were largely undetectable by the start of the vehicle treatment period (me-

dian dapsone concentration, 0; maximum concentration, 1.18 ng/mL) and completely undetectable by week 2 of vehicle treatment.

HEMOLYSIS-RELATED LABORATORY RESULTS

The primary hemolysis-related analysis was performed on the safety-evaluable data set (n=56) (**Table 3**). Both the number of subjects who had a 1-g/dL Hb decrease or greater and the range of Hb changes from baseline were similar between vehicle and dapsone gel treatment regimens at weeks 2 and 12, with all of the low Hb values remaining close to the normal range. The largest decrease in Hb concentration observed in a safety-evaluable subject occurred during vehicle treatment (a 1.7-g/dL decrease at week 2). Three of 56 subjects (5%) experienced a shift in Hb level to below normal during both the vehicle and the dapsone gel treatment regimens. The changes in Hb lev-

Table 3. Hemoglobin Concentration, Changes From Baseline, and Shifts From Normal (Safety-Evaluable Population)[a]

Characteristic	Treatment Group		Within-Subject Difference[b]
	Vehicle	Dapsone, 5%	
Pretreatment measurement	13.36 (1.25) (n=56)	13.44 (1.34) (n=53)	−0.06 (0.59) (n=53)
2 wk			
Measurement result	13.34 (1.25) (n=55)	13.12 (1.36) (n=53)	−0.24 (0.70) (n=52)
Change from baseline (range)	0.01 (0.64) (−1.7 to 1.4)	−0.32 (0.55) (−1.5 to 1.5)	0.32 (0.96) (−2.4 to 2.5)
95% Confidence interval[c]	−0.16 to 0.18	−0.47 to −0.17	0.05 to 0.59
≥1-g/dL drop, No./No. (%)[d]	4/56 (7)	6/56 (11)	NA
Shift to below normal, No./No. (%)[d,e]	3/55 (5)	6/52 (12)	NA
12 wk			
Measurement result	13.37 (1.38) (n=50)	13.42 (1.24) (n=50)	−0.02 (0.64) (n=46)
Change from baseline (range)	0.01 (0.64) (−1.5 to 1.6)	−0.03 (0.59) (−1.5 to 1.4)	0.04 (0.91) (−2.0 to 2.4)
95% Confidence interval[c]	−0.18 to 0.19	−0.20 to 0.14	−0.23 to 0.32
≥1-g/dL drop, No./No. (%)[d]	4/56 (7)	2/56 (4)	NA
Shift to below normal, No./No. (%)[d,e]	4/50 (8)	3/49 (6)	NA

Abbreviation: NA, not applicable

SI conversion factor: To convert hemoglobin to grams per liter, multiply by 10.0.

[a] Unless otherwise noted, data are reported hemoglobin concentrations in mean (SD) grams per deciliter.

[b] Difference is calculated as the vehicle value minus the dapsone gel value in the same subject

[c] Confidence intervals are for the change from baseline (pretreatment value).

[d] Numerators represent the number of affected patients; denominators represent the total number of subjects at baseline.

[e] Based on observed data.

els observed at week 2 were not correlated with plasma dapsone levels, amount of daily dapsone gel use (mean, 1 g/d), or changes in bilirubin concentration (**Figure 2**), relative reticulocyte count (**Figure 3**), haptoglobin concentration (**Figure 4**), or LDH level (**Figure 5**).

Two of 56 subjects experienced a change in Hb concentration of 1 g/dL or higher with a concomitant increase of bilirubin level to above the upper limit of normal (1 subject at 2 weeks and the other at 12 weeks of dapsone gel treatment) but without any other laboratory changes or clinical signs of hemolytic anemia (4%). In addition, the subject with the changes at week 12 had similarly high bilirubin levels at week 2 of dapsone gel treatment and at week 12 of vehicle gel treatment with no concomitant change in Hb level at these time points.

Changes in hemolysis parameters were similar in various subgroups, including G6PD enzyme activity, race, sex, and age. In particular, subjects who were severely G6PD deficient (≤2 U/g Hb) did not appear to be at higher risk for changes (**Table 4**). One subject with preexisting anemia, who should have been precluded from entering the study, was treated with dapsone gel for 9 days before being withdrawn; she showed no change in her
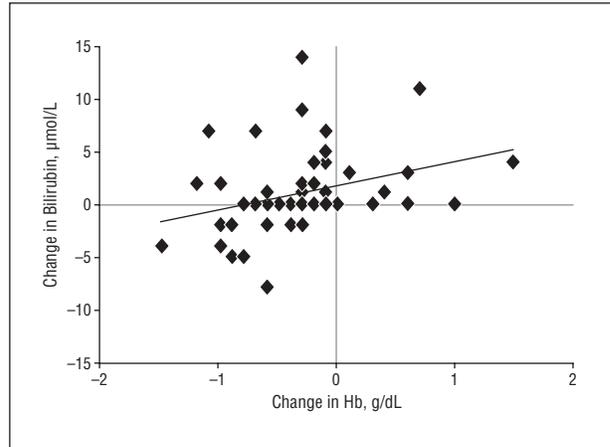

Figure 2. Correlation analysis of the change in hemoglobin (Hb) concentration vs change in bilirubin concentration at week 2 of dapsone gel, 5%, treatment: r^2=0.104 (n=52). The mean bilirubin level was 0.58 mg/dL at baseline and 0.65 mg/dL at week 2. The mean (95% confidence interval) change from baseline in bilirubin level at week 2 was +0.06 (+0.00 to +0.12) mg/dL. (Patient data were collected in SI units and converted to conventional units for summary tables. To convert bilirubin to micromoles per liter, multiply by 17.1; to convert Hb to grams per liter, multiply by 10.0.)
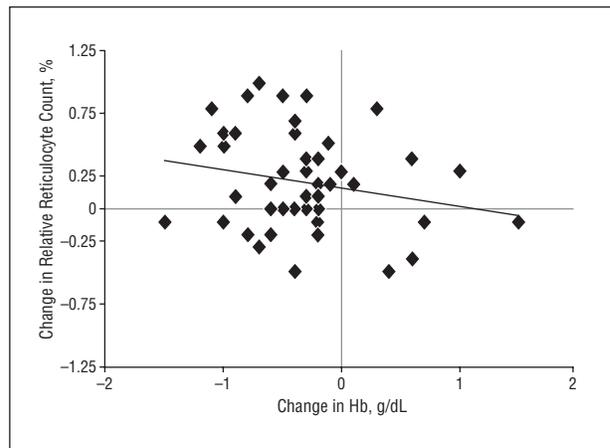

Figure 3. Correlation analysis of the change in hemoglobin (Hb) concentration vs change in relative reticulocyte count at week 2 of dapsone gel, 5%, treatment: r^2=0.043 (n=52). The mean relative reticulocyte count was 1.30% at baseline and 1.51% at week 2. The mean (95% confidence interval) change from baseline in relative reticulocyte count at week 2 was +0.22% (+0.11% to +0.32%). (To convert Hb to grams per liter, multiply by 10.0.)

laboratory parameters. Two subjects with histories of anemia completed the study and showed no changes of dapsone-related hemolysis.

ADVERSE EVENTS

No adverse events were reported that were clinical signs or symptoms of hemolytic anemia. A total of 27 of 63 subjects (43%) in the full safety data set experienced an adverse event regardless of relationship to treatment. Few adverse events were considered by the investigators to be related to dapsone gel treatment (17 of 44 events), and these occurred in only 8 of 63 subjects (13%): 7 during the dapsone gel treatment period and 1 during the vehicle treatment period. Four of these subjects reported local application site reactions of burning, dryness, pru-
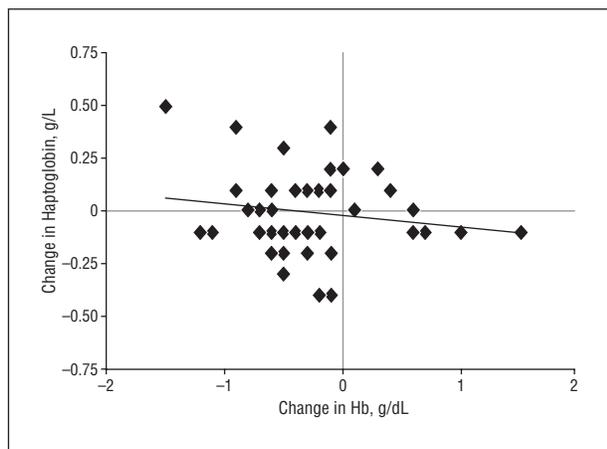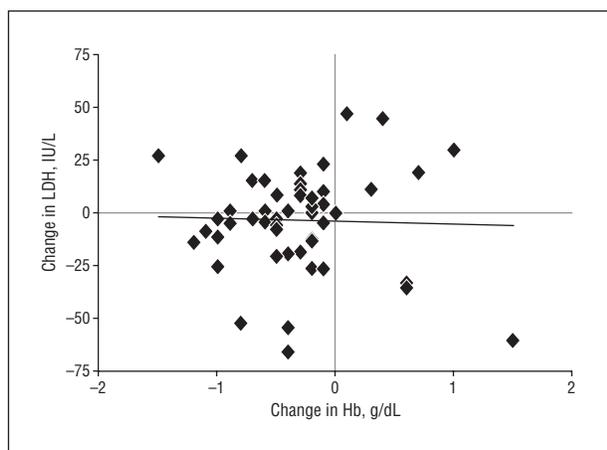
Figure 4. Correlation analysis of the change in hemoglobin (Hb) concentration vs change in haptoglobin concentration at week 2 of dapsone gel, 5%, treatment: r^2=0.027) (n=51). The mean haptoglobin level was 107.9 mg/dL at baseline and 109.1 mg/dL at week 2. The mean (95% confidence interval) change from baseline in haptoglobin level at week 2 was −0.2 (−5.3 to +5.0) mg/dL. (Patient data were collected in SI units and converted to conventional units for summary tables. To convert haptoglobin to grams per liter multiply by 0.01; to convert Hb to grams per liter, multiply by 10.0.)

Figure 5. Correlation analysis of the change in hemoglobin (Hb) concentration vs change in lactate dehydrogenase (LDH) level at week 2 of dapsone gel treatment: r^2<0.001 (n=51). The mean LDH level was 175.0 IU/L at baseline and 171.3 IU/L at week 2. The mean (95% confidence interval) change from baseline in LDH level at week 2 was −3.3 (−10.0 to 3.4) IU/L. (To convert Hb to grams per liter, multiply by 10.0; to convert LDH to microkatal per liter, multiply by 0.016%.)

ritus, or contact dermatitis (all mild). The 1 event of contact dermatitis that led to discontinuation of study treatment was mild, did not require treatment, and resolved within 14 days of study discontinuation. One subject reported a related adverse event of aggravated acne.

Three subjects had related adverse events detected by laboratory test during treatment, but none of these were indicative of hemolytic anemia: elevated bilirubin level at 2 weeks and low hematocrit and red blood cell count at 12 weeks in subject 1; low haptoglobin concentration at 2 weeks and detection of red blood burr cells, poikilocytosis, and elliptocytosis at 12 weeks in subject 2; and low white blood cell count at week 12 in subject 3. In subject 1, the elevation in bilirubin level occurred before the low hematocrit and red blood cell count and is therefore not believed to indicate hemolysis. In subject

2, plasma dapsone levels were below the limit of quantification, even though treatment use was verified by tube weights. Furthermore, the low haptoglobin concentration was present at the baseline blood test as well as week 12, and no other changes in the other hematology parameters occurred, so the laboratory adverse events for this subject are likely not related to dapsone gel treatment. For subject 3, no laboratory or clinical evidence of hemolysis or hemolytic anemia accompanied the low white blood cell count.

COMMENT

This study was designed specifically to evaluate the risk of hemolytic anemia with dapsone gel treatment in subjects with G6PD deficiency. The study used a crossover design to evaluate both dapsone gel and vehicle treatments within the same subject. Subjects were monitored for changes in hemolysis-related laboratory parameters at 2 and 12 weeks of each treatment and for any clinical signs of hemolytic anemia. Because drug-induced hemolytic anemia is a relatively acute phenomenon, the 2-week time point was determined to be the most relevant for observing any laboratory evidence of hemolysis or hemolytic anemia, while the 12-week time point would allow evaluation of any longer-term changes.[16]

An evaluation of the laboratory data shows a mean decrease in Hb level from baseline of 0.32 g/dL after 2 weeks of dapsone gel treatment, which was not seen at 12 weeks even as treatment continued. For several reasons, the decrease in Hb level at week 2 is considered clinically insignificant. Most importantly, no mean changes from baseline occurred in other laboratory markers of hemolysis at either the 2-week or 12-week time point, nor was any relationship found between changes in Hb level and these other parameters, including bilirubin, haptoglobin, and LDH levels and relative reticulocyte count. These findings strongly argue against the presence of clinically relevant hemolysis.

Second, no subjects experienced symptoms of or were diagnosed clinically with hemolytic anemia. No therapeutic interventions or modifications to study treatment were required as a consequence of a laboratory finding, even for subjects who experienced the largest decreases in Hb concentration (−1.7 g/dL and −1.5 g/dL for vehicle and dapsone gel treatment, respectively). Third, no consistent, clinically meaningful relationship was found between changes in Hb level and dapsone gel treatment. The range of Hb level changes and percentages of subjects with shifts below normal or large decreases of Hb level (≥1 g/dL) were similar between vehicle and dapsone gel treatments.

This study also provides substantive data on a subgroup of 14 subjects whose G6PD levels were severely deficient, within the lower 30% of the G6PD-deficient range (≤2 U/g Hb). Results in this subgroup were similar to those of the overall population, consistent with no difference in risk of hemolysis after dapsone gel treatment in G6PD-deficient subjects with the lowest enzyme activity. In addition, 1 subject with preexisting anemia and 2 subjects with histories of anemia participated in the study. The subject with preexisting anemia was

Table 4. Values for Hemoglobin (Hb), Bilirubin, Reticulocyte, Haptoglobin, and Lactate Dehydrogenase by Severity of G6PD Enzyme Activity[a]

Parameter	Visit	Severely G6PD Deficient (n=14)[b]		G6PD Deficient (n=42)[c]	
		Vehicle Gel	Dapsone Gel, 5%	Vehicle Gel	Dapsone Gel, 5%
Hemoglobin, g/dL[d]	Pretreatment	13.96 (0.80)	13.97 (0.81)	13.15 (1.32)	13.25 (1.44)
	2 wk	13.91 (0.98)	13.65 (0.79)	13.14 (1.28)	12.93 (1.48)
	12 wk	13.85 (0.85)	13.86 (1.05)	13.21 (1.50)	13.24 (1.28)
Bilirubin, mg/dL	Pretreatment	0.7 (0.3)	0.7 (0.2)	0.5 (0.3)	0.5 (0.3)
	2 wk	0.7 (0.3)	0.8 (0.3)	0.5 (0.2)	0.6 (0.3)
	12 wk	0.8 (0.3)	0.7 (0.4)	0.6 (0.4)	0.5 (0.3)
Reticulocytes, %	Pretreatment	1.38 (0.42)	1.29 (0.45)	1.33 (0.63)	1.31 (0.47)
	2 wk	1.31 (0.44)	1.59 (0.57)	1.35 (0.55)	1.48 (0.51)
	12 wk	1.45 (0.48)	1.38 (0.53)	1.39 (0.59)	1.53 (0.61)
Haptoglobin, mg/dL	Pretreatment	93.57 (35.86)	99.23 (30.13)	118.10 (53.89)	110.75 (48.17)
	2 wk	107.86 (29.66)	102.14 (42.82)	117.00 (48.42)	111.54 (42.15)
	12 wk	95.38 (32.05)	96.43 (30.54)	117.03 (53.64)	120.57 (50.11)
Lactate dehydrogenase, IU/L	Pretreatment	166.5 (34.5)	162.0 (31.3)	177.5 (38.9)	179.6 (35.8)
	2 wk	165.1 (40.1)	169.2 (32.1)	179.0 (38.3)	172.1 (31.6)
	12 wk	165.8 (33.4)	174.1 (43.8)	180.5 (36.8)	177.1 (34.2)

Abbreviation: G6PD, glucose-6-phosphate dehydrogenase.
SI conversion factors: to convert Hb to grams per liter, multiply by 10.0; bilirubin to micromoles per liter, multiply by 17.1; haptoglobin to g/L, multiply by 0.01; lactate dehydrogenase to microkatal per liter, multiply by 0.0167.
[a] Unless otherwise indicated, data are reported as mean (SD) values.
[b] *Severely deficient* is defined as 2 U/g Hb or lower.
[c] *Deficient* is defined as higher than 2 U/g Hb up to the lower limit of normal at 7 U/g Hb.
[d] Patient data were collected in SI units and converted to conventional units for summary tables.

withdrawn from the study after 9 days of treatment, but the other 2 subjects completed the full 28 weeks of the study. None of these 3 subjects experienced any changes in chemistry and hematology parameters indicative of dapsone-related hemolysis.

The prevalence of G6PD deficiency in African American men can be almost 3 times higher than that of African American women, consistent with its X-linked transmission.[8] In this study, the ratio of male to female subjects with G6PD deficiency was almost equal. One could speculate that because almost 60% of individuals who present at dermatologists' offices for skin concerns are female,[17] and at least 41% of women will have acne at various times in their lives,[18] investigators were able to identify a large number of female patients with both G6PD deficiency and acne. Subgroup analyses of all variables related to hemolysis showed no differences between men and women, and findings were similar to those in the overall safety-evaluable population.

Plasma dapsone and *N*-acetyl dapsone levels were measured before any treatment and at the 2-week and 12-week time points of each treatment period to assess systemic exposure. Dapsone and *N*-acetyl dapsone levels reached steady state within 2 weeks of treatment initiation with dapsone gel and fell rapidly after the cessation of treatment. Exposure to dapsone by the termination of topical dapsone gel treatment was low, considering both the mean (approximately 5-ng/mL) and the maximum (approximately 37-ng/mL) exposures in the study (Table 2). The level of dapsone exposure observed in this study is substantially lower than the levels associated with oral dosing that would be expected to cause hematologic changes.[11] Data from a previous crossover pharmacokinetic study show that systemic dapsone exposure following topical dapsone gel treatment at steady state is approximately 100-fold lower than exposure to a single 100-mg oral dose of dapsone.[13] Pharmacokinetic modeling indicates that steady state systemic dapsone levels after topical dapsone gel treatment would still be approximately 35-fold to 63-fold (area under the curve) lower than the systemic levels of dapsone following a single 50-mg oral dose. The absence of any hemolytic anemia in subjects with G6PD deficiency who used dapsone gel for acne was anticipated based on the low overall systemic exposure to dapsone observed after treatment with dapsone gel.[13,14]

The results from this study demonstrate that there were no clinically significant effects on chemistry and hematology parameters or clinical signs of hemolytic anemia in subjects with G6PD deficiency following treatment of acne vulgaris with dapsone gel. Because G6PD deficiency represents a highly sensitive marker for the hemolytic potential of drugs, this finding can be extrapolated to patients with acne and normal G6PD enzyme activity. Data from this study support the conclusions that the safety profile for topical dapsone gel treatment is excellent, and that the risk of hemolytic anemia during treatment with dapsone gel for acne vulgaris is remote for all patients, including those with G6PD deficiency.

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