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Never Give Up! Continued Progress in Development of Topical Therapies for Acne Is a Good Thing

In July 2022, I will reach the milestone of practicing dermatology for 36 years, with 30 years of experience also devoted to clinical research. My background in pharmacy before attending medical school set the stage for my strong interest in therapeutics with regular participation in educational initiatives at many meetings and in multiple peer-reviewed publications addressing several therapeutic areas. Ultimately, my primary interest is to translate important advances in our understanding of common chronic skin diseases and/or their management to dermatology clinicians who practice day-to-day in the trenches.

Early in my career, at a small dermatology meeting in Myrtle Beach, Virginia, I heard Dr. Jim Leyden present an incredibly interesting and comprehensive lecture on acne vulgaris (AV), which immediately prompted both my academic drive and strong interest in this subject area. Soon after, a dedication to rosacea followed. Although my academic, educational, and research interests cover many disease states and therapeutic areas, my interest and commitment to AV and rosacea have never diminished.

Many of the advances in dermatologic treatments have focused on systemic therapies for psoriasis and atopic dermatitis, mostly with the development of injectable monoclonal antibodies and oral "small" molecules. Expansion of these agents into management of other inflammatory skin diseases is also rapidly emerging, as are a few new nonsteroidal topical agents and combination topical formulations. So now what? What is new for AV? Has this disease state been forgotten by academic and pharmaceutical researchers? Thankfully, there are some new advances, with both FDA-approved topical therapies and others that are progressing through their formal development process.

Despite the common knowledge that androgens are a major contributor to AV pathophysiology, the availability of FDA-approved anti-androgen therapies for AV has been limited to a few combination oral contraceptives that can be used only in females.[1] Finally, a topical androgen receptor inhibitor, clascoterone 1% cream, was FDA-approved in August 2020 and became available in the United States marketplace on November 1, 2021, In fact, topical clascoterone has been shown to be effective and safe in both adult and adolescent males and females with AV due to negligible systemic exposure and lack of systemic safety signals in clinical trials.[2-4] Prior to this, the predominant therapies used by clinicians for AV that reduce the effects of androgens have been oral spironolactone (not FDA-approved for AV) and oral contraceptives (most not FDA-approved for AV), which cannot be used in males with AV due to adverse effects associated with systemic exposure. Importantly, although clascoterone, like many other pharmacologically diverse compounds, incorporates a four-ring steroidal nucleus. However, clascoterone is not a corticosteroid or a mineralocorticoid; rather it is an androgen receptor inhibitor.[1,2] Formal submission for approval of topical clascoterone for AV included two pharmacokinetic and maximal usage studies (pediatric and adult), two vehicle-controlled phase 3 efficacy and safety studies, and one long-term (52 weeks) safety trial with concurrent evaluation of efficacy on the face and trunk; FDA-approval was granted for topical treatment of AV in patients 12 years of age or greater. Studies evaluating for hypothalamic-pituitary-adrenal (HPA) axis suppression (at up to 6-fold higher application exposure than what is used daily for facial AV) and serum chemistry/electrolyte changes (including maximal use study) revealed no requirements for routine laboratory testing, no recommendation for HPA axis evaluation including in phase 3 or phase 4 studies, and no correlation between systemic exposure and development of hyperkalemia based on exposure-response analysis.[5] In a nutshell, the data show that clascoterone 1% cream applied twice daily for AV may be associated with signs of local skin irritation in some patients which do not typically lead to discontinuation of use, with negligible risk of systemic

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side effects. Many clinicians ask about use of topical clascoterone with other topical agents for AV. Although not formally studied, my usual preference is to use clascoterone 1% cream during the daytime and a topical retinoid or topical retinoid-benzoyl peroxide combination formulation in the evening (such as bedtime), coupled with appropriate skin care.

A new FDA-approved topical combination formulation incorporates both encapsulated benzoyl peroxide and encapsulated tretinoin in the same cream for acne, with favorable efficacy and skin tolerability; the encapsulation technology circumvents the degradation of tretinoin by benzoyl peroxide.[6] There have been improved specialized lotion formulations with either tretinoin or tazarotene for acne that reduce potential for skin irritation without loss of clinical efficacy.[7,8] Topical trifarotene is a newer topical retinoid that is formally FDA-approved based on phase 3 studies for both facial and truncal acne.[9] Another advance is topical minocycline 4% foam which is FDA-approved for AV, with pivotal trial data showing avoidance of systemic adverse effects that are sometimes seen with oral minocycline.[10] Lastly, a triple combination of benzoyl peroxide, adapalene, and clindamycin formulated in a gel vehicle (IDP-126) is in development for AV; thus far, highly favorable efficacy as compared to the paired active components, and good skin tolerability, have been demonstrated in studies to date with IDP-126.[11]

As AV remains one of the most common skin disorders encountered in clinical practice, it is important that dermatology clinicians remain knowledgeable about new developments for AV including new compounds, vehicle formulations, and combination products. I am encouraged by the continued desire of both clinical and basic science researchers to develop new topical agents and formulations for AV that expand our menu of choices and help us to optimize therapeutic outcomes. In addition, I hope that efforts to increase affordability and access to these newer therapies for AV and other disease states will be successful.

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