Acne vulgaris affects an estimated 40-50 million individuals in the US and is the most common reason that patients seek care from dermatologists. Despite its high prevalence, the topical prescription tool box used by dermatologists to treat acne has been limited to benzoyl peroxide, topical retinoids, topical antibiotics, and dapsone. For the first time in almost 15 years, a new chemical entity may be coming to the market for the topical treatment of acne vulgaris. Under development by Cassiopea, Cortexolone 17α-propionate (clascoterone) is a novel topical drug that has both anti-androgen and anti-inflammatory properties. If approved, it will be marketed under the brand name Winlevi.

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BY JOSHUA ZEICHNER, MD

Acne vulgaris is thought to be caused by a combination of several pathogenic factors including sebum, follicular hyperkeratinization, *C. acnes* bacteria, and inflammation. In acne patients, there is both increased production of sebum along with an altered lipid composition thought to promote inflammation. Stimulation of the androgen receptor sebocytes by *C. acnes* or androgen hormones like dihydrotestosterone (DHT) increases their activity, producing sebum along with inflammatory cytokines like IL-1β and IL8. Until now, inhibition of sebocyte activity has only been achieved using oral agents, such as isotretinoin or spironolactone. Clascoterone is a first-in-class molecule thought to inhibit sebocyte activity when applied topically.

The structure of clascoterone is a four ring backbone that mimics the structure of both DHT and spironolactone. Clascoterone is thought to be a direct competitor to DHT for binding to the androgen receptor on the sebocyte. Direct binding of clascoterone to the androgen receptor was evaluated during in vitro testing using cultured human primary sebocytes. Clascoterone was shown to antagonize testosterone-stimulated sebocyte transcriptional activity, DHT-induced
Clascoterone was shown to antagonize testosterone-stimulated sebocyte transcriptional activity, DHT-induced production of lipids, and DHT-induced activation of inflammatory pathways.2

THE DATA TO DATE

In the pivotal Phase 3 studies, the safety and efficacy of clascoterone were evaluated relative to vehicle. Fourteen hundred and forty subjects were enrolled across 112 sites in the US and Europe in two identical, paired studies. Participants were patients with moderate to severe acne who were at least nine years old. Subjects applied clascoterone 1% cream or placebo twice daily for 12 weeks. All primary and secondary endpoints were met in both studies. At week 12, treatment success was defined as skin being clear or almost clear with at least a two-point reduction in the Investigator Global Assessment (IGA) score. In the intent-to-treat population, 16.1 percent and 18.7 percent of patients on active drug achieved treatment success compared to 7.0 percent (p=0.0008) and 4.7 percent (p<0.0001) on vehicle. There were also statistically significant differences in reductions of non-inflammatory lesions (-19.4 and -19.4 on active drug versus -13.1 (p=0.0016) and -10.9 on vehicle (p<0.0001), respectively) as well as inflammatory lesions (-19.4 and -20.0 on active drug versus -15.5 (p=0.0029) and -12.6 on vehicle (p<0.0001), respectively).3

The drug was found to be safe and well tolerated in the pivotal studies, and there were no treatment-related serious adverse events. The most common adverse events were local skin reactions, which were predominantly mild and occurred at similar rates in the vehicle arm.

In addition to the 12-week pivotal studies, 609 patients were rolled into an open-label safety study to evaluate patients for a total of 52 weeks. Four hundred and sixteen participants used clascoterone for at least 26 weeks, and 119 used clascoterone for the full 52 weeks. The drug was safe and well-tolerated. Treatment-emergent adverse events occurred in 18.1 percent of patients. The most common adverse events were nasopharyngitis (six percent) and upper respiratory tract infection (1.3 percent). In all, 2.3 percent of patients experienced adverse events deemed to be related to the drug, which were cutaneous adverse events, mainly mild in severity. There were no serious drug-related adverse events.

Though not a primary endpoint, treatment success was evaluated in the study. At week 52, 57 percent of patients were clear or almost clear with at least a 2-grade improvement in acne.

A NEW OPTION

Clascoterone represents a new treatment option for acne patients. Traditional anti-androgen treatments like spironolactone are effective but cannot be used in men because of adverse events like gynecomastia. The action of clascoterone is at the site of application rather than systemically. No sexual side effects or gynecomastia, which have been seen with the use of oral anti-androgens, were observed in the study of topical clascoterone.

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3. Data on file, Cassiopea