Newer Topical Therapies for the Treatment of Acne Vulgaris

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Newer topical therapies approved by the US Food and Drug Administration (FDA) for the treatment of acne vulgaris are dapsone gel 5% and clindamycin phosphate 1.2% and tretinoin 0.025% combination gel. Both are formulated in aqueous-based gel vehicles. These newer topical acne products have been shown to be effective and safe in pivotal 12-week phase 3 trials and long-term studies completed over 12 months. This article reviews applicable pharmacokinetic, efficacy, and safety data reported with both products.

Cutis. 2007;80:400-410.

Topical therapy is a vital component in the management of acne vulgaris, regardless of the severity of disease.[1] In most situations, with the exception of mild cases presenting with predominantly noninflammatory acne lesions, combination topical therapy is considered to be the optimal approach. Systemic treatment, such as oral antibiotic therapy, is added to a topical treatment program in patients presenting with moderately severe to severe involvement or when there is a less than favorable response to topical treatment alone.[1,2] Although complete clearance of acne vulgaris is an unrealistic expectation in all patients, a properly designed acne treatment program that is used consistently can usually achieve marked success if tailored to the severity of the disease and the specific needs of the patient.

Two new topical therapies have been approved by the US Food and Drug Administration (FDA) for the treatment of acne vulgaris. The first is dapsone gel 5%, which is formulated in an aqueous gel base and approved for twice-daily application. The second is a combination aqueous gel formulation containing solubilized clindamycin phosphate 1.2% and solubilized and crystalline tretinoin 0.025%. At present, dapsone gel 5% is not available in the marketplace because the manufacturer has elected to await FDA evaluation of data on use in a cohort of patients with documented glucose 6-phosphate dehydrogenase (G6PD) deficiency.

Accepted for publication September 5, 2007.

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DAPSONE GEL 5%

What information supports the use of topical dapsone for the treatment of acne vulgaris?

Dapsone is a sulfone derivative that has been used orally for the treatment of leprosy and several inflammatory dermatoses, including dermatitis herpetiformis, pyoderma gangrenosum, bullous lupus erythematosus, linear immunoglobulin A dermatosis, and bullous pemphigoid.[3-5] Dapsone exhibits multiple anti-inflammatory activities that support the diversity of its applications, primarily including neutrophilic dermatoses. Biologic activities observed in some reports with dapsone include inhibition of neutrophil and eosinophil myeloperoxidase, inhibition of neutrophil adhesion to vascular endothelium, inhibition of 5-lipogenase product generation by neutrophils and macrophages, suppression of neutrophil recruitment and migration, and release of lysosomal enzymes by neutrophils.[3,4]

Prior to the introduction of oral isotretinoin in the early 1980s, oral dapsone was used when conventional topical and systemic antibiotic therapies proved to be unsuccessful in patients with severe, refractory, inflammatory acne vulgaris. However, the use of oral dapsone was limited by the potential for serious complications, including hemolytic anemia, especially in patients with G6PD deficiency; methemoglobinemia; agranulocytosis; drug

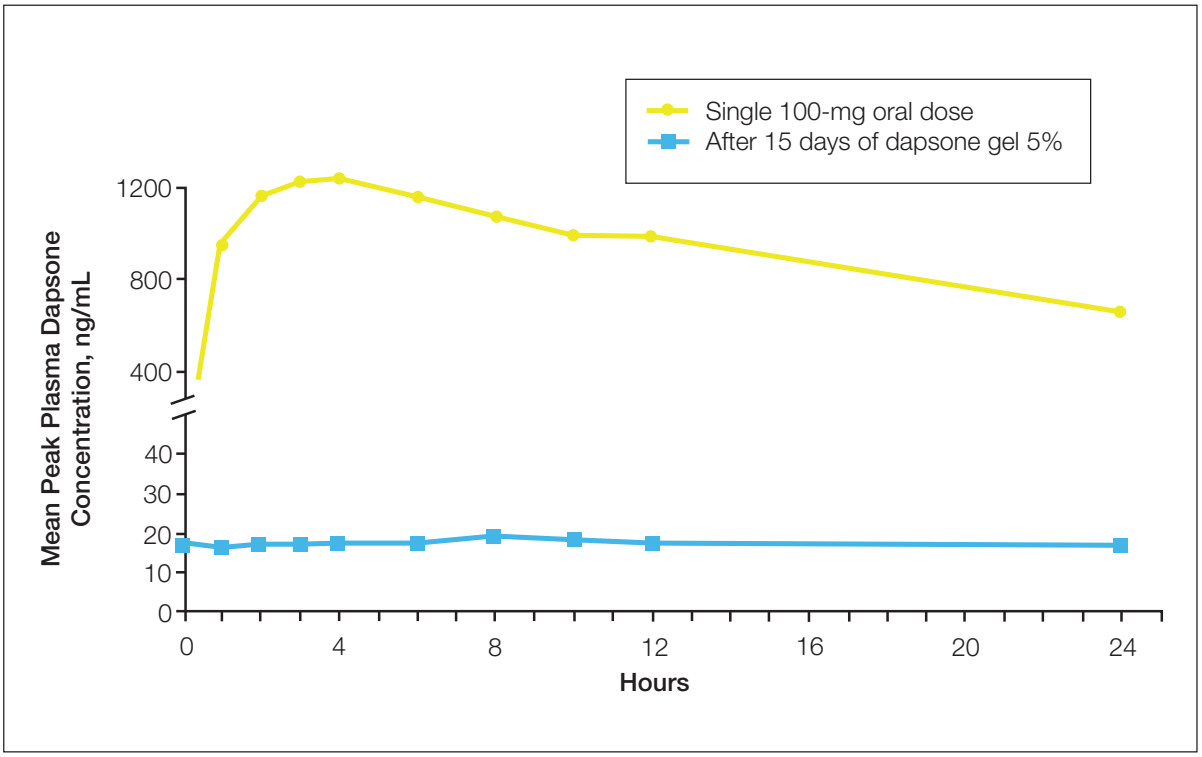

Figure 1. Pharmacokinetics of topical application of dapsone gel 5% over 14 days versus a single 100-mg dose of oral dapsone. Data from Thiboutot et al.[6]

hypersensitivity syndrome; and distal motor neuropathy.[3] Additional factors complicating the use of oral dapsone for the treatment of acne vulgaris are the chronic nature of the disease, which necessitates long-term or repeated use of oral dapsone in many cases, and the likely concern about side effects from parents and/or guardians of patients 18 years and younger who commonly present with severe acne vulgaris and need treatment.

Topical dapsone 5%, formulated in an aqueous-based gel vehicle, has been developed for treatment of acne vulgaris based on the objective of reducing acne lesions through anti-inflammatory activities of the drug, while circumventing toxicities associated with systemic dapsone use. Short-term and long-term pharmacokinetic analyses, pivotal phase 3 and combination therapy studies, and safety evaluations support the use of dapsone gel 5% in patients with facial acne vulgaris.[6-9] In the 2 pivotal multicenter, randomized, double-blind, vehicle-controlled, 12-week phase 3 trials, inclusive of 3010 subjects, 1506 subjects were actively treated topically with dapsone gel 5% twice daily.[7] A randomized, double-blind, 12-week topical combination therapy study examined the use of dapsone gel 5% concomitantly with benzoyl peroxide 4% (n=98), adapalene gel 0.1% (n=100), or vehicle gel (n=103) for the treatment of acne vulgaris.[8] Evaluation of the trials completed with dapsone gel 5% to date has established efficacy, favorable skin tolerability, and safety, with no evidence of clinically relevant hematologic or systemic abnormalities and no reports of hemolytic anemia.

What have the pharmacokinetic studies completed with dapsone gel 5% demonstrated?

The potential toxicity concerns related to oral dapsone use underscored the need for completion of careful pharmacokinetic and safety analysis with dapsone gel 5% applied twice daily. Systemic bioavailability after application of dapsone gel 5% has been evaluated in 14-day (N=18) and 52-week (N=340) pharmacokinetic studies.[6] The mean peak plasma dapsone concentration achieved after administration of a single 100-mg dose of oral dapsone was 1375 ng/mL. After topical application of dapsone gel 5%, the mean peak plasma dapsone level through day 14 was 19.7 ng/mL (Figure 1).[6] In a long-term safety study, 368 and 340 actively treated subjects were followed for 6 months and 12 months, respectively. Continued twice-daily application of dapsone gel 5%

Table 1.

Success Rate at Week 12*†‡

	Study DAP0203		Study DAP0204		Pooled Analysis	
	Dapsone Gel 5%	Vehicle Gel	Dapsone Gel 5%	Vehicle Gel	Dapsone Gel 5%	Vehicle Gel
Subjects achieving GAAS success, %	44.2	35.9	36.9	29.8	40.5	32.8

*GAAS indicates Global Acne Assessment Score.
†Success measured as none or minimal.
‡Study DAP0203, $P<.001$; study DAP0204, $P=.002$; pooled analysis, $P<.001$.

Data from Draelos et al.[7]

over 12 months revealed levels ranging from 7.4 to 11.3 ng/mL, with no increases in plasma dapsone concentrations observed over time.[6] Additionally, use of dapsone gel 5% twice daily in combination with either benzoyl peroxide 4% once daily or adapalene gel 0.1% once daily did not alter the pharmacokinetic profile of dapsone as evidenced by measurements of plasma concentrations obtained in the dapsone gel 5% monotherapy arms and the combination therapy groups.[7,8]

Based on available pharmacokinetic data, dapsone is minimally absorbed after topical application of the 5% aqueous gel. Systemic dapsone exposure is very minimal after repeated topical application (<1% of the applied dose). Plasma dapsone concentrations did not accumulate over time with repeated twice-daily applications over 12 months.[6] Continued topical administration of dapsone gel 5% produced minimal systemic exposure with plasma dapsone concentrations remaining more than 100-fold lower than the mean peak plasma dapsone concentration obtained after a single 100-mg oral dose of dapsone. Additionally, in the 12-month study, safety analyses demonstrated no reports of hemolysis or methemoglobinemia and no clinically significant changes in hemoglobin or hematocrit values over the duration of the trial.[6]

What is the efficacy of dapsone gel 5% for acne vulgaris?

In the 2 pivotal phase 3 trials for acne vulgaris, pooled results revealed that 3010 subjects (12 years or older) were randomized to use dapsone gel 5% (n=1506) or vehicle gel (n=1504) applied twice daily for 12 weeks.[7] The gender distribution was approximately equal with slightly more than 50% of subjects being female. Approximately one fourth of subjects in both the active and vehicle arms were black, Hispanic, Asian, or other. With regard to disease severity, approximately 60% and 33% of subjects in both study arms presented with moderate and mild facial acne vulgaris, respectively. At baseline, a mean of 30.8 and 30.3 inflammatory lesions and 48.2 and 47.8 noninflammatory lesions were noted in the dapsone gel–treated and vehicle gel–treated study groups, respectively. Efficacy parameters included evaluations based on investigator static global assessment of none or minimal acne at week 12, with results depicted in Table 1. The results of percentage reduction of inflammatory, noninflammatory, and total lesion counts at week 12 compared with baseline are reported in Figure 2. Dapsone gel 5% proved to be superior to vehicle, both clinically and statistically, regardless of the efficacy parameter evaluated. Statistically significant greater lesion reductions were observed in the dapsone-treated subjects compared with the vehicle-treated subjects and were noted as early as 4 weeks ($P=.008$), 6 weeks ($P=.007$), and 8 weeks ($P=.003$) for inflammatory, total, and noninflammatory lesions, respectively.[7]

A subset analysis evaluated the efficacy and safety of dapsone gel 5% in adolescents aged 12 to 15 years (n=176) for up to 12 months, based on the 2 pivotal phase 3 trials and a long-term safety study.[9] Efficacy

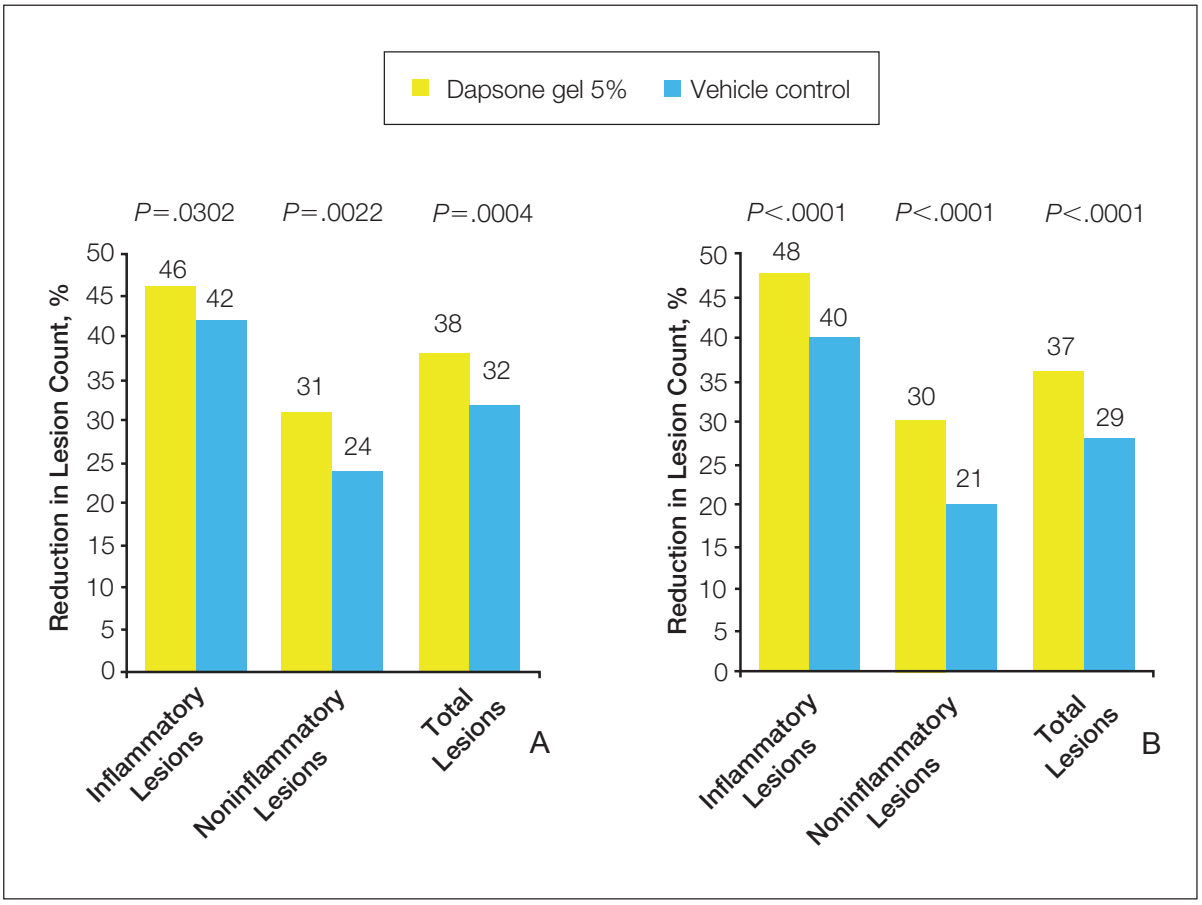

Figure 2. Dapsone gel 5% lesion count reductions from 2 pivotal phase 3 trials (study 1, A; study 2, B). Percentage lesion count reductions at week 12. Data from Draelos et al.[7]

Table 2.

Use of Dapsone Gel 5% in Adolescents With Facial Acne Vulgaris (Efficacy Subset Analysis; Mean Percentage Lesion Reduction)

	Pivotal Studies			Long-term Study*
Efficacy Measure	Dapsone Gel 5% (n=569)	Vehicle Gel 5% (n=544)	*P* Value	Dapsone Gel 5% (n=176)
Baseline mean lesion count	32.0	31.9		34.5
Mean inflammatory lesion reduction, %	44.9	36.8	.0006	43.6
Mean noninflammatory lesion reduction, %	26.9	15.8	.0001	

*Noninflammatory lesions were not components of entry criteria in the long-term study.

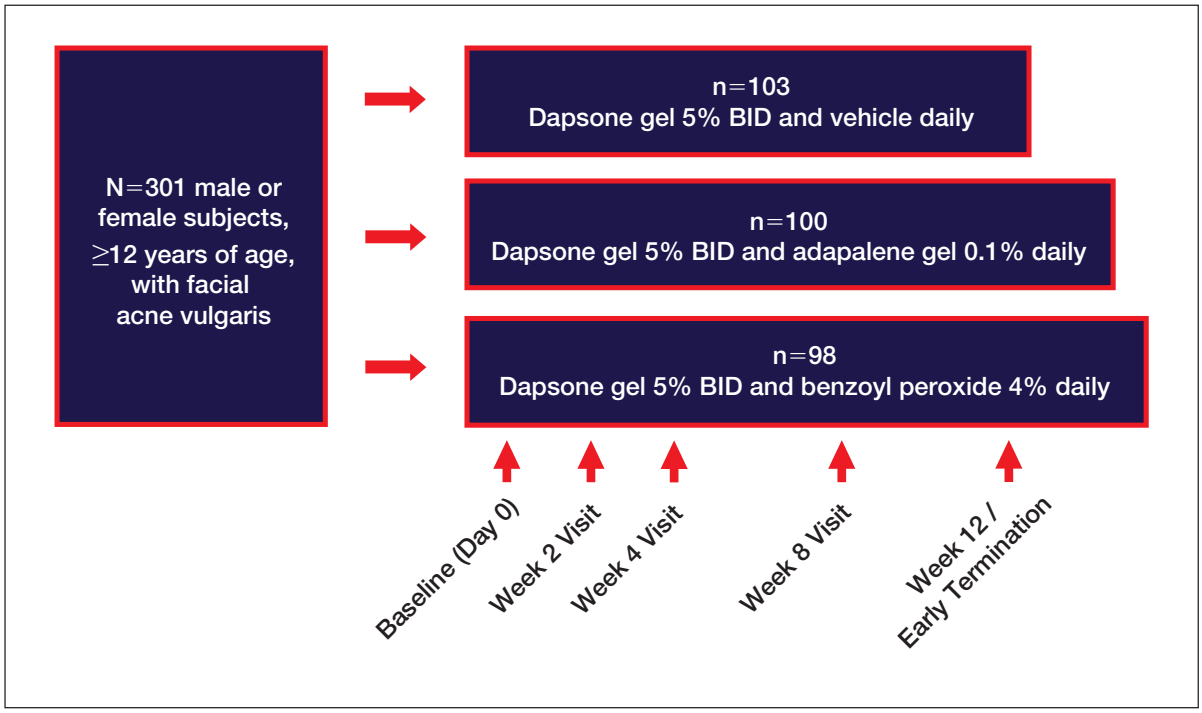

Figure 3. Dapsone gel 5% used in combination with benzoyl peroxide 4%, adapalene gel 0.1%, or vehicle gel for the treatment of facial acne vulgaris. BID indicates twice daily. Data from Fleischer et al.[8]

results from this subset analysis are tabulated in Table 2. The conclusion, based on the evaluation of efficacy and safety data, was that dapsone gel 5% is effective, safe, and well-tolerated.[9]

What combination therapy data exist with dapsone gel 5% for the treatment of acne vulgaris?

As topical treatment for acne vulgaris commonly employs a combination therapy approach, dapsone gel 5% twice daily was studied in patients with facial acne vulgaris who also were treated with either benzoyl peroxide 4% once daily, adapalene gel 0.1% once daily, or vehicle gel once daily (dapsone monotherapy arm) in a double-blind randomized trial. At study entry, most subjects presented with a severity rating of moderate, with baseline lesion count characteristics very similar to those described above for subjects included in the pivotal phase 3 trials.[8]

Figure 3 describes the design of this combination therapy trial. Efficacy data reported as mean percentage reduction in total lesion counts are depicted in Table 3, with similar treatment responses also observed with inflammatory and noninflammatory lesion counts.[8] Importantly, the efficacy results noted with dapsone gel 5% twice daily used in combination with a vehicle gel once daily (essentially reflecting the monotherapy response achieved with topical dapsone) were consistent with those observed in subjects treated with dapsone gel 5% in the pivotal phase 3 studies.[7,8]

What is the skin tolerability and safety of dapsone gel 5% based on available clinical trials?

Based on clinical studies of more than 2000 subjects with facial acne vulgaris who were actively treated with dapsone gel 5%, skin tolerability proved to be favorable.[6-9] In these trials, dapsone gel 5% was predominantly used as monotherapy; however, a study of combination use with either benzoyl peroxide 4% or adapalene gel 0.1% also included tolerability and safety assessments.[8] The fact that dapsone gel 5% was well-tolerated overall may relate to its formulation as an aqueous-based gel devoid of ethanol or other astringent-type alcohols. Dermal safety studies of dapsone gel 5% completed in 385 subjects demonstrated no evidence of photoallergy, phototoxicity, or contact hypersensitivity.[10]

In the 2 pivotal phase 3 trials, all subjects were instructed to use a designated noncomedogenic

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