EDITORIAL

A New Class of Topical Acne Treatment Addressing the Hormonal Pathogenesis of Acne

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Acne affects 85% of adolescents and is the most common skin condition in the United States.[1] For many patients, particularly women, acne can also persist into adulthood.[2] Acne has substantial psychosocial effect and it is responsible for a greater global burden of disease, as assessed by age-standardized disability-adjusted life years, than psoriasis, cellulitis, and melanoma.[3] In the United States, the cost of treatment and lost productivity among those who seek care for acne is more than $1 billion per year.[4]

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The pathogenesis of acne is multifactorial and includes follicular hyperkeratinization, overproduction of sebum, microbial colonization with *Cutibacteruim acnes* (formerly *Propionibacterium acnes*), and inflammation.[5] Within this framework, hormonal factors play a considerable role in the development of acne. At adrenarche, production of androgens and other sebogenic hormones, such as insulin-like growth factor 1, result in increased levels of sebum production within the pilosebaceous unit. This excess sebum facilitates proliferation of *C acnes*, and changes in sebum composition may result in follicular hyperkeratinization and inflammation. Combined, these underlying factors contribute to a primarily Th-17 and Th-1 driven inflammatory process that results in the clinical manifestations of acne.[6]

Classic mainstays of acne treatment include topical retinoids, benzoyl peroxide, and topical antibiotics.[7] Although these medications are effective for many individuals with acne, they are not sufficient to achieve acne clearance in some patients. In addition, both topical retinoids and benzoyl peroxide are irritating, which can limit their use in patients who are unable to tolerate them. Remarkably, no currently available topical medication targets the important role of hormones in the development of acne. Although combined oral contraceptives and spironolactone are effective options that can address the hormonal pathogenesis of acne, these medications have the potential for systemic adverse effects and cannot be used in men with acne.[8]

Clascoterone (cortexolone 17 α-proprionate) cream, 1%, is a topical androgen receptor inhibitor that competes with androgens for binding to the androgen receptor. In results from 2 phase 3 trials published in this issue of *JAMA Dermatology*,[9] 18.4% and 20.3% of subjects who received clascoterone cream, 1%, achieved the treatment success end point compared with 9.0% and 6.5% of those who received vehicle cream in CB-03-01/25 and CB-03-01/26, respectively. In addition, there was a 30.6% and 29.3% decrease in noninflammatory count from baseline among those who received clascoterone cream, 1%, vs 21.6% and 15.6% with vehicle in CB-03-01/25 and CB-03-01/26, respectively. There was a 44.8% and 46.9% decrease in inflammatory lesion count with clascoterone cream, 1%, compared with 36.5% and 29.6% with vehicle in CB-03-01/25 and CB-03-01/26, respectively. The rate of cutaneous adverse effects was low and similar between those who received clascoterone and those who received vehicle cream. Application site erythema and dryness were rare.

However, because clascoterone is rapidly hydrolyzed to cortexolone, there is the possibility for adrenal suppression with its use. In a phase 2 study[10] in which 42 subjects applied 6 g of clascoterone cream, 1%, to their entire face, shoulders, upper chest, and upper back for 14 days, 3 subjects (7%) had abnormal hypothalamic-pituitary-adrenal axis response at day 14, as assessed by a cosyntropin stimulation test. These findings normalized within 4 weeks after discontinuing the cream. While no clinical symptoms of adrenal suppression were observed in this study or the phase 3 trials,[9] this potential adverse effect may be important to consider, particularly when using larger quantities of clascoterone.

Although clascoterone represents an exciting new therapeutic option for patients with acne, many questions remain. First, it will be important to identify where clascoterone fits in our therapeutic ladder for acne treatment. One of the top 10 research priorities for the treatment of acne identified by a recent James Lind Alliance Priority Setting Partnership is to identify what is the best topical product for treating acne.[11] Although results of a small pilot study suggested that clascoterone may have similar or even superior efficacy to tretinoin cream, 0.05%, an active comparator arm was not included in these phase 3 trials.[12] As a result, there is a need for future studies to examine how the effectiveness and tolerability of clascoterone compare with other topical acne medications. In addition, given its novel mechanism of action, it will be important to explore whether it has complementary benefits when used in combination with other treatments.

Another important question is whether there are specific subgroups for whom clascoterone cream is most effective. In the trials reviewed in this issue of *JAMA Dermatology*,[9] approximately 90% of patients were white. The lack of diversity in these phase 3 trials raises questions of whether the results will generalize to other populations and is a weakness of the studies. Additionally, it will be important to examine whether clascoterone may have benefit for certain acne phenotypes, such as adult female acne, which typically responds well to treatments that target the hormonal pathogenesis of acne, such as spironolactone.[8,13] It is notable that clascoterone had good efficacy for both noninflammatory and inflammatory lesions in these trials[9] and it may be particularly help-

ful for patients with more inflammatory acne that may not respond well to other topical medications.

In addition, it will be interesting to examine whether clascoterone can help reduce our reliance on oral antibiotics for the treatment of acne. Oral antibiotics are the most common systemic medication prescribed for acne, and many patients are treated with course durations exceeding the guideline recommendations.[14] As a novel class of topical acne treatment, clascoterone cream, 1%, may help patients for whom other topical treatments failed and may create opportunities for new combination approaches with greater efficacy, such as using it together with a topical retinoid. If more patients can achieve clear skin with these topical regimens, it may reduce the reliance on systemic acne medications, such as oral antibiotics. Furthermore, for patients who do require treatment with oral antibiotics and are able to achieve clearance, clascoterone may provide another option to help with maintenance after the antibiotics are discontinued.

A final question is whether there will be adequate insurance coverage for this new topical acne medication.[15] In recent years, it has been increasingly difficult to obtain coverage for both branded and generic acne products. Some formularies have begun to completely exclude all topical acne treatments. This issue is particularly problematic for older patients, despite evidence that acne often persists into adulthood.[2] As a result, it may be that many patients will experience challenges with coverage and affordability for this new medication.

It is exciting to see the development of a novel class of topical acne medication targeting the hormonal pathogenesis of acne. Although there has been steady introduction of new topical retinoids and topical antibiotics over the past several decades, it is encouraging that clascoterone has a novel mechanism of action that may complement existing treatment options for acne. While there is still much more work to be done, clascoterone cream, 1%, gives us another tool in the armamentarium to help our patients with acne achieve clear skin.

ARTICLE INFORMATION

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Published Online: April 22, 2020. doi:10.1001/jamadermatol.2020.0464

Conflict of Interests Disclosures: Dr Barbieri is supported by the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the National Institutes of Health (32-AR-007465) and receives partial salary support through a Pfizer fellowship grant to the trustees of the University of Pennsylvania.

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