What's New in the Management of Acne Vulgaris

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PRACTICE **POINTS**

- Sarecycline is the first new antibiotic approved for acne in several years.
- Tazarotene foam 0.1% was relaunched to the market. The foam formulation attempts to impart moisturizing effects to offset potential irritation.
- Topical minocycline for acne optimizes the therapeutic effects while reducing systemic effects.
- Clascoterone and cannabidiol currently are under investigation for acne treatment.

Drug development continues to focus on the challenge of treating acne effectively and safely. Inflammation is a backdrop to the commonly cited elements of the pathophysiology of acne: *Propionibacterium acnes* proliferation, increased sebum production with an increase in circulating androgens, and faulty keratinization. As such, there is increased emphasis on targeting inflammation and its effects. Vehicle innovations are optimizing existing active drugs and creating opportunities to deliver new compounds to the skin. Recently approved sarecycline is the first new chemical entity approved for acne in several years. It might be followed in coming years by other new actives, including clascoterone and cannabidiol (CBD).

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Inflammation is a backdrop to the commonly cited elements of the pathophysiology of acne: *Propionibacterium acnes* proliferation, increased sebum production with an increase in circulating androgens, and faulty keratinization.[1,2] In fact, research shows that the initiating lesion of acne vulgaris—the microcomedone—is, in essence, an inflammatory lesion.[3] This realization has clearly influenced the approach to acne treatment but has not yielded a bevy of new treatments.

A better understanding of acne pathophysiology and the role of inflammation has, however, yielded a better understanding of how existing therapies treat the disease and have led to more comprehensive treatment strategies that are multitargeted. Nonetheless, topical and oral antibiotics remain mainstays of acne therapy, along with topical retinoids and benzoyl peroxide. Current guidelines of care for acne emphasize strategies that reduce dependence on antibiotics and minimize the risk for resistance.[4] The therapeutic landscape might at last be shifting, with new chemical entities for acne and several novel formulations in development.

Sarecycline: A Novel Tetracycline

Tetracycline antibiotics have been used to manage acne since the 1950s, but their method of action in the disease has not been fully elucidated.[5] In addition to antibiotic effects, tetracyclines have been shown to confer anti-inflammatory properties and other biologic effects.[6,7]

First-generation tetracycline is broad spectrum. As such, it is associated with increased potential for antibiotic resistance and greater impact on gastrointestinal health. The novel compound sarecycline is a tetracycline with a narrower spectrum of activity compared to other tetracyclines and with reduced activity against enteric gram-negative bacteria[8] (Figure 1). Sarecycline recently was approved by the US Food and Drug Administration (FDA) in a once-daily oral formulation for the treatment of inflammatory lesions of nonnodular moderate to severe acne vulgaris in patients 9 years and older. Sarecycline is dosed at 1.5 mg/kg daily. The FDA approval marks the first new antibiotic approved for acne in 4 decades.

In 2 phase 3 clinical trials, sarecycline demonstrated efficacy in reducing both inflammatory and noninflammatory lesions.[9] At week 12, investigator global assessment (IGA) success (≥2 point reduction in IGA and score 0 [clear] or 1 [almost clear]) rates were 21.9% and 22.6% for active treatment (n=483 and n=519), respectively, in the

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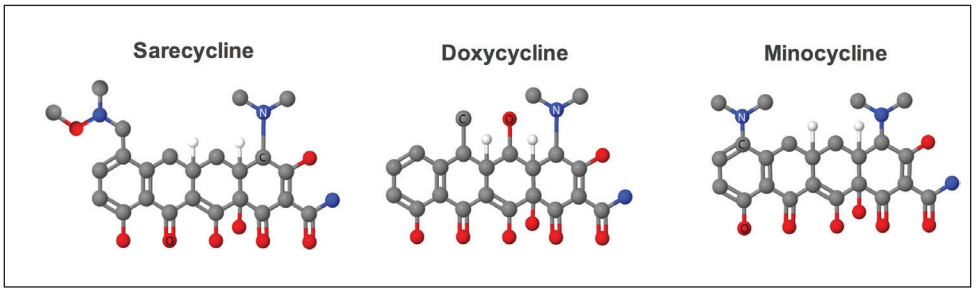

FIGURE 1. Sarecycline has a narrower spectrum of activity compared to other tetracyclines such as doxycycline and minocycline.

2 trials compared to 10.5% and 15.3% (n=485 and n=515), respectively, for controls. Sarecycline demonstrated rapid anti-inflammatory effect. Onset of action against inflammatory lesions was notable by week 3. At week 12, inflammatory lesions were reduced in the active treatment arms by 51.8% and 49.9%, respectively, compared to 35.1% and 35.4%, respectively, for controls.[9]

The most common reported treatment-emergent adverse events (TEAEs) were nausea, nasopharyngitis, headache, and vomiting.[9] Vestibular (dizziness, tinnitus, vertigo) and phototoxic (sunburn, photosensitivity) TEAEs both occurred in 1% or fewer of sarecycline patients. Gastrointestinal TEAE rates for sarecycline were low.[9]

Sarecycline also was assessed in the 2 trials for efficacy in the treatment of back and chest acne; in the active treatment group, IGA success was achieved by 29.6% and 36.6%, respectively, compared to 19.6% and 21.6%, respectively, of controls.[9]

Tazarotene Foam in Focus

Topical tazarotene is commercially available in cream, gel, and foam formulations. Tazarotene foam 0.1% was FDA approved in 2012 for the treatment of acne vulgaris in patients 12 years and older. However, the product was recently relaunched to the market and therefore warrants discussion.

Similar to other retinoids, topical tazarotene has been associated with the potential for application-site irritation. This aqueous foam formulation of tazarotene was designed for ease of application and to attempt to impart moisturizing effects to offset potential irritation. It contains noncomedogenic light mineral oil, which is an emollient. The foam spreads easily, including on hair-bearing skin, with demonstrated penetration of the active drug into the epidermis and dermis. Nonetheless, compared to the gel formulation of tazarotene, the foam formulation was associated with reduced systemic exposure.[10]

The tazarotene foam formulation does not contain alcohol, fragrance, propylene glycol, or parabens. Clinical trial participants, blinded to whether they were on active treatment or vehicle foam, consistently rated the foam formulation favorably for ease of application and spreadability, lack of stickiness or residue, and moisturizing effect. The foam vehicle is suggested to increase compliance and satisfaction in some patients.[11]

The efficacy and tolerability of tazarotene foam 0.1% was investigated in 2 randomized, double-blind, vehicle-controlled, parallel-group studies in the United States and Canada.[12] The studies involved participants aged 2 to 45 years who were randomized to receive treatment with either tazarotene foam 0.1% or vehicle foam once daily for 12 weeks (N=1486). Lesion counts, investigator static global assessment, and subject global assessment were evaluated at baseline and at weeks 2, 4, 8, and 12. At week 12, mean reduction from baseline in noninflammatory lesions was 55.9% for active treatment, mean reduction in inflammatory lesions was 56.1%, and mean total lesion reduction was 56% compared to mean reductions of 37.7%, 45.3%, and 40.8%, respectively, for vehicle. In all, 28.2% of participants achieved treatment success with active treatment compared to 14.7% of controls. There was a greater proportion of active-treatment participants with investigator static global assessment scores of 0 or 1 compared to vehicle. The only adverse events reported by more than 5% of participants in the active-treatment groups in both studies were application-site skin irritation and dryness.[12]

Topical Minocycline

Systemic minocycline is the most commonly prescribed oral antibiotic for acne management.[13] Despite its widespread use, it is not without potential safety concerns. Minocycline is distinct among tetracyclines for posing a small risk for systemic lupus erythematosus and autoimmune TEAE. Gastrointestinal side effects and bluish discoloration also are reported.[14] Topical application of minocycline for acne would optimize the therapeutic effect while reducing systemic effects. FMX101 4%, an investigational minocycline foam, is being studied for the treatment of moderate to severe acne.

In a pharmacokinetic study, minocycline exposure was 730- to 765-times lower with foam application vs oral minocycline.[15] No evidence of minocycline accumulation was identified over the 21 days of application of minocycline foam 4%. Minocycline foam 4% appeared to be safe and well tolerated, without serious TEAEs, treatment-related TEAEs, or TEAEs that led to treatment discontinuation.[15]

In 2 identical phase 3 studies in which 961 participants were randomized (2:1) to once-daily minocycline foam 4% or foam vehicle for 12 weeks, participants in the active-treatment group demonstrated a significantly greater reduction in both inflammatory and noninflammatory lesions in both studies (both $P<.05$) and a greater rate of

treatment success (≥2 point reduction in IGA and score of 0 [clear] or 1 [almost clear]) in 1 study. Treatment was generally safe and well tolerated, with skin-related adverse events reported in fewer than 1% of participants receiving active treatment.[16]

In an open-label safety extension study that enrolled 657 patients, treatment with FMX101 continued for as long as 40 weeks.[17] In total, 291 participants completed 52 weeks of therapy. Rates and types of reported TEAEs in the open-label extension phase were similar to those seen in the phase 3 trials. Application-site TEAEs occurred in fewer than 2% of participants. Participants reported a high level of treatment satisfaction at week 52.[17]

In a more recent phase 3 study, 1507 participants were randomized (1:1) to once-daily minocycline foam 4% or foam vehicle for 12 weeks to further evaluate the efficacy and safety of FMX101 4% for moderate to severe acne vulgaris.[18] The study met both primary end points: absolute change from baseline in the inflammatory lesion count (−16.93 vs −13.40; $P<.0001$) and the noninflammatory lesion count (−18.80 vs −15.89; $P<.05$), as well as percentage of participants with IGA treatment success at week 12 (30.80% vs 19.63%; $P<.0001$). The percentage reduction in the inflammatory lesion count was statistically significantly greater for minocycline foam 4% compared to vehicle as early as week 3 ($P<.0001$). The safety profile was found to be consistent with the 2 earlier phase 3 studies.[18]

Topical Minocycline in Rosacea

A similar foam formulation of minocycline (1.5% concentration) has shown benefit in 2 identical phase 3 studies.[19] A total of 1522 participants were enrolled in 2 phase 3, randomized, multicenter, double-blind, vehicle-controlled, 2-arm studies in participants 18 years and older with moderate to severe papulopustular rosacea. Participants were randomized (2:1) to either minocycline foam 1.5% or vehicle once daily to the face for 12 weeks.[19]

Treatment was associated with a statistically significant reduction in counts of inflammatory lesions of rosacea (Study FX2016-11: −17.57 vs −15.65 [$P=.003$]; Study FX2016-12: −18.54 vs −14.88 [$P<.0001$]) and a significantly higher rate of IGA treatment success compared to vehicle (Study FX2016-11: 52.1% vs 43.0% [$P=.027$]; Study FX2016-12: 49.1% vs 39.0% [$P=.008$]), highlighting the anti-inflammatory action of the topically applied agent.[19]

The most common TEAE for both studies was upper respiratory tract infection; there were no serious TEAEs. Overall, 9 participants across both studies discontinued because of a TEAE (foam, 7 participants; vehicle, 2 participants).[19]

Clascoterone: First-in-Class Topical

Clascoterone cream 1% is a new chemical entity under investigation for the treatment of moderate to severe acne in patients 9 years and older. Clascoterone targets androgen receptors in the skin to block the effects of circulating endogenous androgens; chemically, it shares a 4-ring backbone identical to dihydrotestosterone and spironolactone (Figure 2). Clascoterone competes with dihydrotestosterone for binding to the androgen receptor to limit or block transcription of androgen-responsive genes and modify specific gene expression.[20]

Androgens are known to promote both sebum production and inflammatory responses within the follicle, contributing to the cycle of acne.[21] Antiandrogen therapy would, therefore, inhibit excess sebum production and directly reduce the presence of certain inflammatory mediators in skin. This effect is expected to lead to reduced follicular plugging and a reduction in growth of *P acnes* and its inflammatory by-products.

Direct and indirect hormonal modulation have been successfully employed to manage acne in women; however, such therapies have not been considered first-line interventions for the disease.[22] Although systemic antiandrogens and hormonal modulation are effective for certain women with acne, there may be concerns about systemic exposure[23]; no hormone-modulating agent has been adopted for use in men with acne.

As an androgen inhibitor, clascoterone is thought to displace androgen hormones from androgen receptors located at the sebaceous gland and hair follicle, thus inhibiting the cycle of physiologic events that leads to acne formation. Clascoterone is applied topically and acts locally on androgen receptors in the skin, with no systemic exposure seen. In phase 2 trials, clascoterone was found to be safe and effective with no systemic exposure and was suggested to have better tolerability than topical tretinoin.

Preliminary individual study analysis of data from 2 phase 3 trials showed that topical clascoterone met its primary end points, achieving statistically significantly greater rates of IGA treatment success (≥2 point reduction

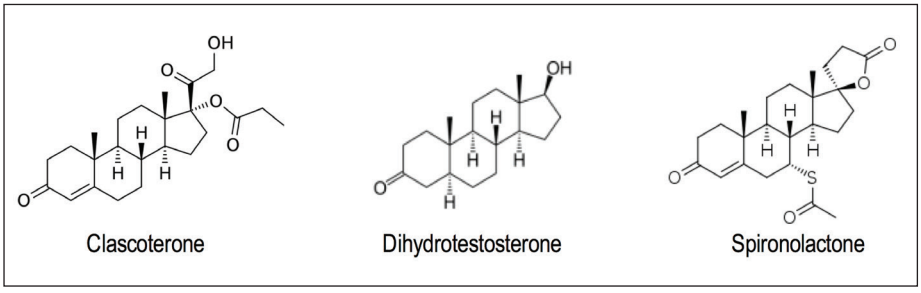

FIGURE 2. Clascoterone shares a 4-ring backbone identical to dihydrotestosterone and spironolactone.

in IGA and score of 0 [clear] or 1 [almost clear]) at week 12 ($P<.0001$).[24] Rates of treatment success for actively treated participants were 16.1% and 18.7%, respectively, compared to 7% and 4.7%, respectively, for vehicle. The study population included both males and nonpregnant females 9 years and older who had a baseline IGA score of 3 (moderate) or 4 (severe). At baseline, participants had a mix of inflammatory lesions (≥30, to a maximum of 75) and noninflammatory lesions (≥30, to a maximum of 100).[24]

Intention-to-treat analysis at week 12 showed a mean total lesion reduction from baseline for active treatment of 37.1% and 37.7%, respectively, compared to 28.5% and 22.2%, respectively, for controls.[24] Mean reductions from baseline in noninflammatory lesions for active treatment were 30.7% and 29.3%, respectively, compared to 21.9% and 15.8%, respectively, for controls. Mean reductions from baseline in inflammatory lesions for active treatment were 44.8% and 47%, respectively, compared to 36.6% and 29.8%, respectively, for controls. Similarly low rates of TEAEs were reported in active and placebo groups in both studies. No TEAE suggested systemic antiandrogen exposure.[24]

Advancements in Cannabinoids

Advancements in pharmaceutical development of cannabinoid compounds have largely coincided with the controversial national movement to legalize medical marijuana and decriminalize recreational marijuana use. Despite the temporal connection, the 2 topics are entirely distinct. Importantly, pharmaceutical development is largely focused on the effects of cannabidiol (CBD), which is 1 of approximately 113 cannabinoids identified from *Cannabis sativa*. Cannabidiol is not tetrahydrocannabinol, or THC, the compound responsible for marijuana's psychoactive effects and addictive properties; CBD does not have any psychoactive effects and is not addictive (Figure 3).[25]

A CBD oral solution agent recently gained FDA approval for seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years and older; it is estimated that more than 180 trials of CBD are ongoing in the United States for various indications.[26] A notable question in the development of CBD-based therapies is: What is the role of natural plant-derived CBD compared to a pure synthetic form of CBD? The latter is akin to a pharmaceutical process in which a single molecule is developed as the active drug.[27] Although the potency and composition of plant-derived CBD can vary with crop conditions, plant strains, and the extraction process, a synthetic molecule would allow for consistency in safety, potency, and pharmacokinetic properties, as well as efficacy, as a consequence.[26]

There are intriguing data to suggest a potential use for topical CBD in the management of skin diseases, including acne vulgaris. Researchers have, for at least a decade, been investigating the role of the endocannabinoid system, which has physiologic regulatory functions in proliferation, differentiation, apoptosis and cytokine, mediator, and hormone production of various cell types in skin, hair follicles, and sebaceous glands.[28] Cannabidiol has been shown to suppress proliferation of sebocytes through activation of transient receptor potential vanilloid 4 ion channels and to have anti-inflammatory effects on sebocytes.[29] It has been shown to inhibit human keratinocyte proliferation through a non-CB1/CB2 mechanism[30] and to possess potent antimicrobial activity against gram-positive bacteria such as *P acnes*.[31]

Given these effects on sebocytes, modulation of keratinocyte proliferation, and anti-inflammatory and antibacterial effects, CBD could prove beneficial in the management of acne vulgaris. A new synthetic CBD topical formulation, BTX 1503, is under investigation for the treatment of acne vulgaris.

Early clinical data confirm both the anti-inflammatory effects of topical BTX 1503 as well as its effects on noninflammatory lesions, with 4-week reductions in inflammatory lesion counts similar to what are reported in clinical trials for leading FDA-approved topical therapies in the same time frame.

The phase 1b trial was a 4-week, open-label study in participants with moderate to severe acne vulgaris.[32] The primary end point was safety, as demonstrated by the incidence of TEAE, laboratory monitoring, and assessment of cutaneous tolerability. Exploratory end points included changes in inflammatory and noninflammatory lesion counts and IGA score. A total of 21 participants aged 18 to 65 years with moderate to severe acne vulgaris were enrolled. BTX 1503 was applied topically twice daily. At baseline, eligible participants had 20 to 50 inflammatory lesions and 20 to 100 noninflammatory acne lesions on the face, an IGA of 3 (moderate) or 4 (severe), and 3 or fewer nodular or cystic lesions (>5 mm in diameter). No serious or severe TEAEs were reported; no participants withdrew due to a TEAE. Slight erythema, slight scaling, slight dryness, and slight burning and stinging were

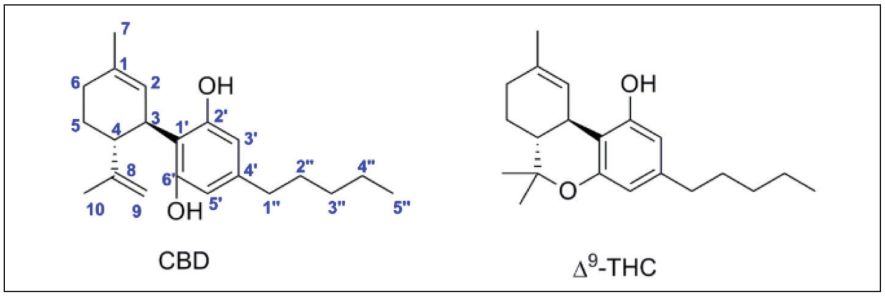

FIGURE 3. Cannabidiol (CBD) is not tetrahydrocannabinol (THC), the compound responsible for marijuana's psychoactive effects and addictive properties.

reported; there were no reports of irritant or allergic contact dermatitis. Only 1 TEAE was thought to be possibly related to treatment: mild pain at the application site.[32]

In addition to presenting a potential new chemical entity for the topical treatment of acne, the novel topical vehicle formulation of BTX 1503 represents an innovative approach to drug delivery. The formulation utilizes proprietary technology to deliver high doses of drug into the skin without controversial penetration enhancers, preservatives, or other potential irritating additives. Instead, volatile excipients are used that evaporate upon application to the skin, leaving a so-called superconcentrated secondary formulation on the skin. The concentration gradient effect then drives the concentrated drug into skin. Although the formulation efficiently delivers active drug into the skin and its appendages, systemic exposure has been reported to be very low. A phase 2 randomized, double-blind, vehicle-controlled trial ongoing in the United States and Australia in 360 patients with moderate to severe acne vulgaris will provide key data to confirm the efficacy and safety of BTX 1503 (ClinicalTrials.gov Identifier NCT03573518).

Conclusion

Drug development continues to focus on the challenge of treating acne effectively and safely. Vehicle innovations are optimizing existing active drugs and creating opportunities to deliver new compounds to the skin. The approval of sarecycline as the first new chemical entity approved for acne in several years may be followed in coming years by other new actives, including clascoterone and CBD.

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