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).

**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. In addition to antibiotic effects, tetracyclines have been shown to confer anti-inflammatory properties and other biologic effects. 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 (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. 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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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 discontinuation.\(^9\)

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.\(^15\)

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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 discontinue 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 exposure23; 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](https://www.mdedge.com/dermatology/cohort-future-032021.jpg)

**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 ($P<.0001$). 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 ($\geq 30$, to a maximum of 75) and noninflammatory lesions ($\geq 30$, to a maximum of 100).

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. 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.

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).

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. 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. 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.

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. 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. It has been shown to inhibit human keratinocyte proliferation through a non-CB1/CB2 mechanism and to possess potent antimicrobial activity against gram-positive bacteria such as P. acnes.

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. 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

![Image of Cannabidiol (CBD) and Δ9-THC](image-url)

**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.\footnote{Smith JA, Narahari S, Hill D, et al. Tazarotene foam, 0.1%, for the treatment of acne vulgaris: safety and efficacy from a phase 3 randomized, double-blind, vehicle-controlled study. J Drugs Dermatol. 2018;17:333-338.}

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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