Game Changer in Acne Treatment

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Of the four primary pathogenic factors that drive acne vulgaris—androgen excess, increased sebum production, faulty keratinization, and overgrowth of C. acnes—androgen excess has been the most elusive therapeutic target. Oral contraceptive pills (OCPs) have direct effect on circulating hormones, but their potential use is limited to a subset of women. As such, a sizable portion of the population affected by acne vulgaris cannot even consider treatment with OCPs. While these systemic agents are generally associated with a low risk profile and have a history of safe and effective use, they are not entirely risk-free. Indirect androgen modulation through the use of spironolactone has become increasingly popular. Again, while generally safe and effective, this systemic treatment is not without risks and contraindications and it is also limited to a subset of female patients.

As noted, acne is a multifactorial process. However, it is essentially an inflammatory disease. Each of the four above-named disease drivers contributes to the underlying inflammation that is a hallmark of acne vulgaris. Therapy targeting excess androgens is thought to reduce inflammation in two key ways. Androgens have been shown to promote sebum production, thus supporting the overgrowth of C. acnes and its inflammatory by-products. Additionally, androgens are shown to directly promote inflammatory responses within follicles.[1]

Enter clascoterone, a first-in-class topical androgen receptor agonist now under review by the U.S. Food and Drug Administration (FDA) in a novel 1% cream formulation. Clascoterone is a new chemical entity that has been studied in the treatment of moderate to severe acne in individuals as young as age 9. Importantly, it is appropriate for use by a vast majority of male and female patients, with no significant systemic effects observed in users to date.

Clascoterone shares a 4-ring backbone identical to dihydrotestosterone (DHT) and spironolactone. It targets androgen receptors in the skin to block the effects of circulating endogenous androgens and competes with DHT for binding to the androgen receptor to limit or block transcription of androgen responsive genes. Additionally, it has downstream impact on sebum production and inflammation.[2]

Data for topical clascoterone, described in the pages ahead, are very promising. Preliminary analysis of data from two phase 3 trials suggest that topical clascoterone is an effective treatment for acne vulgaris, particularly with regards to reduction of inflammatory lesions. In fact, the treatment met its primary endpoints, achieving statistically significantly greater rates of IGA Treatment Success (≥2-point reduction in Investigator Global Assessment (IGA) and score Clear (0) or Almost Clear (1)) at week 12. The study population included both males and non-pregnant females with both inflammatory and non-inflammatory lesions and baseline IGA score of 3 (moderate) or 4 (severe). There were no adverse events that suggested systemic anti-androgen exposure with topical treatment. And the rates of Treatment-Emergent Adverse Events (TEAE) were similarly low in the active and placebo groups in both studies.

Clearly, the notion of hormonal modulation to manage acne is not new. However, options have been limited to women and have not been considered first-line interventions for the disease.[1] Clascoterone may change all that. It appears to have no effects beyond the site of application; as a topical androgen inhibitor with seemingly no systemic effects, clascoterone may become a treatment option for a majority of acne patients, inhibiting the cycle of physiologic events and associated inflammation that leads to acne lesion formation. Clinical experience will determine an ideal role for the drug, whether as a stand-alone treatment or in combination with other treatments shown to target the complex pathogenesis of inflammatory acne vulgaris.

DISCLOSURE

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REFERENCES

1. Park JH, Bienenfeld A, Orlow SJ, Nagler AR. The Use of Hormonal Antiandrogen Therapy in Female Patients with Acne: A 10-Year Retrospective Study. *Am J Clin Dermatol.* 2018 Jun;19(3):449-455.
2. Data on file, Cassiopea.