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.

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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.

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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

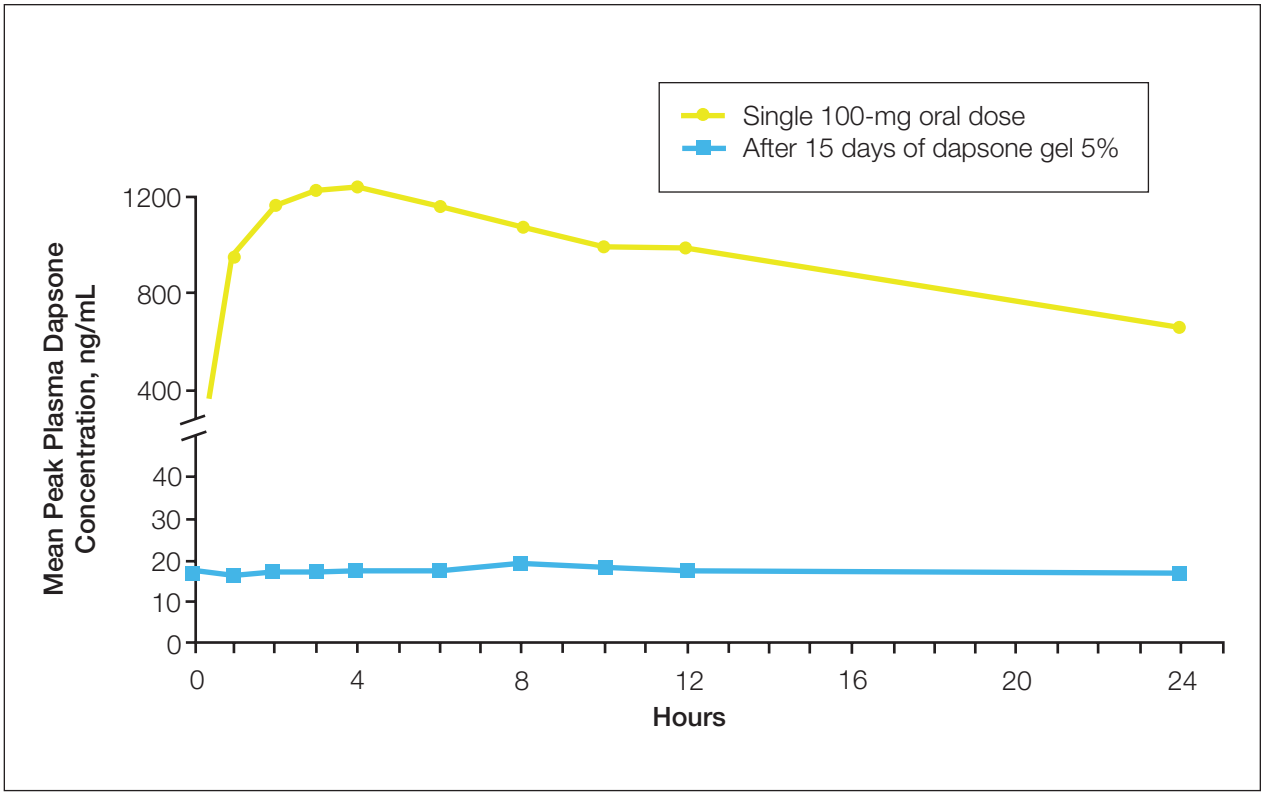

Figure 1. Pharmacokinetics of topical application of dapsone gel 5% over 14 days versus a single 100-mg dose of oral dapsone. Data from Thiboutot et al.[6]

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

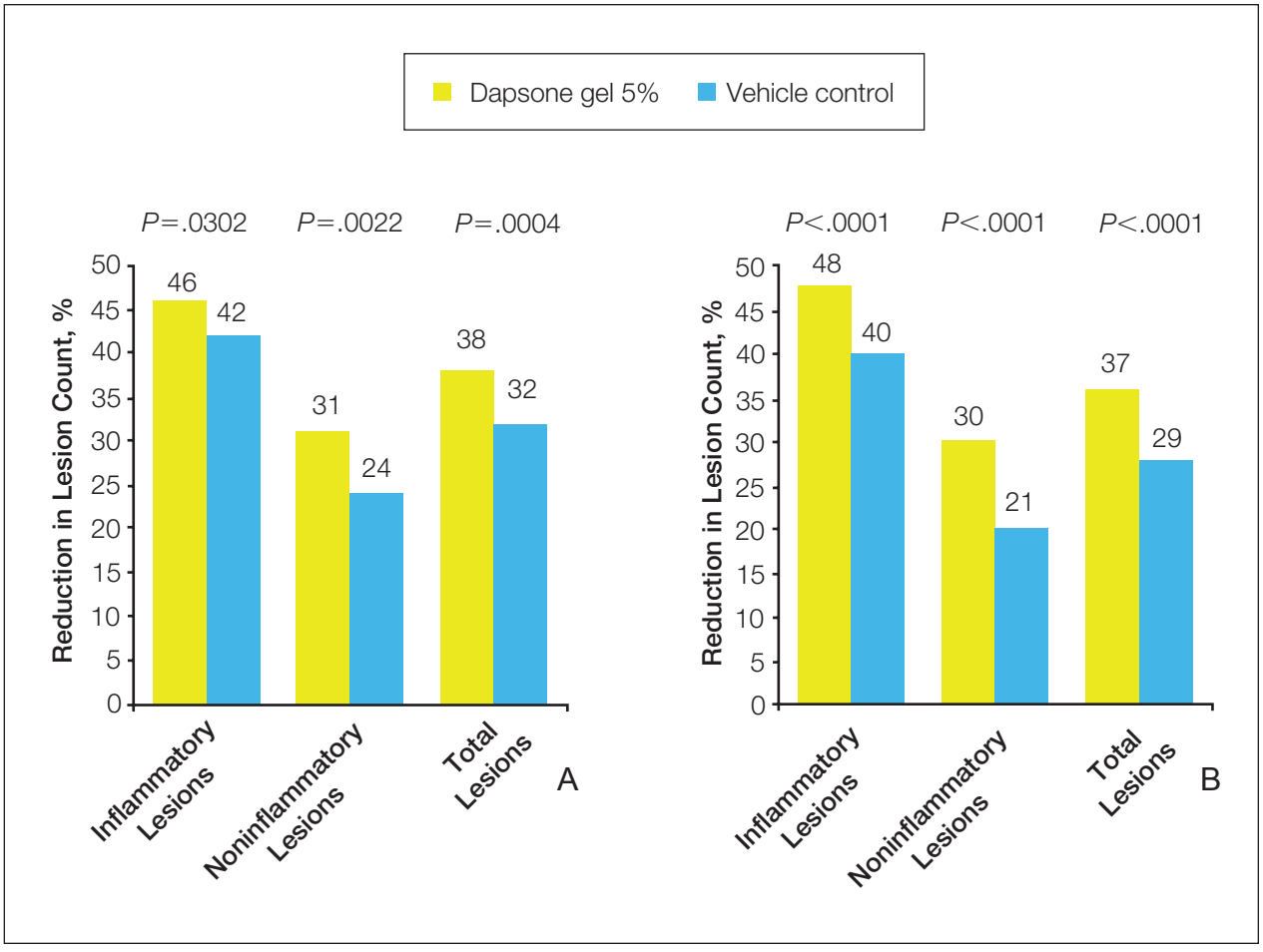

Figure 2. Dapsone gel 5% lesion count reductions from 2 pivotal phase 3 trials (study 1, A; study 2, B). Percentage lesion count reductions at week 12. Data from Draelos et al.[7]

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.

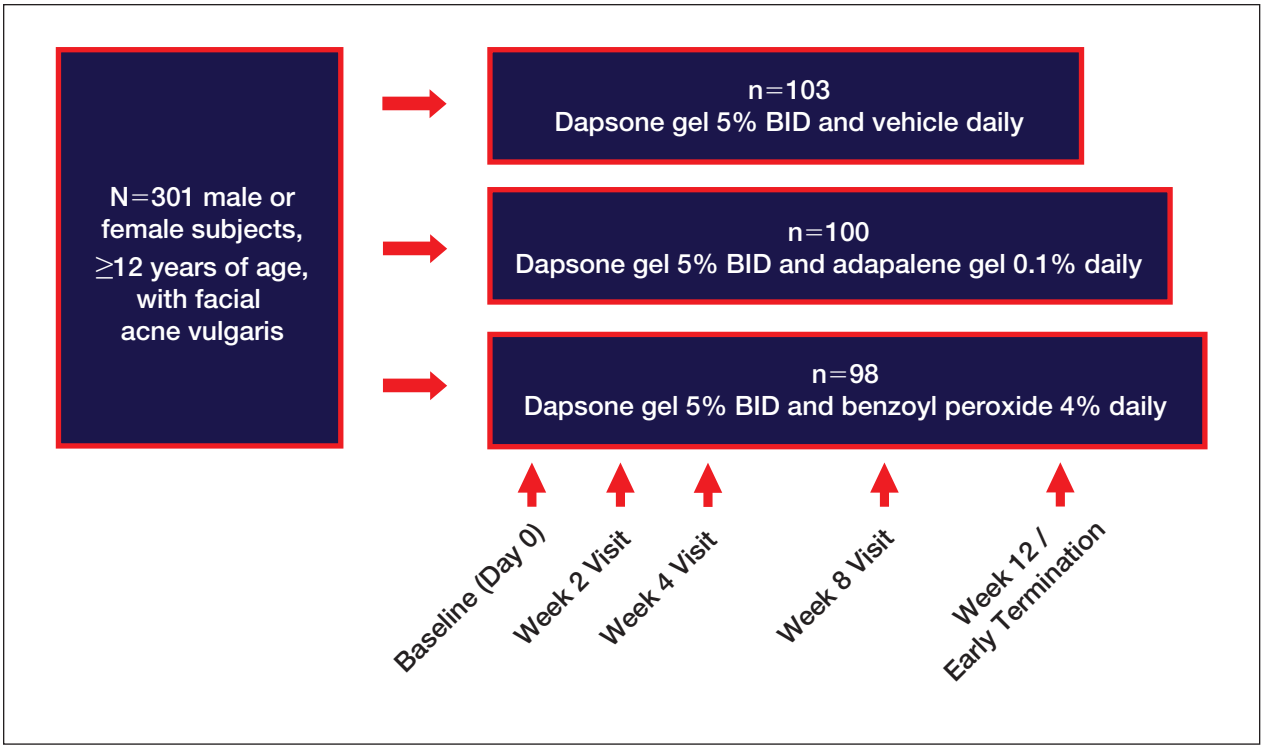

Figure 3. Dapsone gel 5% used in combination with benzoyl peroxide 4%, adapalene gel 0.1%, or vehicle gel for the treatment of facial acne vulgaris. BID indicates twice daily. Data from Fleischer et al.[8]

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

Table 3.

Topical Dapsone Combination Therapy Study (Mean Percentage Reduction in Total Lesion Counts From Baseline to Week 12)*†‡

Efficacy Measurement	Treatment Group		
	Dapsone Gel 5% + Vehicle (n=103)	Dapsone Gel 5% + Adapalene Gel 0.1% (n=100)	Dapsone Gel 5% + Benzoyl Peroxide 4% (n=98)
Baseline, mean±SD	84.7±35.4	81.4±43.4	82.2±38.7
Mean lesion reduction, %	39.3	50.6	46.4

*Dapsone gel 5% + vehicle vs dapsone gel 5% + adapalene gel 0.1%; *P*=.0041.
†Dapsone gel 5% + vehicle vs dapsone gel 5% + benzoyl peroxide 4%; *P*=.0564.
‡Dapsone gel 5% + adapalene gel 0.1% vs dapsone gel 5% + benzoyl peroxide 4%; *P*=.6198.

Data from Fleischer et al.[8]

soap-free liquid cleanser.[7] The most commonly observed application-site reactions associated with use of dapsone gel 5% were erythema and dryness.[7,9] Based on the 2 pivotal phase 3 trial results, erythema and dryness were reported in 16.3% and 20.0% of dapsone-treated subjects and in 16.1% and 18.9% of vehicle-treated subjects, respectively, with similar results observed in the subset analysis of adolescent subjects.[7,9]All subjects were monitored for adverse events at each study visit, including specifically being queried regarding application-site reactions, with the events tabulated irrespective of whether or not they were judged by the investigator to be related to study medication.[7,9] It is important to note when analyzing facial skin tolerability results that subjects included in the 2 pivotal phase 3 trials were assessed at baseline regarding signs and symptoms, including dryness, erythema, and peeling. The baseline evaluations documented the presence of erythema, dryness, and peeling in 14.8%, 2.7%, and 1.3% of subjects, respectively, prior to initiation of study drug.[7]

Long-term safety analysis demonstrated an application-site reaction rate of less than 3.1%.[6] Application-site symptoms such as burning and pruritus have been reported in less than 2% of study subjects as determined by both spontaneous reporting and elicited responses.[6,7]

Clinical and laboratory evaluations were included in the 2 pivotal phase 3 trials and long-term safety study with dapsone gel 5%. In multiple studies completed with dapsone gel 5% to date, there have been no reports of major adverse events associated with the use of topical dapsone, such as hemolytic anemia, methemoglobinemia, or agranulocytosis, even among 19 dapsone-treated subjects with documented G6PD deficiency.[6,7,9] Also, no major safety concerns emerged during the combination therapy trial, and study discontinuations were uncommon, with only one subject discontinuing treatment because of lack of efficacy.[8]

Short-term and long-term pharmacokinetic data, including studies of twice-daily application of dapsone gel 5% as monotherapy or in combination with other topical acne therapies, coupled with clinical and laboratory evidence from large controlled studies, support that dapsone gel 5% is not associated with a risk of systemic toxicities that are sometimes observed with oral dapsone therapy.[6-9]

CLINDAMYCIN PHOSPHATE 1.2% AND TRETINOIN 0.025% COMBINATION GEL

What is clindamycin phosphate 1.2% and tretinoin 0.025% combination gel?

Clindamycin phosphate 1.2% and tretinoin 0.025% combination gel is a dual-component combination topical formulation.[11] This aqueous gel contains tretinoin 0.025% that is both solubilized and crystalline in suspension, in combination with clindamycin phosphate 1.2% in solution. It has been evaluated in several

Table not available online

trials, including three 12-week phase 3 trials and a 52-week study. Collectively, 4550 patients were enrolled in phase 3 studies that included subjects aged 12 years and older with mild, moderate, and severe facial acne vulgaris.[11-13] The clindamycin phosphate 1.2% and tretinoin 0.025% combination gel proved superior in efficacy to either active component alone and to vehicle, regardless of acne severity.[11,13]

What is unique about the clindamycin phosphate 1.2% and tretinoin 0.025% combination gel formulation?

Unique characteristics of the clindamycin phosphate 1.2% and tretinoin 0.025% patented combination formulation are the usage and stabilization of both solubilized and crystalline tretinoin in suspension, the stringent control of tretinoin particle sizes, and the use of an aqueous-based gel vehicle that also contains clindamycin phosphate in solution.[11,14] The ability of the vehicle to maintain tretinoin stability is believed to allow for slow release of the active ingredient.[11]

What is the efficacy of clindamycin phosphate 1.2% and tretinoin 0.025% combination gel in the treatment of acne vulgaris?

In order to properly evaluate the efficacy of the clindamycin phosphate 1.2% and tretinoin 0.025% combination gel, this combination formulation (n=845) applied once daily was compared with once-daily monotherapy with tretinoin 0.025% aqueous gel (n=846), clindamycin phosphate 1.2% aqueous gel (n=426), and vehicle aqueous gel (n=423).[11,13] The identically designed, multicenter, randomized, double-blind, active-controlled and vehicle-controlled, parallel-group phase 3 studies evaluated treatment response in subjects older than 12 years with facial acne vulgaris. As mentioned above, the clindamycin phosphate 1.2% and tretinoin 0.025% combination gel proved superior in efficacy to either active

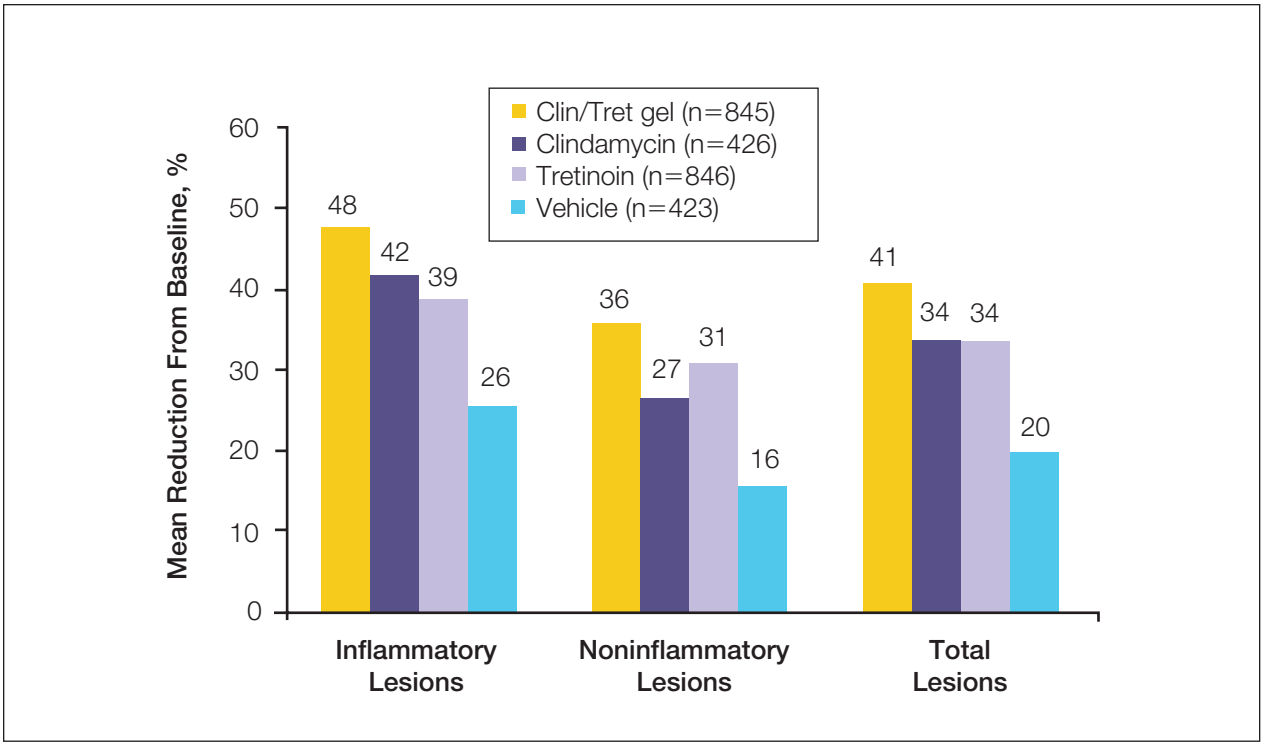

Figure 4. Mean percentage lesion reduction from 2 pivotal 12-week phase 3 trials (pooled data). Clin/Tret indicates clindamycin phosphate 1.2% and tretinoin 0.025% combination gel. Data from Schlessinger et al.[11]

component alone and to vehicle, regardless of acne severity, and was shown to be effective in reducing both inflammatory and noninflammatory acne lesions.[11,13] The pooled demographic data from subjects enrolled in 2 pivotal phase 3 trials are tabulated in Table 4, with efficacy data reported as mean percentage inflammatory, noninflammatory, and total lesion reductions depicted in Figure 4.[11]

In a third 12-week phase 3 trial, the efficacy and safety of clindamycin phosphate 1.2% and tretinoin 0.025% combination gel applied once daily (n=1088) was compared with clindamycin phosphate 1.2% aqueous gel applied once daily (n=1002) in subjects with facial acne vulgaris.[11] The demographic data from subjects included in this trial were very similar to the data depicted in Table 4. At week 12, clindamycin phosphate 1.2% and tretinoin 0.025% combination gel was superior to monotherapy with topical clindamycin in all efficacy parameters. Mean percentage reductions in inflammatory, noninflammatory, and total lesion counts were 61%, 50%, and 54%, respectively, in the combination gel–treated subjects, versus 45%, 41%, and 47%, respectively, in the clindamycin-treated subjects. The differences between groups were statistically significant for mean percentage reduction in inflammatory, noninflammatory, and total lesions ($P<.001$ for all).[11]

Did subset analysis of trials evaluating clindamycin phosphate 1.2% and tretinoin 0.025% combination gel reveal any clinically relevant information?

An unprecedented acne study subset analysis derived from 2 pivotal 12-week phase 3 trials evaluated acne flares, defined as a 20% or more increase in inflammatory lesions, after 2 weeks of application of study medication.[11,15] The data from this subset analysis are tabulated in Figure 5, with differentiation based on acne severity rating at baseline. Overall, the percentage of subjects exhibiting a 20% or more increase in inflammatory acne lesions within the first 2 weeks of the study was highest in the tretinoin 0.025% aqueous gel and vehicle aqueous gel study arms.[11] Subjects treated with the clindamycin phosphate 1.2% and tretinoin 0.025% combination gel exhibited a 30% to 60% lower rate of increase in inflammatory acne lesions, which was comparable to the rate observed in subjects treated with the clindamycin phosphate 1.2% aqueous gel alone.[11,15]

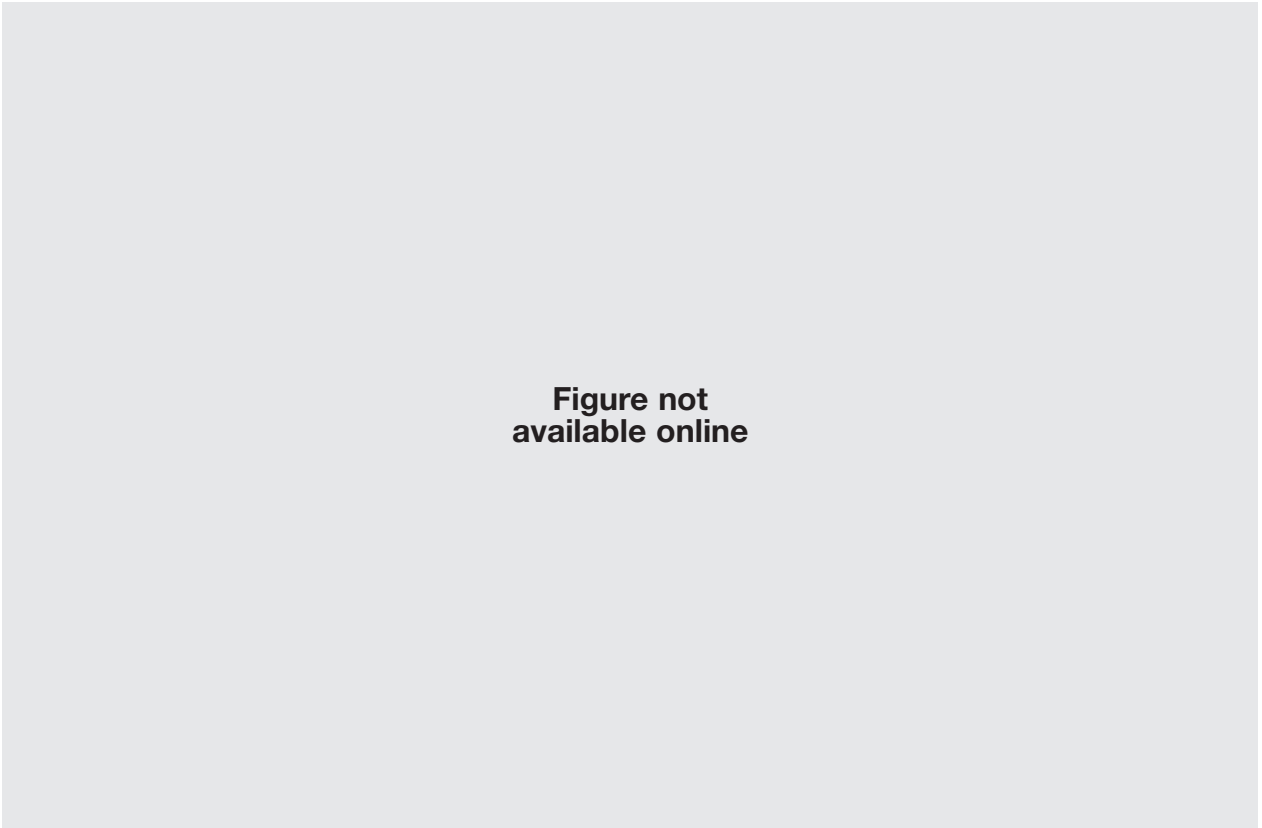

Figure 5. Subjects with acne flares (20% or more increase in inflammatory lesions) after 2 weeks of application of study medication. Clin/Tret indicates clindamycin phosphate 1.2% and tretinoin 0.025% combination gel. Adapted with permission from Schlessinger et al.[11]

It is important to consider that the 20% or more increase in inflammatory acne lesions after 2 weeks of study treatment may actually reflect natural disease progression of acne in many of these subjects as opposed to a true acne flare. Acne lesion counts at baseline are collected after defined washout periods from previous acne therapies and in subjects who often present with acne that is poorly controlled by prior treatments. Additionally, enrolled subjects present with an acne severity rating that makes them eligible for study inclusion based on stringent criteria. It would not be unexpected for acne lesions to increase in number during the first 2 weeks of a study, at least in some subjects, as the onset of activity of study medication may not be operative within that initial short time frame, thus reflecting natural acne progression rather than an actual flare related to the study drug itself. Nevertheless, regardless of acne severity at baseline, once-daily application of clindamycin phosphate 1.2% and tretinoin 0.025% combination gel was associated with a markedly lower percentage of subjects demonstrating a 20% or more increase in inflammatory lesions over the first 2 weeks of therapy compared with tretinoin 0.025% aqueous gel or vehicle aqueous gel. In subjects presenting with facial acne vulgaris rated at baseline as mild or moderate in severity, the percentage of acne flares was approximately twofold lower in the clindamycin phosphate 1.2% and tretinoin 0.025% combination gel treatment group compared with the tretinoin 0.025% aqueous gel treatment group.[11]

What is the tolerability and safety of clindamycin phosphate 1.2% and tretinoin 0.025% combination gel in the treatment of acne vulgaris?

In a cumulative irritation study, clindamycin phosphate 1.2% and tretinoin 0.025% combination gel alone and its aqueous gel vehicle alone were markedly less irritating than conventional tretinoin gel 0.025%.[14]

In 12-week phase 3 studies, the incidence of local tolerability reactions in subjects treated with clindamycin phosphate 1.2% and tretinoin 0.025% combination gel was minimal or decreased in

frequency at study end point compared with baseline. Erythema, scaling, pruritus, burning, and stinging were reported in 35%, 13%, 10%, 2%, and 2% of enrolled subjects at baseline, respectively, and in 26%, 17%, 4%, 4%, and 2% of study subjects at end of treatment, respectively.[11] The adverse reactions noted in all active study arms included in the pivotal phase 3 trials were consistent with those previously reported for the individual ingredients after topical application. Study discontinuations due to adverse events were less than 1%, and no major adverse events or safety concern signals were observed in any of the study groups.[11,13]

In a 52-week open-label trial, subjects used clindamycin phosphate 1.2% and tretinoin 0.025% combination gel (N=442) for the treatment of acne vulgaris as either monotherapy (78%) or in combination with other agents (22%). The overall discontinuation rate due to adverse reactions was less than 1% in those subjects treated for up to 6 months and 0% in those treated for up to 12 months.[12] The combination gel was well-tolerated with 91%, 94%, and 92% of subjects reporting complete absence of burning, stinging, and pruritus, respectively.[12]

COMMENT

The pivotal phase 3 trials evaluating dapsone gel 5% demonstrate results achieved with monotherapy for facial acne vulgaris, predominantly in subjects presenting with moderate severity. Importantly, data from one study suggests that dapsone gel 5% may be used in combination with other topical agents, such as benzoyl peroxide or a topical retinoid.[8] The cutaneous tolerability profile of dapsone gel 5%, either alone or in combination with benzoyl peroxide or topical adapalene, appears to be very favorable based on clinical trials. Importantly, both short-term and long-term pharmacokinetic, clinical, and laboratory analyses performed to date indicate that dapsone gel 5% is devoid of systemic toxicities associated with oral dapsone use, such as hemolytic anemia, methemoglobinemia, and agranulocytosis.

The dual-component combination aqueous gel containing solubilized clindamycin phosphate 1.2% and solubilized and crystalline tretinoin 0.025% has been shown to be effective, well-tolerated, and safe in both 12-week double-blind studies and in a 52-week open-label trial. A major distinguishing feature of this combination aqueous gel formulation is the small particle size of tretinoin, which may contribute to reduced skin irritation. A clinical concern regarding use of the clindamycin phosphate 1.2% and tretinoin 0.025% combination gel for treatment of acne vulgaris is the potential for promotion and emergence of strains of *Propionibacterium acnes* that are less sensitive to clindamycin. This potential problem may be obviated by concomitant use of a benzoyl peroxide–containing product. Another clinical consideration is whether or not a topical combination product containing benzoyl peroxide and clindamycin can be used concomitantly with clindamycin phosphate 1.2% and tretinoin 0.025% combination gel because this would result in the clindamycin component being applied twice daily. Use of a benzoyl peroxide–clindamycin gel combination product once daily in the morning and clindamycin phosphate 1.2% and tretinoin 0.025% combination gel once daily in the evening is a very logical treatment approach. Twice-daily application of clindamycin should not be a major concern since twice daily use is the FDA-approved application frequency with some topical clindamycin products.

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