Advances in Topical Acne Therapy

Even severe acne patients can be safely—and effectively—treated with topicals today.

BY JOSHUA ZEICHNER, MD

Acne is a pervasive inflammatory disease of the pilosebaceous unit. It affects upward of 40 million Americans and carries a heavy burden on patients, as it can lead to both physical and emotional scarring. In fact, acne’s negative effect on quality of life is thought to be on par with that of systemic diseases such as diabetes. Early, effective interventions can clear acne lesions, prevent scarring, and improve quality of life. Currently available topicals have improved vehicles compared to their predecessors and have demonstrated enhanced efficacy and tolerability, even in severe disease. Moreover, a number of new chemical entities are being developed and will continue to improve the landscape of available acne treatments.

The following summarizes data from some of the newest clinical studies on the topical treatment of acne.

ADVANCES IN TREATING SEVERE ACNE

In a sub-population analysis of the Phase 3 pivotal study evaluating adapalene (ADA) 0.3% / benzoyl peroxide (BPO) 2.5% gel (Epiduo® Forte, Galderma), efficacy as topical monotherapy in patients with severe acne was assessed. Severe acne patients were defined as having an investigator’s global assessment (IGA) score of 4, with 20-100 inflammatory lesions, 30-150 comedonal lesions, and no more than two nodules. Two hundred and fifty-two patients were evaluated, 88.5 percent of whom completed the study. Of these, 31.9 percent of patients were considered a treatment success (IGA of 0 or 1), which was statistically better than 11.8 percent seen among patients treated with the vehicle, \( p=0.029 \). The absolute lesion count and mean percent lesion count reductions were also statistically superior to vehicle \( p<0.001 \) at week 12. The drug was well tolerated, though showed slightly more irritation than ADA 0.1% / benzoyl peroxide 2.5% gel (Epiduo®, Galderma), which was used as a tolerability comparator in the study.

ADVANCES IN TOPICAL TOLERABILITY

In a double-blind, split-faced comparator study, the irritation potential of clindamycin phosphate (CP) 1.2% / BPO 3.75% gel (Onexton®, Valeant), was compared to ADA 0.3%/BPO 2.5% gel (Epiduo® Forte, Galderma). Neither investigator nor subject knew which product was being applied to either side of the face. Fifty-two patients were enrolled and applied the study drugs once daily for 21 days. The mean cumulative change from baseline for erythema evaluation scores was found to be statistically higher in the ADA 0.3%/ BPO 2.5% group compared to the CP 1.2%/ BPO 3.75% gel group as early as day nine, and remained significant for the duration of the study. The mean cumulative change from baseline for dryness evaluation scores were similarly statistically higher in ADA 0.3%/ BPO 2.5% patients compared to the CP 1.2%/ BPO 3.75% treated sides.

ADVANCES IN TOPICAL DRUG DEVELOPMENT

Topical Dapsone 7.5% Gel. Topical dapsone 5% gel (Aczone®, Allergan) is currently available for the treatment of acne with twice daily dosing. A higher concentration formulation (7.5%) of topical dapsone was recently FDA approved for acne and will be available soon. In two identically designed, large, multicenter, randomized, placebo-controlled trials, patients aged 12 and up were treated with dapsone 7.5% gel once daily for 12 weeks. Entry criteria for this study were more stringent than that of trials for the 5% formulation, as patients needed greater severity of lesions to be enrolled. In both studies, the percent of patients achieving a treatment success (clear or almost clear) was statistically higher in the active compared to vehicle at weeks 8 and 12. In one of the studies, significance was achieved as early as week 4. Significant differences in inflammatory lesion count reductions were observed at week 4 and continued throughout the study. There was approximately a 55 percent reduction in inflammatory lesions at the week 12 endpoint. Statistical differences in comedonal lesions count reductions were observed at week 8 in both studies and continued to be significant until week 12. The drug was well tolerated, with minimal local cutaneous adverse events. In fact, the active drug demonstrated less burning/stinging and dryness than the vehicle arm.

Topical Sebum Inhibitors. Sebum production is a key driver of acne development. Newer acne drugs use sebum inhibition...
as a therapeutic target. DRM01 is a topical drug that inhibits coenzyme-A carboxylase, a key enzyme involved in fatty acid synthesis. The drug has demonstrated dose-dependent inhibition of lipid synthesis in human sebocyte cultures and reduced the size of sebaceous glands in an animal model. In a first-in-human, Phase 2a study, its safety and efficacy were evaluated for the treatment of moderate-to-severe facial acne in 108 subjects. Twice daily application of DRM01 7.5% gel demonstrated statistical reductions in both inflammatory and comedonal lesions as early as week 4 (inflammatory, p = 0.0666; comedonal, p = 0.0328) and at the end of the study at week 12 (inflammatory, p = 0.0006; comedonal, p = 0.0025). In addition, at week 12, a greater proportion achieved a ≥ 2-grade improvement in IGA compared to vehicle (p=0.0070). The drug was well tolerated with minimal local cutaneous adverse events reported.5 DRM01 is being developed by Dermira.

SB204. Nitric oxide (NO) is an endogenous, short-acting molecule with both anti-microbial and anti-inflammatory activity. NO has demonstrated activity against P. acnes, is anti-inflammatory, and has been shown to inhibit lipogenesis. SB204 is a topical NO containing gel that has been evaluated in the treatment of acne. In a Phase 2a study, two concentrations of SB204 (1% and 4%) were compared to vehicle. Statistical decreases in the mean percent change in both inflammatory and comedonal lesions were observed in the 4% formulation compared to vehicle at week 12 (p<0.05), with approximately a 55 percent and 25 percent reduction in inflammatory and comedonal lesions, respectively. Moreover, total sebum levels were found to be reduced at the end of the study along with a dose-dependent decrease in squalene and percent of free fatty acids in the sebum.6 SB204 is being developed by Novan Therapeutics.

**Topical Minocycline.** Minocycline is a lipophilic tetracycline class antibiotic currently used orally for the treatment of acne. Historically, attempts to formulate topical minocycline have been unsuccessful because it is highly unstable. Currently, several topical minocycline formulations are under development. Topical application of an antibiotic is advantageous in that it avoids the risks associated with systemic antibiotic use, including bacterial resistance. BPX-01 is a unique, stable topical minocycline in a hydrophilic gel. Both in-vitro and in-vivo studies have shown that minocycline in the BPX-01 formulation is delivered to the epidermis and pilosebaceous units at efficacious levels. In an in-vitro evaluation of human facial skin samples, quantitative high performance liquid chromatography (HPLC) analysis demonstrated effective delivery of minocycline to the skin. In in-vivo studies on hairless rats, the drug was effectively absorbed through the skin and observed not only in the stratum corneum but also detected within the pilosebaceous unit. A repeat dose pharmacokinetics study in rats showed no toxic effects.7 BPX-01 is being developed by BioPharmX Corp.

**CONCLUSION**

Advances in topical drug formulation have brought better therapies to add to our acne tool belt. Even severe patients may be effectively treated with topical therapies alone, and in some cases avoiding oral therapies altogether. Improvements in vehicles and drug delivery systems minimize cutaneous tolerability and simplify regimens, which translates to better adherence. Finally, new chemical entities address pathogenic factors that up until this point required systemic medications, along with their potential risks. Collectively, these innovations bring better, safer drugs that ultimately will improve therapeutic outcomes in treating acne.

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