Harnessing the Anti-inflammatory Effects of Topical Dapsone for Management of Acne

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ABSTRACT

Data continue to establish the role of inflammation, not only in the pathogenesis of acne but also in the development of its most devastating sequelum, scarring. Although topical therapy is preferred by most acne patients and the physicians who treat them, historically no topical intervention has provided primarily anti-inflammatory effects. Topical dapsone 5% gel offers documented efficacy for the reduction of both inflammatory and non-inflammatory acne lesions. It has been proven safe, presenting none of the hematologic risks associated with oral dapsone. Data suggest the vehicle formulation enhances healing and contributes to tolerability, making topical dapsone 5% gel a worthwhile anti-inflammatory treatment for many patients with mild-to-moderate acne vulgaris.

INTRODUCTION

Although acne is one of the most common skin disorders, its pathogenesis is not clearly understood. *Propionibacterium acnes (P. acnes)* is a commensal organism that plays an active role in acne vulgaris. *P. acnes* thrives in the presence of excess sebum and has been shown to mediate inflammatory processes at the site of the sebaceous follicle, contributing to the formation of free radical species and generating pro-inflammatory cytokines.[1] Coupled with faulty keratinization, excess sebum production and *P. acnes* colonization contribute to the formation of microcomedones, ultimately leading to development of the comedones, papules, pustules and cysts characteristic of acne.

While the appearance of active acne vulgaris can have a significant impact on a person's appearance and can be associated with potential physical discomfort, the scarring following acne is the most devastating sequelum to the patient. A better understanding of the pathophysiology of acne and associated scarring has been gained with the most recent in vivo research by Kang et al.[2] They reported a marked increase in inflammatory cytokine gene transcripts in active acne lesions, including TNF-□ and IL-1b. Importantly, these pro-inflammatory cytokines amplify NF-kB signaling pathways that originally led to their production while also stimulating nearby cells, according to the authors. This investigation also identified significant increases in IL-8 and IL-10. In addition to NF-kB, Activator Protein-1 (AP)-1 is also elevated in acne lesions, leading to elevated matrix metalloproteinases, which degrade collagen—up to 2.5-fold compared to normal skin. Furthermore, the authors note that the inflammatory process is localized to the pilosebaceous unit.[2]

The most common sequelum of inflammatory acne is scarring, which is devastating to patients. The best way to prevent scarring is, of course, to prevent and treat inflammatory lesions as early as possible. Also, any agent blocking (AP)-1, which increases matrix metalloproteinases that cause scarring via collagen degradation, will be useful in scar prevention.

Topical treatment options for acne include retinoids, antimicrobials, such as erythromycin and clindamycin, and benzoyl peroxide (BPO). Different combination formulations of retinoids, antibiotics and BPO are also available. Topical retinoids primarily act to normalize hyperkeratinization and have been suggested to confer mild anti-inflammatory effects. Topical antimicrobials and benzoyl peroxide target *P. acnes*, diminishing colonization. Topical antimicrobials may also confer anti-inflammatory effects.

Despite the well-known and recently re-affirmed role of inflammation in acne, no primarily anti-inflammatory topical therapy has been available for acne. Anti-inflammatory topical dapsone 5% gel (Aczone Gel 5%, Allergan, Irvine, CA) is now available for topical treatment of acne.

Mechanisms of Action

Although dapsone has proven to be a very powerful treatment in several neutrophilic dermatoses (such as dermatitis herpetiformis) through its anti-inflammatory effects, the mechanism of action of this effect is not well understood. There are several in vitro studies that show the anti-inflammatory effect of dapsone. The successful use of oral dapsone in several sub-epidermal blistering diseases is associated with anti-inflammatory effects by the suppression of neutrophil and eosinophil functions. This effect was demonstrated through dapsone's inhibition of IL-8 release in cultured human keratinocytes.[3]

It also has been shown that dapsone suppressed leukocyte integrin function, thus inhibiting migration of neutrophils to extravascular sites.[4] Further, in vitro studies by Debol et al. show that dapsone inhibits chemoattractant-induced G-protein activation and suppresses the subsequent signal transduction cascade.[5]

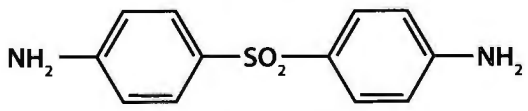
Other in vitro work revealed dapsone's inhibition of calcium-dependent function of neutrophils[6] and release of inflammatory mediators, such as prostaglandins, leukotrienes and lysosomal acid hydrolases.[7] A study by Abe et al. revealed that dapsone may confer anti-inflammatory activity in cutaneous lupus erythematosis by decreasing TNF-a produced by activated mononuclear cells.[8] There is also a suggestion that dapsone's beneficial effects in inflammatory dermatological conditions come from its inhibition of 5-lipooxygenase metabolites.[9]

Historical Context

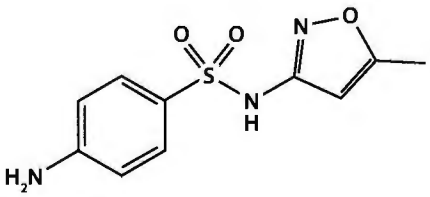
Systemic dapsone has a long history of use for numerous inflammatory diseases, such as pemphigus vulgaris, leprosy and dermatitis herpetiformis. Although the chemical structure of dapsone is similar to that of the sulfonamide antibiotics, it is distinctly different from the sulfonamides (Figure 1) and is actually classified as a sulfone.[10] Of note, history of allergic reaction to sulfonamide non-antibiotics or sulfonamide antibiotics or history of adverse reactions to sulfonamides does not predict cross-reactivity with other sulfa drugs.[11]

Dapsone confers anti-inflammatory and antipyretic effects.[12–14] It also appears to have antioxidant effects and has been shown to target inflammatory proteinases and the oxidant hypochlorous acid.[15] Systemic dapsone has been associated with notable risks. Hemotoxicity (methemoglobinemia) has been reported. About 50 percent of the dose is excreted within 24 hours (mostly through urine). After absorption from the gastrointestinal tract, dapsone is metabolized to either by N-hydroxylation—producing hydroxylamine, a potentially toxic metabolite produced by cytochrome P-450 enzymes—or N-acetyltransferase, which yields non-toxic metabolites (monoacetyl dapsone and diacetyl dapsone).[16] People with a glucose-6-phosphate dehydrogenase (G6PD) deficiency, methemoglobin reductase deficiency or hemoglobin M disease are at highest risk for hemotoxicity, and the package insert for oral dapsone requires regular screening of full blood counts, unlike in the case of topical dapsone, where no laboratory testing is required.

FIGURE 1. Chemical structures.



Dapsone



Sulfamethoxazole

In clinical trials, twice-daily topical application of dapsone as directed for the treatment of acne did not induce significant changes in hemoglobin or other hematologic indicators, even in G6PD-deficient patients.[17–20] An analysis of data from two phase 1 pharmacokinetic studies and one phase 3 long-term safety study found that overall total systemic exposures to dapsone and its metabolites were approximately 100-fold less for dapsone gel than for oral dapsone (even with co-administration of trimethoprim/sulfamethoxazole). Mean plasma dapsone concentrations associated with topical application ranged from 7.5–11 ng/mL over 12 months in the long-term safety study.[20] Therefore, continuous use of dapsone 5% gel is not associated with an increase in plasma concentrations of the drug. Concomitant use of topical BPO or adapalene has not been shown to affect the pharmacokinetic profile of dapsone 5% gel.[18] A 0.32-g/dL decrease in hemoglobin concentration occurred from baseline to two weeks during dapsone gel treatment. This was not accompanied by changes in other laboratory parameters, including reticulocytes, haptoglobin, bilirubin and lactate dehydrogenase levels, and was not apparent at 12 weeks as treatment continued. Current labeling for topical dapsone does not include requirements for glucose-6-phosphate dehydrogenase (G6PD) screening or blood monitoring.

Efficacy

Dapsone 5% gel applied twice daily has been shown to decrease both the inflammatory and non-inflammatory lesions of acne vulgaris. In two 12-week, double-blind, randomized, parallel group, phase 3 studies conducted under identical protocols, a total of 3,010 patients age 12 or older were assigned to apply either dapsone gel 5% twice daily or vehicle gel to affected areas of the face.[19] Pooled analysis of the data shows that treated patients experienced significantly greater reductions from baseline to 12 weeks in inflammatory, non-inflammatory and total lesion counts compared to controls (Figures 2–4). The greatest reduction occurred in inflammatory lesion counts, which were reduced by nearly half in treated patients (47.5 versus 41.8 percent). Response to treatment was rapid, starting at week 2, and was maintained throughout the study. In fact, a slight difference in inflammatory lesion counts between the active and vehicle groups that was evident by week 2 was highly statistically significant at week 4. Treated patients achieved superior Global Acne Assessment Scores, regardless of whether baseline acne was more or less severe (as determined by acne lesion counts).

Tolerability

Importantly, topical dapsone treatment was well tolerated with similar numbers of patients reporting adverse events in the active and control groups (58.2 percent of treated patients and 58.6 percent of controls). Most events were of mild to moderate intensity, resolved during treatment, and did not result in treatment discontinuation. Just 0.6 percent of treated patients

discontinued participation due to lack of efficacy, while 0.4 percent withdrew due to an adverse event.

Long-term Study

Similar efficacy and tolerability were evident in a one-year open-label, non-comparative trial of topical dapsone involving a total of 506 patients age 12 or older.[20] Patients applied dapsone for a mean of 253 days over the 12-month study period. The protocol directed twice-daily application to affected facial areas. Patients could discontinue application to a particular area once clear, but could reinitiate application to that site if necessary.

FIGURE 2. Mean percentage change in non-inflammatory lesion count.

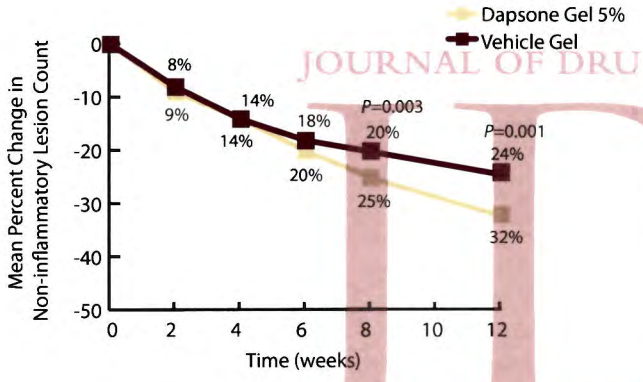


FIGURE 3. Mean percentage change in inflammatory lesion count.

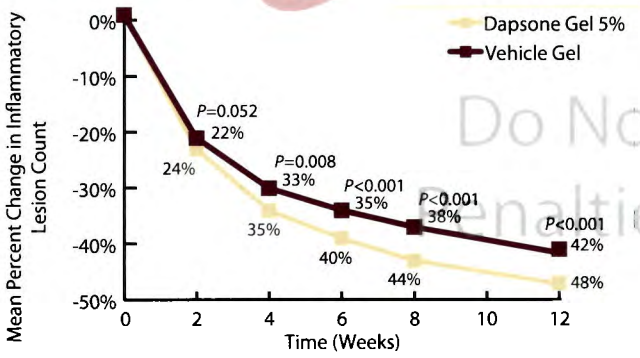
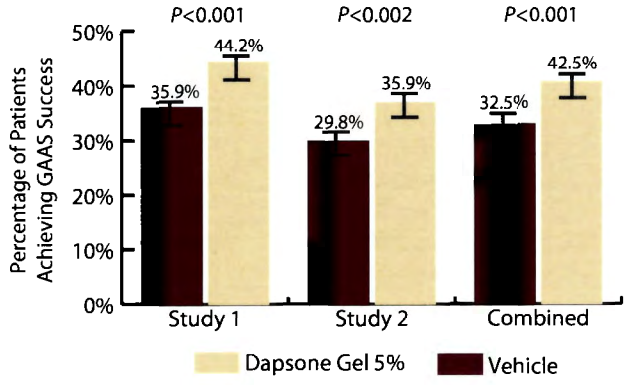


FIGURE 4. Percentage of patients achieving GAAS success.



Improvement in inflammatory lesions was more significant than improvement in non-inflammatory lesions, and was evident by week 4. Lesion counts continuously decreased through month 6; these improvements were maintained through 12 months. Mean inflammatory lesion counts decreased from 48.1 at baseline to 23.1 at month 3, 20.4 at month 6 and 18.4 at 12 months. Mean non-inflammatory lesions counts for the same respective periods were 38.5, 30.1, 26 and 25.1. Twelve-month mean percent reduction in lesion counts from baseline was 58.2 percent for inflammatory lesions and 19.5 percent for non-inflammatory lesions. At month 3, 96 patients initiated concomitant systemic or topical acne therapy according to study protocols, but ad hoc analysis of the data revealed no clinically apparent differences in lesion count reductions for this sub-population at month 3 or 12.

Approximately two-thirds of patients (68 percent) experienced at least one adverse event during the course of the study, but investigators judged just 9.5 percent of these to be treatment related. Reported application site reactions (reported by 13.8 percent of patients) included dryness, rash and sunburn. Treatment was well tolerated: 0.8 percent of patients withdrew due to lack of efficacy, while 2.2 percent withdrew due to an adverse event.

Combination Study

There was also a combination trial comparing dapsone alone to dapsone plus adapalene and dapsone plus benzoyl peroxide 4%.[18] Dapsone gel in the combinations investigated was found to provide greater mean percentage reduction in total lesion and in non-inflammatory lesion counts than dapsone alone, with the most significant decrease associated with dapsone plus adapalene. However, it is notable that there was no statistically significant difference between topical dapsone alone versus the combination regimens for inflammatory lesions. These findings actually reveal that topical dapsone alone is a very powerful agent against inflammatory lesions.

Unique Vehicle

These results support the efficacy of this new, patented formulation that is exclusively used with topical dapsone. Data confirm that optimally designed formulations work synergistically to deliver active agents into viable tissue while enhancing the barrier function essential for healthy skin. Aczone's gel formulation contains diethylene glycol monoethyl ether (DGME), which facilitates the permeation of active ingredients into the skin and helps undissolved dapsone to remain in the pilosebaceous unit, according to in vitro data.[21]

Penetration enhancers such as DGME have been shown to increase the efficacy of topical molecules. However, some penetration enhancers are limited by their potential toxicity and irritancy. DGME improved the skin penetration of topical steroids and its lower toxicity has been established, leading to approval by FDA for cosmetic use.[22] DGME is a hydroscopic liquid with an excellent solubilizing characteristic and cutaneous biocompatibility. One of its important functions is to increase cutaneous accumulation of topical compounds without increase of transdermal permeation, as shown in a study of ultraviolet absorbers.[23] Another study revealed skin retention of dexamethasone and hydrocortisone, creating an intracutaneous depot for these molecules without increasing transdermal delivery.[24]

These specific properties of DGME help topical dapsone in this novel formulation to remain in the pilosebaceous unit and subsequently increases its efficacy in the treatment of acne vulgaris.

CONCLUSION

Inflammation plays a significant role not only in the pathogenesis of acne but also in the development of its most devastating sequelae, scarring. Although topical therapy is preferred by most acne patients and the physicians who treat them, historically no topical intervention has provided primarily anti-inflammatory effects. Topical dapsone 5% gel is a novel agent that targets inflammation with proven efficacy for the reduction of both inflammatory and non-inflammatory acne lesions.

While the risks of life-threatening hematologic events associated with oral dapsone require that clinicians institute therapy with caution, studies confirm that topical application of dapsone does not produce worrisome plasma concentrations. In fact, the safety of topical dapsone is sufficiently obvious that the FDA has withdrawn the requirement for baseline blood monitoring (particularly G6PD screening).

Aczone gel 5% represents a valuable treatment option for patients with acne vulgaris. Studies document the excellent tolerability of the new aqueous gel formulation. Given the current understanding of the role of inflammation in the pathogenesis of acne and scarring, a targeted anti-inflammatory agent is a welcome addition to the treatment arsenal, especially for sensitive skin patients who cannot tolerate other topicals.

DISCLOSURES

Dr. Kircik has served as an investigator, consultant or speaker for Allergan, Inc. and QLT.

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