IN-DEPTH REVIEWS

Status Report on the Safety of Topical Dapsone Therapy for Dermatologic Disease

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ABSTRACT

Systemic dapsone therapy has historically been used to treat leprosy, inflammatory dermatoses, and severe cases of acne vulgaris. This article reviews the pharmacokinetics, short and long-term safety, drug-drug interactions, gender, and age effects of topical dapsone 5\% and 7.5\% gel formulations. In 20 human studies and 7 case reports, 39 of 6,384 total patients (<1\%) experienced adverse effects that were considered more than mild or resulted in discontinuation of topical dapsone. The literature supports topical dapsone 5\% and 7.5\% gels as safe and effective medications for the treatment of dermatologic disease.

INTRODUCTION

Dapsone is a synthetic sulfone antibiotic that was synthesized in 1908 and initially used for the treatment of leprosy (Figure 1).\textsuperscript{1-3} At that time, clinicians incidentally noticed that administration of oral dapsone led to a marked improvement of acne, including in patients with severe inflammatory disease.\textsuperscript{2,4} Subsequently, dapsone was widely adopted to treat severe cases of acne prior to the development of oral isotretinoin.\textsuperscript{5} Today, oral dapsone is used as a primary or adjuvant therapy in many rare and refractory dermatological conditions (Table 1).\textsuperscript{2,3,6}

The efficacy of dapsone in treating dermatologic disease is largely attributed to its anti-inflammatory and anti-microbial properties. Dapsone’s anti-inflammatory action is secondary to monoacetyl dapsone and dapsone hydroxylamine (DDS-NOH), two metabolites activated by enzymatic reactions occurring within cutaneous polymorphonuclear leukocytes.\textsuperscript{2} Several \textit{in vitro} studies have demonstrated that...
Dapsone decreases inflammation by scavenging reactive oxygen species, inhibiting neutrophil myeloperoxidase, inhibiting eosinophil peroxidase, and suppressing hypochlorous acid production.\textsuperscript{2,7-10} The anti-microbial properties of dapsone are due to competitive inhibition of bacterial para-aminobenzoic acid (PABA) which decreases the production of dihydrofolic acid.\textsuperscript{11} Studies of acne vulgaris have also shown that dapsone has antibacterial activity against \textit{Propionibacterium acnes}.\textsuperscript{2}

Dapsone and its metabolites effectively treat many dermatologic diseases, however, systemic accumulation may cause adverse hematologic and neurologic events.\textsuperscript{2} High systemic exposure can lead to dose-dependent reactions including methemoglobinemia, hemolysis, and agranulocytosis among others (Table 2).\textsuperscript{2} Topical 5% and 7.5% semi solid-gel formulations of dapsone have since been developed with markedly reduced systemic accumulation, minimizing many of the concerns regarding systemic toxicity.\textsuperscript{12-14} However, long term safety data for topical dapsone is limited.\textsuperscript{8} The purpose of this review is to comprehensively outline the safety evidence from relevant studies evaluating dapsone 5% and 7.5% gel as topical therapy for dermatologic disease.

Table 1. Reported indications for dapsone (oral and topical)

| Chronic Skin Conditions | Sulfone Sensitive Dermatoses | Other |
|-------------------------|------------------------------|-------|
| Acropustulosis infantilis | Bullous pemphigoid | Leprosy (multibacillary and paucibacillary) |
| Dermatitis herpetiformis | Chronic idiopathic urticaria | Rheumatoid Arthritis |
| Erythema elevatum et diutinum | Cutaneous lupus erythematosus | Antimalarial |
| IgA pemphigus | Eosinophilic folliculitis | Eosinophilic fasciitis |
| Linear IgA dermatosis | Leukocytoclastic vasculitis | Immune thrombocytopenia |
| Prurigo pigmentosa | Lichen ruber pemphigoides | Asthma bronchiale |
| Subcorneal pustular dermatosis | Loxoscelism | Glioblastoma |
| *Acne vulgaris | Mucous membrane pemphigoid | Seizures |
| *Papulopustular Rosacea | Pemphigus vulgaris | Prophylaxis in AIDS |
| **Granuloma faciale | Pyoderma gangrenosum | **Granuloma faciale |
| **Lupus erythematosus | Recurrent neutrophilic dermatosis of dorsal hands | **Dermatitis Herpetiformis |
| **Hidradenitis | Relapsing polychondritis | **Venous stasis ulcer |
| **Dermatitis Herpetiformis | Sweets syndrome | **Erosive pustular dermatosis of the scalp |
| **Venous stasis ulcer | Inverse and Pustular psoriasis | **Erythema elevatum diutinum |

*topical dapsone gel 5% indication on U.S. Market
**off-label reported use of topical dapsone 5% gel, noted in literature to respond
Table 2. Adverse effects of oral dapsone

| Hematologic          | Cutaneous                      | Gastrointestinal       | Nervous System            | Other                             |
|----------------------|--------------------------------|------------------------|---------------------------|-----------------------------------|
| Methemoglobinemia    | Exfoliative dermatitis         | Anorexia               | Peripheral neuropathy     | *Hypersensitivity syndrome        |
| Hemolysis            | Erythema multiforme            | Abdominal pain         | Motor function loss       | Albuminuria                       |
| Agranulocytosis      | Urticaria                      | Nausea                 |                           | Insomnia                          |
|                      | Erythema nodosum               | Vomiting               |                           | Psychosis                         |
|                      | morbilliform                   | LFT abnormalities      |                           | Electrolyte abnormalities         |
|                      | Scarlatiniform exanthema       | Prehepatic jaundice    |                           | Atrioventricular block            |
|                      | Toxic epidermal necrolysis     | Cholestatic hepatitis  |                           |                                   |
|                      | photosensitivity               |                        |                           |                                   |
|                      | Rash in AIDS patients          |                        |                           |                                   |

*Fever, rash, lymphadenopathy, hepatic dysfunction

METHODS

A PUBMED search for any randomized clinical trials (RCT) related to topical dapsone, dapsone gel, or the trade name, Aczone® [Allergan, Dublin, Ireland] was performed. Studies that were not randomized or placebo controlled were included only if performed on a large number of patients. Considerable effort was made to find all available articles from the United States and other countries. The primary objective of the review was to include all studies that reported adverse events, side effects, toxicity, and laboratory parameter changes caused by topical dapsone 5% and 7.5% gel.

RESULTS

Overall, 20 clinical studies and 7 case reports met the criterion for this review that analyzed the pharmacokinetics, short-term safety, gender effects, age effects, long-term safety, drug-drug interactions, and safety in high risk patients utilizing topical dapsone 5% or 7.5% gel (Table 3).

Pharmacokinetic Studies

The systemic exposure of topical dapsone was evaluated by testing the difference in plasma concentrations of patients using topical vs. oral dapsone[16]. Thiboutot et al studied 18 patients who received 14 days of topical dapsone 5% gel twice daily, followed with a 14-day washout period. Patients were then given a one-time 100 mg dose of oral
Table 3. Adverse effects of topical dapsone reported in clinical trials

| Study Human Studies | Year | N  | Study Details | Outcomes/Adverse Events | Withdrawal from study secondary to treatment AE |
|---------------------|------|----|---------------|--------------------------|-----------------------------------------------|
| Thiboutot, et al    | 2007 | 18 | Evaluate systemic concentrations of oral and topical dapsone | Application Site AE’s: Not evaluated. | Steady state exposure of topical versus oral dapsone was 126 fold lower. No hematologic AE’s. |
| Thiboutot, et al    | 2007 | 17 | Drug interaction study: dapsone gel and oral TMP/SMX | Application Site AE’s: Not evaluated. | Plasma concentration of dapsone was increased when combined with TMP/SXT. No hematologic AE’s. |
| Lucky, et al        | 2007 | 486| Long term safety of dapsone | Mild to moderate application site AE’s: dryness, rash, sunburn, burning, erythema, pruritus, acne aggravated, peeling, rash nonspecific, contact dermatitis, irritation, seborheic dermatitis, and caustic injury(8.2%) | Mean plasma concentration of dapsone remained low. No hematologic AE’s. |
| Draelos, et al      | 2007 | 3010| Short term efficacy and safety of topical dapsone | Mild to moderate application site AE’s: oiliness, erythema, dryness, and peeling(38%) | Lab abnormalities related to treatment (0.25%): elevated creatinine kinase No other hematologic AE’s. |
| Raimer, et al *subanalysis | 2008 | 1306| Assess safety of topical dapsone in adolescents (12-15 yo) | Mild application site AE’s: dryness, erythema(20.2%) | I increased blood creatinine phosphokinase level. No other hematologic AE’s. |
| Study                  | Year | N     | Study Details                                                                 | Outcomes/Adverse Events                                                                 |
|-----------------------|------|-------|------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Tanghetti, et al      | 2012 | 2898  | Assess efficacy and tolerability of dapsone in female versus male patients    | *Mild application site AE’s:* erythema (~15%), oiliness (~20%), dryness (~3%), peeling (~1%) |
|                       |      |       |                                                                              | None reported                                                                           |
|                       |      |       |                                                                              | No hematologic AE’s.                                                                     |
| Del Rosso, et al      | 2015 | 781   | Assess efficacy and tolerability of dapsone in adult versus adolescent females | *Mild application site AE’s:* erythema (14%), dryness (3%), oiliness (15%), and peeling (2%) |
|                       |      |       |                                                                              | None reported                                                                           |
|                       |      |       |                                                                              | No hematologic AE’s.                                                                     |
|                       |      |       |                                                                              | Not reported                                                                            |
| Piette, et al         | 2008 | 63    | Safety of topical dapsone in G6PD deficient patients                         | *Mild to moderate application site AE’s:* burning, dryness, pruritus, contact dermatitis and aggravated acne (12.7%) |
|                       |      |       |                                                                              | None reported                                                                           |
|                       |      |       |                                                                              | 3 patients (4.7%) experienced a lab abnormality: elevated bilirubin, low haptoglobin, low white blood cell count |
|                       |      |       |                                                                              | No significant change in hemoglobin between dapsone and control.                         |
| Faghihi, et al        | 2014 | 58    | Assess efficacy of dapsone 5% gel combined with oral isotretinoin            | *Mild application site AE’s:* burning (24%), erythema (14%) and dryness (10%), exfoliation (3.4%), pruritus (3.4%), photosensitivity (3.4%) (62% total 18/29) |
|                       |      |       |                                                                              | 1 contact conjunctivitis.                                                                |
|                       |      |       |                                                                              | Not evaluated.                                                                          |
|                       |      |       |                                                                              | No hematologic AE’s.                                                                     |
|                       |      |       |                                                                              | 0                                                                                      |
| Tanghetti, et al      | 2011 | 171   | Assess safety and efficacy of dapsone when combined with tazarotene        | *Mild application site AE’s:* dryness (2.3%), erythema (2.3%)                            |
|                       |      |       |                                                                              | Not evaluated.                                                                          |
|                       |      |       |                                                                              | No hematologic AE’s.                                                                     |
|                       |      |       |                                                                              | 0                                                                                      |
| Study              | Year | N     | Study Details                                                                 | Outcomes/Adverse Events                                                                 |
|--------------------|------|-------|-------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Fleischer, et al   | 2010 | 292   | Assess safety and efficacy of dapsone when combined with adapalene, BPO, or moisturizer | Mild application site AE’s: erythema (most common), oiliness, dryness, peeling, burning, pruritus, rash (average 10.67%) Non-application site AE’s: nasopharyngitis, upper respiratory tract infection, headache, pharyngitis, nasal congestion, cough, sinusitis, abrasion, ear pain, and fungal vaginosis (average 35%) drug interaction (7 patients in dapsone/BPO group only) plasma dapsone and N-acetyl dapsone levels remained low Withdrawal from study secondary to treatment AE 9 (3%) |
| Grove, et al       | 2013 | 140, (25 topical dapsone) | Assess tolerability and irritation potential of duac gel compared with dapsone(aczone) | Mild application site AE’s: erythema, sebum production, perceived burning, stinging, and dryness. *based on scores not percentages or numbers of patients Non-application site AE’s: Headache occurred in all groups (>11%), nausea in dapsone group (8%) No hematologic AE’s. 0 |
| Lynde, et al       | 2014 | 101   | Assess efficacy, tolerability, and safety of topical dapsone in adult women with sensitive skin | Mild application site AE’s: skin irritation (2%) Not evaluated. No hematologic AE’s. 2 (2%) |
| Faghihi, et al     | 2015 | 56    | Efficacy of dapsone gel + oral doxycycline compared to metronidazole gel+ oral doxycycline in treating papulopustular rosacea | Mild application site AE’s: dryness, burning, pruritus, scaling, photosensitivity and erythema (average 27.38%) Not evaluated. No hematologic AE’s. 2 (7.14%) |
| Stein Gold, et al  | 2016 | 948   | Assess efficacy, safety, and tolerability of once daily dapsone gel, 7.5% | Mild-moderate application site AE’s: erythema (0.6%), exfoliation (0.6%), pain (0.2%) Non-application site AE’s: nasopharyngitis (1.9%), upper respiratory tract infection (1.4%), headache (1.3%), influenza (1.1%), oropharyngeal pain (1.0%) No hematologic AE’s. 4 (0.4%) |
| Study Name                        | Year | N   | Study Details                                                                 | Application Site AE’s                                                                 | Outcomes/Adverse Events                                                                 |
|----------------------------------|------|-----|-------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| Eichenfield, et al               | 2016 | 1026| Assess efficacy, safety, and tolerability of once daily dapsone gel, 7.5%     | Mild-moderate application site AE’s: dryness(1.5%), pain (0.6%), pruritus (1.0%)        | Non-application site AE’s: nasopharyngitis (1.8%), upper respiratory tract infection (1.5%), headache (1.8%), nasal congestion (1.0%) | No hematologic AE’s. 2 (0.2%)                                                         |
| Thiboutot, et al *Subanalysis    | 2016 | 2161| Assess efficacy and safety of once-daily topical dapsone gel, 7.5%            | Mild-moderate application site AE’s: dryness(1.2%), pruritus(1.1%), pain(0.5%)         | Non-application site AE’s: headache(1.6%), nasopharyngitis(1.9%), upper respiratory tract infection(1.5%) | No hematologic AE’s. 3 (0.15%)                                                         |
| Draelos, et al *Subanalysis      | 2017 | 2161| Assess relationship of age, sex, and race to treatment response of once daily dapsone gel, 7.5% | Mild-moderate application site AE’s: dryness, erythema, pruritus                         | Non-application site AE’s: upper respiratory tract infection, headache, nasopharyngitis, nasal congestion, oropharyngeal pain | No hematologic AE’s. Not reported.                                                     |
| Jarratt, et al                   | 2016 | 72  | Evaluate pharmacokinetics, safety, tolerability of once-daily dapsone gel, 7.5% and twice daily dapsone gel, 5% | Mild-moderate application site AE’s: dryness, scaling, erythema, pruritus              | Non-application site AE’s: cough, headache, pharyngitis, upper respiratory tract infection, dysmenorrhea, oropharyngeal pain | Systemic exposure of once daily dapsone gel 7.5% was 25-40% lower than twice daily dapsone gel 5% |
| Brown, PC Allergan              | 2016 | 33  | Evaluate for phototoxicity when using dapsone gel 7.5%                       | No application site or phototoxicity AE’s reported.                                   | No non-application site AE’s reported.                                                  | No hematologic AE’s. 0                                                                |
dapsone. The mean plasma concentration in patients using topical dapsone was 19.4 ng/mL vs. 1,375 ng/mL in those taking dapsone orally. The steady-state concentration of topical dapsone was 126-fold lower than that observed following a one-time dose of 100 mg oral dapsone. No hematologic adverse events were reported.16

In 2007, Thiboutot et al studied the effects of trimethoprim-sulfamethoxazole (TMP-SMX) (160/800mg) on dapsone metabolism and its potential for increasing the risk of hemolytic anemia.16 Seventeen non-G6PD deficient patients aged 17-50 years were given TMP-SMX monotherapy for 7 days followed by a 7-day washout period. Topical dapsone was then administered twice daily for 21 days. Topical dapsone and TMP-SMX were subsequently co-administered without a washout period for 7 days. Serum concentrations of dapsone were increased when applied topically in combination with oral TMP-SMX (222-320 ng-h/mL). Increased serum levels of dapsone metabolites, monoacetyl dapsone and dapsone hydroxylamine were reported as well (73-88 ng-h/mL and 18-44 ng-h/mL, respectively). No hematologic adverse events were reported.16

Clinical Studies

Two studies conducted by Draelos et al evaluated the efficacy and safety of topical dapsone in treating acne vulgaris.17 Three thousand and ten patients with moderate acne vulgaris were randomized to either 5% dapsone gel or vehicle gel twice daily for 12 weeks. Adverse events were reported at similar rates in the treatment (58.2%) and vehicle control groups (58.6%). Application site adverse reactions occurred at similar rates in both treatment and vehicle control groups (38% vs. 37.8%, respectively) of which only 1% were considered treatment-related. Two patients withdrew from the dapsone treatment group due to pruritus, burning, dryness, erythema, stinging, and/or peeling. Twenty of the patients (1.3%) treated with dapsone gel experienced laboratory abnormalities (most commonly elevated creatinine kinase), of which 4 were considered related to treatment. No significant changes in hemoglobin or other laboratory parameters were reported in any patients with or without G6PD deficiency.17

Subanalyses of the original studies described above have further evaluated the safety and efficacy of dapsone 5% gel in specific populations. Raimer et al analyzed safety data in adolescents 12-15 years of age (n=1306) and found no previously unrecognized adverse effects or safety concerns.18 Tanghetti et al analyzed differences in the efficacy and tolerability of dapsone 5% gel (n=2,898) between men and women in treating acne vulgaris.19 The adverse effects reported did not differ significantly based on gender or treatment arm (P>0.05 at 12 weeks). Additionally, Del Rosso compared the efficacy and safety of topical dapsone therapy in adult women (≥18 years of age) and adolescent women (12 to 17 years of age) with acne vulgaris (n=781).20 This sub-analysis demonstrated that adolescent and adult female patients using dapsone 5% gel reported fewer application site adverse events after 12 weeks of use than at baseline.

An open label, non-comparative study to evaluate the long-term safety of topical dapsone 5% gel in treating mild to moderate acne vulgaris was performed by Lucky et al.21 Four hundred and eighty-six patients were given topical dapsone 5% gel twice daily for 12 months. The study reported 9.5% (46/486) of patients experienced an adverse event related to treatment; 8.2%
(40/486) of patients experienced mild to moderate application site adverse events which led to withdrawal from the study for ten patients. Non-application site adverse events were experienced on average in 10% of patients and led to withdrawal in only one patient who experienced nausea, dizziness, and weakness secondary to drug odor. Average plasma dapsone levels were 11.0 ng/mL after one month and 7.5 ng/mL at month twelve. There were no clinically significant changes from baseline hematology or serum chemistries. Five patients were G6PD deficient and their hemoglobin levels remained stable throughout the course of therapy.\(^{21}\)

A phase one, randomized, parallel-group, active-controlled, multiple-dose study was conducted by Jarratt et al. to compare the safety, tolerability, and pharmacokinetic profile of topical dapsone 7.5% gel to that of topical dapsone 5% gel. Blood samples were collected from 72 patients 16-35 years of age with moderate acne throughout the study to evaluate the plasma concentration of dapsone and its metabolites. One treatment related adverse event, mild pruritus, occurred in a patient receiving dapsone 5% gel. Mean combined dermal tolerability scores for dryness, scaling, and erythema were low for both treatment groups. No adverse clinical or laboratory adverse events led to study discontinuation in any patient.\(^{35}\)

Two similarly designed phase III randomized, double-blind, vehicle controlled, multi-center studies were conducted to evaluate the efficacy and safety of dapsone 7.5% gel for treating acne vulgaris in patients aged 12 years and older.\(^{36,37}\) Patients (n=3977) with moderate acne vulgaris were given either 7.5% dapsone gel or vehicle gel once daily for 12 weeks. Adverse events were reported at similar rates in the treatment and vehicle control groups. In the first study, 19.1% and 20.6% of patients in the treatment and vehicle-controlled groups reported adverse events, respectively. The second study did not demonstrate a significant difference in adverse events in treatment (17.6%) and vehicle-controlled (17.1%) groups. Reported adverse events included mild to moderate application site erythema, exfoliation, dryness, pain, and pruritus. Five of the six patients who withdrew from the study cited the development of application site acne, dermatitis, pruritic rash, vesicles, swelling, and erythema. One patient withdrew following a diagnosis of acute myeloid leukemia.

Pooled subanalyses of these phase III studies showed similar tolerability of topical dapsone 7.5% gel when grouped by age, sex, and race.\(^{38}\) Thiboutot et al sub-analyzed the safety and tolerability of topical dapsone 7.5% gel in comparison to vehicle only.\(^{39}\) Treatment-related adverse events were similar between dapsone 7.5% gel groups and vehicle groups, 18.3% and 18.8% respectively. Tolerability of topical dapsone 7.5% was comparable to tolerability of vehicle gel. Stinging/burning, dryness, scaling, and erythema were most commonly reported (<0.5 mean tolerability scores for topical dapsone, 0=none, 1=mild) and <1% had a significant decrease in dermal tolerability throughout the study.\(^{39}\)

A 2014 phase I study was completed to evaluate for topical dapsone-induced phototoxicity in 33 healthy volunteers 18-65 years of age. Topical dapsone gel was applied daily to the skin of patients over four days and no adverse phototoxic effects were reported.\(^{40,41}\)

The therapeutic benefit and safety of topical dapsone in combination with other
established acne therapies was studied including topical tazarotene, adapalene, benzoyl peroxide (BP), clindamycin phosphate, as well as oral isotretinoin and TMP/SMX (previously described) (total n=717). Only 11 patients withdrew from these studies due to dapsone intolerance or mild adverse events. Seven patients using topical dapsone with BP described a “temporary tan residue” following concurrent application. For all treatment groups, plasma dapsone and monoacetyl dapsone levels remained low. All application site adverse events were mild in severity and no clinically significant changes in laboratory parameters were reported.\(^\text{22-26}\)

A study of 63 patients was conducted by Piette et al to assess the safety of topical dapsone 5% gel in high-risk patients with G6PD deficiency.\(^\text{27}\) Fourteen patients were considered severely G6PD deficient, yet no signs or symptoms of hemolytic anemia were detected in this group. Eight of 63 patients reported adverse events considered related to the study treatment. Laboratory testing detected adverse events in 3 study subjects. A mean reduction of hemoglobin by 0.32 g/dL was noted 2 weeks after initiating therapy, however, these changes were transient.\(^\text{27}\) Laboratory parameters suggestive of hemolysis (i.e decreased haptoglobin, increased bilirubin, LDH, or reticulocyte counts) did not accompany these findings.

Lynde evaluated the safety, efficacy, and tolerability of topical dapsone 5% therapy in patients with sensitive skin (n=101).\(^\text{28}\) Adult women with mild to moderate inflammatory acne applied dapsone 5% gel twice daily. Two patients withdrew from the study due to mild skin irritation. Of the women experiencing skin irritation, most developed a tolerance over time with repeated use of topical dapsone. No other adverse effects were reported.\(^\text{28}\)

**Case Reports**

Two case reports of topical dapsone 5% gel induced methemoglobinemia have been reported.\(^\text{15,29}\) Swartzenruber reported methemoglobinemia in a 19-year-old female being treated with topical dapsone for acne vulgaris. A second report by Graff describes methemoglobinemia in a 19-month old girl who inappropriately applied topical dapsone over a large surface area. Both patients recovered and remained asymptomatic after methylene blue administration without signs of hemolysis or need for further treatment.\(^\text{15,29}\)

Other case reports describe topical dapsone treating dermatitis herpetiformis, venous stasis ulcers, erosive pustular dermatosis of the scalp, erythema elevatum diutinum, granuloma faciale, lupus erythematosus, and hidradenitis suppurativa.\(^\text{13,30-34}\) No adverse events or safety concerns were reported in these studies.

**DISCUSSION**

The literature evaluated in this review support that topical dapsone [5%, 7.5%] gel can be used to effectively treat cutaneous diseases with limited systemic absorption and without fear of serious side effects. Most reported adverse events were mild in severity of skin irritation, and were transient in nature. The largest reviewed study did not report any non-application site adverse events associated with topical dapsone 7.5% gel therapy (n=3977). Less than 1% of patients (n=3010) experienced non-application site adverse events related to dapsone 5% gel therapy\(^\text{17,36,37}\) in another study. Thirty-nine of 6,384 (0.61%) total patients from the studies included in this
review experienced an adverse event that was considered to be more than mild and/or resulting in discontinuation of therapy.

Plasma dapsone levels were not affected by long-term topical treatment. Safety concerns about using topical dapsone in combination with TMP/SMX, isotretinoin, tazarotene, adapalene, BP gel, or clindamycin/BPO were limited and not determined to be clinically relevant; however, application of topical dapsone and topical BP when used in a combination topical regimen are best completed at different times during the day to avoid the potential for a temporary orange discoloration of skin. Of the 49 patients studied with G6PD deficiency, none experienced adverse hematologic effects in the short or long-term safety trials.\textsuperscript{17,21,35} Finally, both cases of methemoglobinemia, although seemingly questionable regarding cause and effect, reinforce the need for clinicians to remain vigilant about signs and symptoms and/or symptoms of adverse events related to increased systemic exposure.

**CONCLUSION**

Clinical trials have demonstrated the effective use of topical dapsone for the treatment of acne vulgaris. Additional publications suggest the potential for selected use of topical dapsone for the treatment of other skin conditions such as dermatitis herpetiformis, venous stasis ulcers, erosive pustular dermatosis of the scalp, crythema elevatum diutinum, granuloma faciale, lupus erythematosus, and hidradenitis suppurativa. The present aggregation of studies finds that the rates of adverse events were similar between dapsone gel treated groups and vehicle control groups. Local adverse signs and symptoms decreased over the course of therapy. The literature supports topical dapsone as a minimally irritating, well-tolerated, and effective medication. Further research and pharmacovigilance are warranted to optimally maintain our understanding of the long-term effects of topical dapsone therapy.

**Conflict of Interest Disclosures:** Dr. Del Rosso is a consultant, researcher, and speaker for Allergan.

**Funding:** none.

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