The Role of Dapsone Gel in the Acne Armamentarium

The authors discuss how this agent's dual anti-inflammatory and anti-microbial effects may make it a safe and effective multimodal monotherapy for acne. However, they add, further studies are needed. Acne vulgaris, which is characterized by inflammatory and non-inflammatory lesions beginning during adolescence, is most often manifested on the face and neck. Acne formation is multi-factorial, and includes: disordered keratinocyte desquamation, sebum secretion, inflammation, and Propionibacterium acnes. Most current treatments for acne focus on limiting one or more of these factors.1 Many topical and oral acne treatments involve anti-bacterial action, but problems arise when bacteria develop resistance, rendering treatment less effective. **Benzoyl peroxide** (BPO) is widely considered **first-line topical antibacterial treatment** for acne, but it can cause irritation at high concentrations and bleaches clothing and/or hair. **Topical and oral antibiotics** are also common **treatments for inflammation** in acne, but present a problem due to the aforementioned resistance. A newer therapy for acne is 5% dapsone gel, with initial studies indicating that it is both effective and safe; but further studies remain.

Dapsone Properties

Dapsone is a sulfone that has been used mainly as an **oral medication** for leprosy and less commonly as a treatment for acne vulgaris. Although dapsone is classified as an **antibiotic** due to its inhibition of bacterial DNA synthesis, it is also an **effective anti-inflammatory agent**. Nevertheless, due to the concerning side effects that come along with ingestion of the drug (hematologic and hepatic issues), a topical formulation has been produced. Blood dapsone levels following **topical dapsone gel treatment** at steady state was demonstrated to be approximately 100-fold lower than exposure to a single 100-mg dose of orally administered dapsone.2 In 2005, the FDA approved dapsone for acne patients under the condition that they test negative for G6PD deficiency; however, following a phase IV trial, the FDA removed this restriction, improving feasibility. Dapsone's **dual anti-inflammatory and anti-microbial effects** may offer physicians a novel **multimodal monotherapy for targeting acne**. Aczone, the trade name for 5% dapsone gel, is marketed by Allergan and is available to prescribers and their patients.

Dapsone Efficacy

Clinical trials have demonstrated reductions in acne lesions with 5% dapsone gel use, particularly for inflammatory lesions. One such study enrolled 506 patients older than 12 years of age with a

clinical diagnosis of moderate to moderately severe acne vulgaris.[1] Patients applied treatment twice daily to affected areas. The clinical trial lasted 12 months. There was a 58.2% decrease in inflammatory lesions, a 19.5% reduction in non-inflammatory lesions, and a total lesion reduction of 49% (P values all below 0.05). Acne lesion counts decreased over the first 6 months, then leveled out over the next 6 months. Of note, almost 20% of the participants used prohibited acne medications in addition to twice daily dapsone gel. Another study assessed the efficacy of 5% daspone gel in treating acne vulgaris using global acne assessment score (GAAS) and mean lesion count reductions. Two similar 12-week studies of 3,010 patients were combined to generate the data.3 In the first study, 44% of the experimental group (vs. 36% of the control group) achieved success using the GAAS scale. In the second study, 37% of the experimental group (vs. 30% of the control group) achieved success using this scale. Combined, 40% had success with dapsone gel, and 33% had success in the control group (P <0.001). In comparing the mean lesion counts, the dapsone group demonstrated greater reductions in inflammatory (48% vs. 42%), non-inflammatory (32% vs. 24%), and total lesion counts (39% vs. 32%) compared to the control group. Like the previous study, dapsone was more effective in reducing inflammatory lesions than in reducing noninflammatory lesions. As early as week 2, a small difference could be seen between control and experimental groups, and this difference grew to statistical significance by week 8. To put this data in perspective, we compared the results from the three large clinical trials to those seen with other commonly used acne treatments. **Table 1** — which focuses on inflammatory lesion reduction — displays results from the clinical trials involving dapsone gel, as well as those from selected trials of other acne preparations. Although we found trials testing the efficacy of other topical gels — as opposed to creams, lotions, solutions, etc.— it is impossible to make a clear comparison, as gel formulations can contain a wide variety of ingredients. Thus, the relative efficacy (found by subtracting lesion reduction percentage in the vehicle group from that of the drug treatment group) may not be comparable between treatments.[4] As stated above, although the listed trials are each quite different in character, dapsone gel appears to be similarly effective in reducing inflammatory acne lesions to benzoyl peroxide, topical retinoids, topical antibiotics and oral antibiotics. Its relative efficacy, which appears somewhat lower than other agents, is questionable, as the gel formulations themselves may be promote or inhibit acne formation.[4] Furthermore, other confounding variables, including study design and study population, may be responsible for this finding, and further head-to-head comparative trials are called for. In the meantime, dapsone may serve an important function in those who develop intolerance to the currently established acne agents or are unable to use them secondary to side effects.

Dapsone Tolerability

The primary tolerability concern with dapsone is **hematological reactions**. Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency in particular are at increased risk of hemolysis and hemoglobin denaturation with oral dapsone. These worries led the FDA to initially condition topical dapsone approval on mandatory G6PD deficiency screening. However, the aforementioned

trials of dapsone gel indicated that patients are not at increased risk of hemolytic anemia, methemogoblinemia, or drops in hemoglobin levels, including those with G6PD deficiency.3 Furthermore, a 12-week study examining 64 patients with G6PD deficiency (14 were severely deficient) using twice daily 5% dapsone gel found a clinically insignificant 0.32 g/dL decrease in Hb level 2 weeks after beginning therapy, which was no longer observed at 12 weeks of treatment.[5] Additionally, no relationships were found between changes in Hb level and bilirubin, haptoglobin, LDH levels and relative reticulocyte count, arguing against clinically relevant hemolysis. Finally, no clinical signs of hemolytic anemia were observed in subjects applying the dapsone gel. There are local side effects associated with 5% dapsone gel. The most common local adverse reactions are oiliness, dryness and erythema — each in nearly 20% of the patients.[3] A much smaller proportion (2% or less) of the participants reported burning, pruritus, and irritation at the application site. However, it is important to note that these adverse reactions were reported at comparable rates in the control group, which received vehicle gel treatment. Thus, adverse reactions are probably attributable to the gel vehicle rather than dapsone.

Limitations — Studies Needed (Table 2)

Due to the fact that dapsone was only recently approved for use in acne treatment, there remains a **lack of studies on the bacterial resistance** caused by **dapsone gel**. Oral dapsone used in leprosy does result in resistance and must be given in combination with other drugs.[6] What remains to be seen is whether dapsone gel will cause similar resistant strains in acne vulgaris. Such studies have been performed in the past with other acne treatments.[7] Another study that could help put dapsone's efficacy into better perspective would be a controlled **head-to-head clinical trial comparing different acne treatments**, including BPO, tetracycline agents, clindamycin, erythromycin and topical retinoids, to dapsone gel. Such a study would help clinicians determine which drug is best under a given circumstance, as well as where dapsone fits in the plethora of effective acne agents (**Figure 1**). In comparing other topical treatments with dapsone gel, we must realize that acne treatment vehicles are not placebos, oftentimes exhibiting considerable activity.**4** In order to appropriately compare topical acne agents to each other, it would be prudent to use the same vehicle (ie, other topical gels of the same formulation). In this regard, we must also examine the **interactions of different drugs, both oral and topical, with dapsone**, and how they can work with or against each other. Such a study would make it possible to understand dapsone combinations are effective and/or safe and which are not. We are most interested to see if dapsone, in combination with other agents, improves efficacy, or if dapsone deactivates or is deactivated by another agent. Furthermore, data are also needed on the effect of combination use on side effects.

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