Efficacy and Safety of Dapsone Gel 5% for the Treatment of Acne Vulgaris in Adolescents

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Two 12-week, randomized, vehicle-controlled, double-blinded pivotal studies and a 12-month, long-term, open-label, noncomparative safety study were conducted to evaluate the efficacy and safety of dapsone gel 5% in patients with acne vulgaris. Of 3516 participants enrolled in the 3 trials, 1306 participants (37%) were adolescents aged 12 to 15 years and comprised the subgroup reported here. Participants randomly were assigned to twice-daily treatment with dapsone gel (n=578) or vehicle gel (n=547) in the pivotal studies and received open-label treatment with dapsone gel in the long-term safety study (n=181). In the pivotal studies, success based on achieving a Global Acne Assessment Score (GAAS) of 0 (none) or 1 (minimal) at week 12 was significantly greater for the dapsone gel–treated adolescent participants (40.1%; 232/578) compared with the vehicle gel–treated adolescent participants (28.2%; 154/547)(P<.001). Treatment with dapsone gel in adolescents also resulted in clinically meaningful improvements in acne lesion counts by week 12 in the pivotal studies and for up to 12 months in the long-term safety study. The incidence of adverse events, including application-site events, was low and similar between treatment groups in the pivotal studies and was similarly low in the long-term safety study. Results from the large number of adolescent participants in these 3 studies show that dapsone gel is an effective and safe topical therapy for the treatment of acne vulgaris in adolescents aged 12 to 15 years for up to 12 months.

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Acne vulgaris is a common skin disease presenting in late childhood and adolescence, with a peak onset in early adolescence. Approximately 85% of the adolescent population is affected by acne to some degree.[1] Acne development is initiated during adrenarche when the adrenal glands begin to secrete androgenic hormones, thereby increasing sebum production in the sebaceous glands. Around the time of puberty, the ovaries and testes begin to produce androgens, which can further increase sebum production and promote the development of acne.[2] Prompt treatment is essential, as the often early onset of acne can result in a prolonged disease state; potentially long-lasting disfigurement; and negative effects on psychologic and social functioning, including academic and vocational performance.[3]

The pathogenesis of acne vulgaris is multifactorial. Known contributors include follicular hyperproliferation,

excess sebum, inflammation, and the presence and activity of *Propionibacterium acnes*.[4] The sequence of events in the pathogenic process of acne development remains unclear. Historically, inflammation was thought to be a secondary response to *P acnes*. According to Jeremy et al,[5] expression of IL-1α was identified in the microcomedone, the earliest subclinical acne lesion, suggesting that inflammation may play a primary role in the development of acne. Inflammation, manifested by the presence of CD4 cells around acne lesions, also has been linked to scarring.[6]

Dapsone, a sulfone that exhibits antimicrobial and anti-inflammatory activity, has been used for decades to treat various dermatologic diseases, including acne[7-10]; however, its oral use has been limited because of the potential to cause dose-related adverse hematologic reactions such as hemolytic anemia.[11-13] Individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency may be more susceptible to these reactions.[7] Recently, a topical gel formulation of dapsone was developed for the treatment of acne. It was hypothesized that a topical product would offer the local antimicrobial and anti-inflammatory benefits of dapsone, with minimal systemic exposure. Two 12-week, randomized, vehicle-controlled, double-blinded pivotal studies and a 12-month, long-term, open-label, noncomparative safety study assessed the efficacy and safety of dapsone gel 5% in study participants with acne vulgaris. The 12-week pivotal studies provided strong evidence of efficacy, while the 12-month long-term safety study provided additional support for the safe use of dapsone gel in a long-term setting. More than 1300 adolescents aged 12 to 15 years were followed in these 3 clinical trials, offering a substantial amount of efficacy and safety data on the treatment of acne with dapsone gel in early adolescence. Results for this participant subgroup are presented here.

Methods

One hundred eight study centers in the United States and Canada enrolled participants; all study protocols were reviewed and approved by an institutional review board or ethics committee, and participants and their parents/guardians gave written informed assent and consent prior to the start of study procedures.

Study Design—Two 12-week, randomized, vehicle-controlled, double-blinded pivotal studies and a 12-month, long-term, open-label, noncomparative safety study were conducted. Additional description of study methods have been published by Lucky et al[14] and Draelos et al.[15]

Participants—Individuals 12 years or older with acne vulgaris were eligible for enrollment; the subgroup of participants aged 12 to 15 years is presented here. In the pivotal studies, enrollment criteria included the presence of 20 to 50 inflammatory lesions (papules and pustules) and 20 to 100 noninflammatory lesions (comedones) above the mandibular line at baseline. In the long-term safety study, enrollment criteria included the presence of at least 20 inflammatory lesions at baseline (10 or more lesions on the face). In the pivotal studies, participants were randomly assigned (1:1) to receive either dapsone gel or vehicle gel[15] and received open-label treatment with dapsone gel in the long-term safety study.[14] Randomization was not stratified by any baseline characteristic, such as age.

Treatment Plan—After washing with a standard noncomedogenic soap-free cleanser, participants applied a thin film of dapsone gel or vehicle gel to acne-affected areas for 12 weeks in the pivotal studies (face only) and for 12 months in the long-term safety study (face, back, shoulders, and chest, as needed, with dapsone gel only).

Efficacy Assessments—In the pivotal studies, the primary efficacy variables were success rate based on a Global Acne Assessment Score (GAAS) of 0 or 1 on a 5-point scale (0=none, 1=minimal, 2=mild, 3=moderate, 4=severe) and reduction from baseline in acne lesion counts (inflammatory, noninflammatory, total lesions) at week 12. Efficacy parameters were evaluated at baseline and at weeks 2, 4, 6, 8, and 12 in the pivotal studies. In the long-term safety study, the primary end point was safety, but efficacy information was assessed by evaluating acne lesion counts (inflammatory, noninflammatory, total lesions) at baseline and at months 1, 3, 4, 6, 9, and 12.

Safety Assessments—Safety was assessed by monitoring the frequency and severity of adverse events (regardless of relationship to study medication) and the results of routine laboratory tests and physical examinations. Participants were screened for G6PD deficiency at baseline in the pivotal studies and at month 6 in the long-term safety study. Adverse events were categorized as application or nonapplication site at the time of data collection. Local signs or symptoms of oiliness, peeling, dryness, and erythema at the application site were elicited at each visit in the pivotal studies and were spontaneously reported in the long-term safety study. Worsening of any local sign or symptom from baseline, or the appearance of a unique local sign or symptom, was reported as an application-site adverse event.

Statistical Methods—The efficacy and safety analyses were performed on all adolescent participants aged 12 to 15 years who were part of the intention-to-treat (all enrolled participants who were dispensed study drug) and safety-evaluable populations (all participants who applied study drug). Efficacy results are presented using last observation carried forward for the pivotal studies and observed data for the long-term safety study (an ad hoc last observation carried forward

Table 1.

Participant Demographics and Baseline Disease Characteristics of Adolescents (Intention-to-Treat Population)[a]

	12-Wk Pivotal Studies		12-Mo Long-term Safety Study
	Dapsone Gel 5% (n=578)	Vehicle Gel (n=547)	Dapsone Gel 5% (n=181)
Sex, n (%)			
Male	331 (57.3)	322 (58.9)	108 (59.7)
Female	247 (42.7)	225 (41.1)	73 (40.3)
Race/Ethnicity, n (%)			
White	471 (81.5)	435 (79.5)	157 (86.7)
Black	55 (9.5)	52 (9.5)	9 (5.0)
Hispanic	45 (7.8)	39 (7.1)	10 (5.5)
Asian	2 (0.3)	8 (1.5)	2 (1.1)
Other	5 (0.9)	13 (2.4)	3 (1.7)
GAAS, n (%)[b]			
0	0 (0)	0 (0)	N/A
1	33 (5.7)	28 (5.1)	N/A
2	184 (31.8)	175 (32.0)	N/A
3	348 (60.2)	320 (58.5)	N/A
4	13 (2.2)	24 (4.4)	N/A
Acne Lesion Counts			
Inflammatory			
Mean (SD)	32 (11)	32 (10)	34 (22)
Minimum, maximum	14, 114	18, 88	10, 189
Noninflammatory			
Mean (SD)	53 (24)	54 (24)	38 (32)
Minimum, maximum	20, 156	8, 125	0, 270
Total lesions			
Mean (SD)	85 (29)	86 (28)	72 (41)
Minimum, maximum	40, 219	37, 200	12, 299

Abbreviations: GAAS, Global Acne Assessment Score; N/A, not applicable.

[a]Subgroup analysis of participants aged 12 to 15 years from two 12-week, randomized, vehicle-controlled, double-blinded pivotal studies and a 12-month, long-term, open-label, noncomparative safety study.[14,15] Intention-to-treat population includes all participants who were dispensed study drug.

[b]GAAS 5-point scale: 0=none, 1=minimal, 2=mild, 3=moderate, 4=severe.

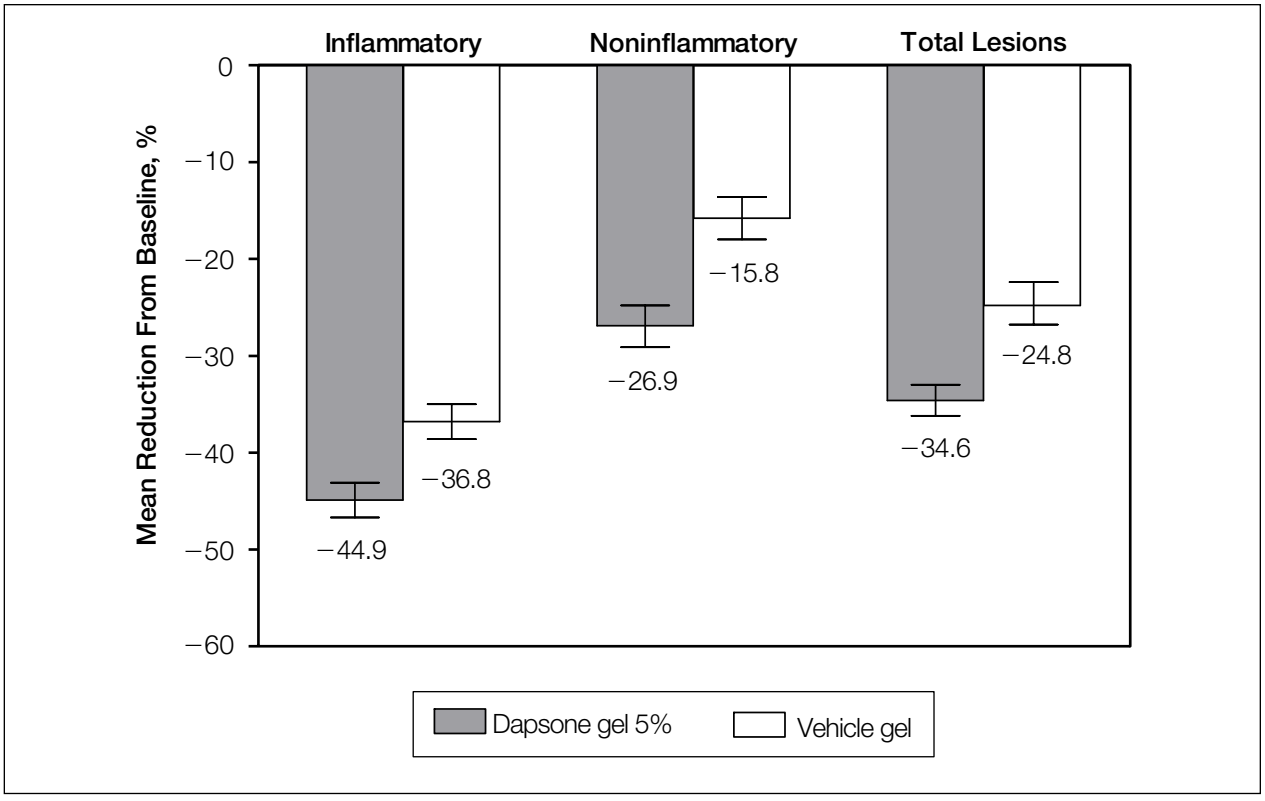

Figure 1. Mean percentage reduction from baseline in acne lesion counts at week 12 for adolescent participants (12-week pivotal studies). *P* values were calculated using an analysis of variance ($P<.001$ for all). Mean calculated using least squares method. Error bars indicate SE.

analysis showed similar outcomes). Subgroup efficacy analyses categorized by age (12–15 years, >16 years) were prospectively planned for the primary efficacy end points in the pivotal studies, and statistical comparisons of the 2 treatment groups used a significance level of .05. In the long-term safety study, all efficacy and safety measures were summarized using descriptive statistics, and additional retrospective analyses were performed to evaluate the statistical significance of the mean reduction from baseline in acne lesion counts for the adolescent subgroup using a paired *t* test at $\alpha=.05$. Additional description of statistical analyses has been provided by Lucky et al[14] and Draelos et al.[15]

Results

Participant Disposition and Baseline Disease Characteristics—Of 3516 participants enrolled in the pivotal and long-term safety studies,[14,15] 1306 participants (37%) were adolescents aged 12 to 15 years. In the pivotal studies, approximately 88% of participants in the dapsone gel (509/578) and vehicle gel (484/547) treatment groups completed the 12-week studies, while approximately 76% of participants (137/181) completed the 12 months of the long-term safety study. Less than 2% of adolescent participants (22/1306) discontinued the studies because of adverse events or lack of efficacy, and the remainder (12%; 154/1306) discontinued for administrative reasons (ie, lost to follow-up, voluntary withdrawal, protocol violation, treatment noncompliance). Participant demographics and baseline disease characteristics are listed in Table 1.

Treatment Exposure—In the pivotal studies, adolescent participants in both treatment groups applied the study treatment for approximately 99% of study days (mean, 81 days). Dapsone gel–treated participants used a mean of approximately 1.25 g/d of study treatment, and vehicle-treated participants used a mean of approximately 1.30 g/d. Similar compliance (97%) was observed in the long-term safety study, and the mean amount of study drug used also was similar (approximately 1.19 g/d). Additionally, 76% of adolescent participants (134/176) in the long-term safety study used dapsone gel as a single agent for more than 9 months (safety-evaluable population).

Efficacy Assessments—In the pivotal studies, dapsone gel was significantly more effective than vehicle gel for all measured efficacy parameters. At week 12, 40.1% of dapsone gel–treated adolescent participants (232/578) achieved GAAS success (defined as a GAAS of 0 or 1)

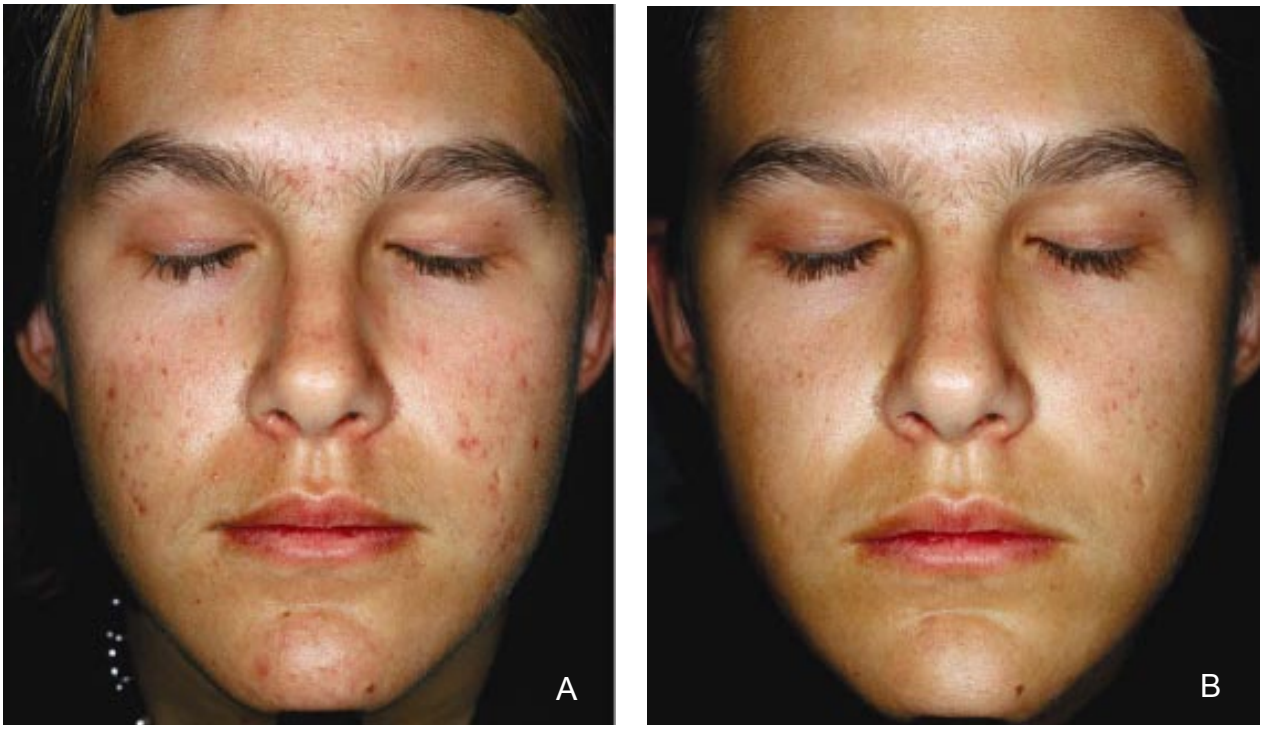

Figure 2. Effect of dapsone gel 5% on a 15-year-old study participant with a Global Acne Assessment Score of 2 (mild) at baseline (A) and 1 (minimal) at week 12 (B).

versus 28.2% of adolescent participants treated with vehicle gel (154/547)($P<.001$). These results are similar to adult participants 16 years and older, in which 40.7% of participants (378/928) compared with 35.5% of participants (340/957), treated with dapsone gel and vehicle gel, respectively, achieved GAAS success ($P=.002$). For all acne lesion counts, the mean percentage reduction from baseline at week 12 was statistically significantly greater in the dapsone gel–treated adolescents compared with the vehicle gel–treated adolescents ($P<.001$ for all) (Figure 1). Figure 2 depicts improvement in acne lesions for an adolescent participant treated with dapsone gel in the 12-week pivotal studies. In the long-term safety study, a gradual reduction in all acne lesion types was observed during the first 4 to 6 months of treatment to levels that were sustained throughout the 12-month treatment period (Figure 3).

Safety Assessments—Results for safety are based on the safety-evaluable population. In the pivotal studies, at week 12, the percentage of adolescent participants reporting application-site and nonapplication-site adverse events was similar for both the dapsone gel and vehicle gel treatment groups (Table 2). Only application-site adverse events were considered by the investigator to be possibly related to treatment. Most events were mild or moderate in severity, and only 2 dapsone gel–treated and 5 vehicle gel–treated adolescent participants discontinued study treatment because of adverse events (dapsone gel–treated adverse events: increased blood creatinine phosphokinase level, contact dermatitis; vehicle gel–treated adverse events: application-site dryness and pruritus, application-site erythema, aggravated depression, application-site erythema and rash, impetiginous rash and aggravated acne). There also was a reduction from baseline to week 12 in the incidence of local signs or symptoms (ie, oiliness, peeling, dryness, erythema) for both the dapsone gel and vehicle gel treatment groups. At week 12 (observed data), the most common local signs or symptoms among adolescent participants were erythema and oiliness, reported in 33.4% (178/533) and 23.8% (127/533) of dapsone gel–treated participants, respectively (difference from baseline, −16.5% and −26.5%, respectively), versus 37.7% (193/512) and 30.1% (154/512) of vehicle gel–treated participants, respectively (difference from baseline, −13.8% and −18.2%, respectively).

In the long-term safety study, approximately 2% of adolescent participants (4/176) experienced application-site adverse events. Four participants reported one application-site adverse event each: application-site reaction, burning, pruritus, and irritation. The most frequently reported nonapplication-site adverse events were headache and nasopharyngitis (Table 2) and most were not considered related

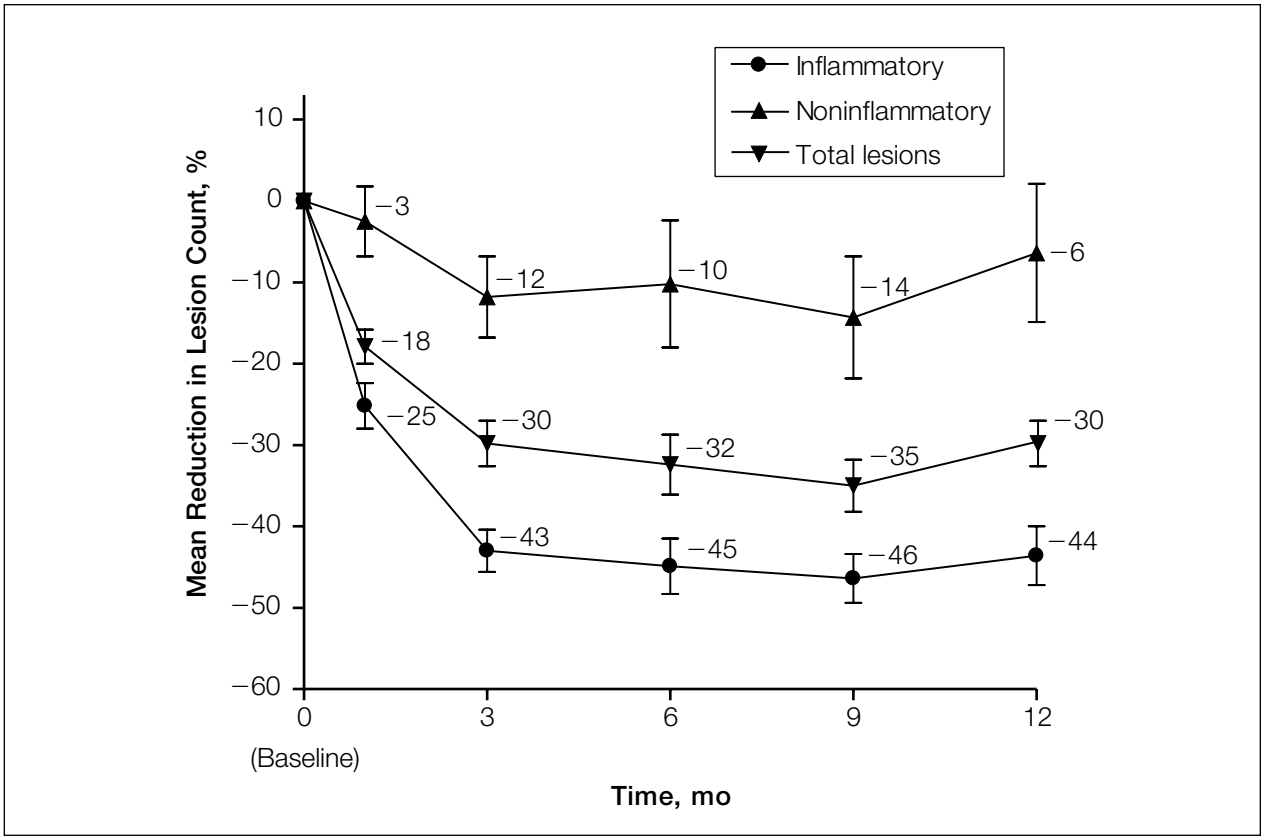

Figure 3. Mean percentage reduction from baseline in acne lesion counts from baseline to month 12 for adolescent participants (12-month long-term safety study). Error bars indicate SE. Paired *t* test compared month 0 (baseline) to month 12 for each lesion category (inflammatory lesions, $P<.001$; noninflammatory lesions, $P=.454$; total lesions, $P<.001$).

to treatment with dapsone gel. No adolescent participants discontinued treatment in the long-term safety study because of adverse events.

Laboratory Profiles—No clinically meaningful changes in hematology or serum chemistry values were observed in adolescent participants during any of the studies. In the pivotal studies, 13 adolescent participants (7 dapsone gel treated, 6 vehicle gel treated) were G6PD deficient at baseline. Twelve of these participants had hemoglobin values within reference range at baseline and throughout the study; one patient treated with vehicle gel had a hemoglobin value that shifted from within the reference range at baseline to slightly below the reference range at week 12. In the long-term safety study, one adolescent participant was G6PD deficient. The hemoglobin value for this participant was within reference range at baseline and remained within reference range throughout the study.

In the long-term safety study, the frequency of abnormal laboratory values observed during the study up to month 12 was similar to baseline, and no clinically important differences in mean change from baseline for hematology or serum chemistry parameters were identified throughout the study duration. Thiboutot et al[16] reported the pharmacokinetic results for the total population of the long-term safety study.

Comment

In the pivotal studies, clinical improvement was demonstrated for dapsone gel–treated adolescent participants based on significantly improved GAAS ($P<.001$) and statistically significant reductions in inflammatory, noninflammatory, and total lesions from baseline to week 12 ($P<.001$ for all). Although this is a subgroup of the randomized population, it is a large number of participants, and the subgroup analysis was prospectively planned as part of the original study design. Furthermore, the demographics of the 2 treatment groups were balanced at baseline and the results were similar to those of the entire randomized intention-to-treat population.[15] The responses seen in the dapsone gel–treated participants for the percentage reduction of acne lesion counts at week 12 fall within the range of responses observed in clinical trials of currently available topical therapies for individuals with acne vulgaris.[17-20] In the long-term safety study, clinically meaningful decreases from baseline to month 12 in the number of lesions in all 3 lesion categories also were observed for adolescent participants.

Table 2.

Common Adverse Events in Adolescent Participants (Safety-Evaluable Population)[a]

Adverse Event	Participants, n (%)	
	Dapsone Gel 5%	Vehicle Gel
12-Wk Pivotal Studies	n=569	n=544
Application-site adverse events[b]		
Application-site reaction[c]	115 (20.2)	120 (22.1)
Dryness	109 (19.2)	91 (16.7)
Erythema	88 (15.5)	92 (16.9)
Nonapplication-site adverse events		
Nasopharyngitis	44 (7.7)	46 (8.5)
Headache	27 (4.7)	19 (3.5)
12-Mo Long-term Safety Study[d]	n=176	N/A
Nonapplication-site adverse events		
Headache	41 (23.3)	N/A
Nasopharyngitis	29 (16.5)	N/A
Pharyngitis	23 (13.1)	N/A
Upper abdominal pain	14 (8.0)	N/A
Dysmenorrhea	13 (7.4)	N/A
Sinusitis	12 (6.8)	N/A
Cough	11 (6.3)	N/A
Upper respiratory tract infection	10 (5.7)	N/A
Influenzalike illness	9 (5.1)	N/A
Joint sprain	9 (5.1)	N/A
Pyrexia	9 (5.1)	N/A
Toothache	9 (5.1)	N/A

Abbreviation: N/A, not applicable.
[a]Any adverse event experienced by at least 5% of participants. The safety-evaluable population includes all participants who applied study drug.
[b]Application-site adverse events were elicited at each visit in the pivotal studies and were spontaneously reported in the long-term safety study. Local signs or symptoms were reported as adverse events if they worsened from baseline or were unique.
[c]Includes facial oiliness and peeling.
[d]No application-site adverse event occurred at an incidence of ≥1% of adolescent participants in the long-term safety study.

Notably, a quick onset of action was observed with dapsone gel; response was seen as early as one month. Although all lesions responded to treatment in all 3 studies, the greatest response was seen in inflammatory lesions following treatment with dapsone gel. Presuming that inflammation is a key event in the formation of acne, these findings are not unexpected; dapsone is known to exhibit anti-inflammatory properties.[7,21]

Dapsone gel was well-tolerated by these adolescent study participants, and the incidence of adverse events did not increase during the 12-week

or 12-month studies. Most adverse events judged as associated with dapsone gel in the pivotal studies occurred at the site of drug application and were generally mild or moderate in severity. Application-site reactions were rarely reported in the long-term safety study. The tolerance of dapsone gel was further confirmed by the treatment compliance observed among adolescent participants in all 3 studies. Adolescent participants used the study drug for 97% to 99% of study days, and more than three quarters of participants in the long-term safety study used dapsone gel as a single agent for more than 9 months. Although adherence to treatment tends to be better in clinical trials, these findings are noteworthy, as adolescents are known to have high rates of noncompliance with treatment.[22]

Conclusion

Data from the adolescent subgroup of these 3 studies supported that dapsone gel was effective, safe, and well-tolerated for periods of up to one year in the treatment of acne in participants aged 12 to 15 years, similar to the overall study population.[15] The availability of a topical gel that delivers a clinically effective dose of dapsone with minimal systemic exposure[16] provides physicians with an additional treatment option for individuals with acne vulgaris, either used as monotherapy or in combination with other therapies. Furthermore, this new treatment could allow physicians to target the inflammation associated with acne by mechanisms that may differ from conventional antibiotics.

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REFERENCES

1. Weiss JS. Current options for the topical treatment of acne vulgaris. *Pediatr Dermatol*. 1997;14:480-488.
2. Bergfeld WF. The pathophysiology of acne vulgaris in children and adolescents, part 1. *Cutis*. 2004;74:92-97.
3. McConnell RC, Fleischer AB Jr, Williford PM, et al. Most topical tretinoin treatment is for acne vulgaris through the age of 44 years: an analysis of the National Ambulatory Medical Care Survey, 1990-1994. *J Am Acad Dermatol*. 1998;38:221-226.
4. Harper JC, Thiboutot DM. Pathogenesis of acne: recent research advances. *Adv Dermatol*. 2003;19:1-10.
5. Jeremy AH, Holland DB, Roberts SG, et al. Inflammatory events are involved in acne lesion initiation. *J Invest Dermatol*. 2003;121:20-27.
6. Holland DB, Jeremy AH, Roberts SG, et al. Inflammation in acne scarring: a comparison of the responses in lesions from patients prone and not prone to scar. *Br J Dermatol*. 2004;150:72-81.
7. Zhu YI, Stiller MJ. Dapsone and sulfones in dermatology: overview and update. *J Am Acad Dermatol*. 2001;45:420-434.
8. Fredenberg MF, Malkinson FD. Sulfone therapy in the treatment of leukocytoclastic vasculitis. report of three cases. *J Am Acad Dermatol*. 1987;16:772-778.
9. Ross CM. The treatment of acne vulgaris with dapsone. *Br J Dermatol*. 1961;73:367-370.
10. Kaminsky CA, de Kaminsky AR, Schicci C, et al. Acne: treatment with diaminodiphenylsulfone. *Cutis*. 1974;13:869-871.
11. Bluhm RE, Adedoyin A, McCarver DG, et al. Development of dapsone toxicity in patients with inflammatory dermatoses: activity of acetylation and hydroxylation of dapsone as risk factors. *Clin Pharmacol Ther*. 1999;65:598-605.
12. Ciccoli L, Ferrali M, Rossi V, et al. Hemolytic drugs aniline and dapsone induce iron release in erythrocytes and increase the free iron pool in spleen and liver. *Toxicol Lett*. 1999;110:57-66.
13. Jollow DJ, Bradshaw TP, McMillan DC. Dapsone-induced hemolytic anemia. *Drug Metab Rev*. 1995;27:107-124.
14. Luckt AW, Maloney JM, Roberts J, et al. Dapsone gel 5% for the treatment of acne vulgaris: safety and efficacy of long-term (1 year) treatment. *J Drug Dermatol*. 2007;6:981-987.
15. Draelos ZD, Carter E, Maloney JM, et al; United States/Canada Dapsone Gel Study Group. Two randomized studies demonstrate the efficacy and safety of dapsone gel, 5% for the treatment of acne vulgaris. *J Am Acad Dermatol*. 2007;56:439.e1-e10.
16. Thiboutot D, Willmer J, Sharata H, et al. Pharmacokinetics of dapsone gel, 5% for the treatment of acne vulgaris. *Clin Pharmacokinet*. 2007;46:697-712.
17. Cunliffe WJ, Poncet M, Lowsche C, et al. A comparison of the efficacy and tolerability of adapalene 0.1% gel versus tretinoin 0.025% gel in patients with acne vulgaris: a meta-analysis of five randomized trials. *Br J Dermatol*. 1998;139(suppl 52):48-56.
18. Benzaclin Topical Gel [package insert]. Berwyn, PA: Dermik Laboratories; 2003.
19. Duac Topical Gel [package insert]. Coral Gables, FL: Stiefel Laboratories, Inc; 2003.
20. Jeremy AH, Holland DB, Roberts SG, et al. Inflammatory events are involved in acne lesion initiation. *J Invest Dermatol*. 2003;121:20-27.
21. Haider A, Shaw JC. Treatment of acne vulgaris. *JAMA*. 2004;292:726-735.
22. Matsui DM. Drug compliance in pediatrics. clinical and research issues. *Pediatr Clin North Am*. 1997;44:1-14.