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Targeting Acne Pathogenesis With Topical Therapies

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Topical Acne Therapies and Their Pathogenic Targets

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We, as dermatologists, are exceedingly lucky. We can watch our patients improve before our eyes. In clinical practice, we don't often track a quantitative metric to gauge success but rather measure the success of our treatment by the appearance of our patients' skin. For those suffering from acne, we know the improvement is more than skin-deep. As their skin improves, so does their self-confidence and quality of life. But how do we get our patients from point A to point B? How do we improve their skin? Our menu of oral and topical agents to choose from is expanding every year. As our options widen, we need to know which agent is the best, which will give our patients optimal results. But to fully appreciate this, we must have an understanding of each agent's mechanism of action and a knowledge of acne's pathophysiology.

Although we have a plethora of scientific studies looking at the pathogenesis of acne, more questions have arisen as the years have gone by. Aristotle said, "The more you know, the more you realize you don't." This is so true of our understanding of acne. Ten years ago, we didn't speak of *C. acnes* phylotypes or biofilms. Now, we are just beginning to realize the role that these entities may play in acne and yet more questions abound as to their impact on acne. The more we learn, the more questions arise. This exceedingly common disease has a tremendously complex pathogenesis. The different factors in acne interplay with one another making it impossible to say that one step always precedes or follows the other. Rather, there seems to be a complicated relationship between hyperkeratinization, *C. acnes*, sebum production, and inflammation that ultimately causes this ubiquitous disease.[1]

As our patients often seek to find a safe approach to treating acne, many want to steer away from systemic treatments. Our topical options abound yet no single topical treatment addresses every step in acne pathogenesis. Many acne studies are monotherapy studies and do not evaluate different topical agents in combination simultaneously. It is often up to the clinician to use their clinical judgment as to which topical treatments should be combined in use. To understand how to choose the best topical treatment, or to understand which topical treatments can be used in combination to have an additive effect, rather than a redundant effect, a clinician must understand both the pathogenesis of acne and the mechanism of action of the various topical therapeutics. To watch our patients improve before our eyes, we need to understand what is going on below the skin. We need to know how to treat what we can't see – the sebum production, the inflammatory cascade, the hyperkeratinization, the *C. acnes*. Choosing the best therapeutic to address the complicated pathogenesis under the skin is key to bettering both our patients' skin and lives.

DISCLOSURE

Dr Graber has received honorarium and served as a consultant, speaker and researcher for several companies that make acne related products including: Almirall, Cutera, Galderma, La Roche Posay, L'Oreal, Ortho Dermatologics and WoltersKluwer Health; also a Cutera shareholder.

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Pathophysiologic Targets of Acne Treatment

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ABSTRACT

Acne vulgaris is an extremely common dermatologic condition. Individuals with acne present not only to dermatologists, but also to internists, family medicine physicians, pediatricians, estheticians, and beauty counters alike in search of a treatment. The diagnosis of acne is relatively straightforward, leading many to believe that acne is a simple condition. However, the pathophysiology of acne is anything but simple. Decades of research has ultimately revealed a complex interaction of pathogenic factors that lead to acne. This includes sebum production, *C. acnes* colonization, inflammation, and follicular hyperkeratinization. Understanding each of these features has been fundamental to the development of anti-acne medications. Topical agents are often used as an initial therapy given their safety and efficacy. While some topical therapies have been used for decades, new creams, gels, and lotions continue to be added to the list of approved acne treatments. Given the number of topical acne products on the market, we present an updated review of the current landscape of topical acne treatments and how each choice functions mechanistically to fight against acne.

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INTRODUCTION

Despite being an exceptionally common disease, the exact pathogenesis of acne has not yet been fully elucidated. The hair follicle and sebaceous gland make up the pilosebaceous unit and acne vulgaris is the most common inflammatory disorder of the pilosebaceous unit. There are four key pathogenic factors in acne development: 1) increased sebum production, 2) presence of *Cutibacterium acnes* (*C. acnes*, formerly known as *Propionibacterium acnes*), 3) inflammation, and 4) follicular hyperkeratinization.[1]

However, the temporal order and the individual impact of each of these steps are debated and uncertain. As one example of this temporal confusion, it was long assumed that the comedo was the initial lesion incited by hyperkeratinization. It has therefore long oft been referred to as a "non-inflammatory" lesion as it was assumed that inflammation had not yet afflicted this early lesion in acne pathogenesis and that inflammation was reserved for papules, pustules, and nodules. However, as will be discussed in further detail later, inflammation has been found even in micro-comedones making the reference to comedones as "non-inflammatory" lesions incorrect and outdated. While each of the four pathogenic steps plays a role in lesion development, we cannot say for certain that one of these steps proceeds the other or is more important than the other. As will be evident from the science presented herein, each step influences the other and the pathogenesis of acne is likely a complicated dance amongst sebum, hyperkeratinization, *C. acnes*, and inflammation.

While there is no single topical therapeutic agent that affects all four steps in acne pathogenesis, clinicians often use multiple topical therapies in combination to obtain maximal reduction in acne lesions. Knowledge of which pharmaceutical affects which step in acne pathogenesis will allow the clinician to choose products wisely, picking combinations of products that are not redundant but add a different mechanism of action and therefore block additional steps in the formation of acne. Theoretically, a topical agent that combats the most steps in the pathogenesis of acne will have the greatest success in treating this common pilosebaceous disease. The clinician must have a basic understanding of acne pathogenesis as well as an understanding of how various therapeutics target acne pathogenesis to choose the best anti-acne topical medication for their patient. We herein will present an overview of acne pathogenesis as well as a review of the mechanisms of action of topical acne medications.

PATHOPHYSIOLOGY OF ACNE

Hyperkeratinization

Normally, keratinocytes, the predominant cells in the epidermis, shed gradually from the follicular lining. However, in follicular hyperkeratinization (also known as retention hyperkeratosis and ductal hypercornification), this shedding process becomes dysregulated, and the corneocytes become adhesive and do not shed as they normally would from the pilosebaceous ostium (ie, the point at which the pilosebaceous unit opens to the surface of the stratum corneum; Figure 1). The cohesion of corneocytes results from the increased number of tonofilaments and desmosomes.[2] The impaction of these adhered corneocytes within the pilosebaceous unit leads to the formation of a keratinous plug or microcomedo. Initially, this microcomedo is invisible to the naked eye but as the plug further obstructs the follicular opening, preventing sebum from extruding normally through the pilosebaceous ostium, the dilation of the pilosebaceous unit becomes more pronounced thus leading to a clinically visible comedo. Microcomedones develop under the surface of the skin about 8 weeks before an acne lesion is visible on the surface.[2] When dilation of the pilosebaceous unit occurs superiorly at the ostium, an open comedo will develop. However, when dilation of the pilosebaceous unit occurs more inferiorly in the lower infundibulum or the isthmus, a closed comedo will result. The trapped sebum, combined with cellular debris, creates an anaerobic environment conducive to the overgrowth of *C. acnes*. The plug of material can accumulate, further distending the pilosebaceous unit and clinically resulting in a papule or pustule (see Figure 1).

Although we do know that hyperkeratinization and follicular plugging occur, we are not exactly sure of the mechanism through which this takes place, yet several theories have been proposed. The lack of linoleic acid in the pilosebaceous unit of those with acne has been theorized as one trigger of hyperkeratinization. A deficiency of epidermal lipids may cause hyperkeratinization and a genetic loss of the steroid sulfate enzymes (leading to a deficiency of epidermal lipids) may also trigger hyperkeratinization.[3] Additionally, androgens may cause hyperkeratinization,[4] and certain cytokines, such as interleukin-1 have been shown to trigger hyperkeratinization.[5]

Increase in Sebum Production

Sebaceous glands are the largest and most numerous in the skin on the face, back, and chest, thus alluding to their role in acne development. These glands function by holocrine secretion, meaning that the death of the sebocytes within the gland leads to the excretion of their contents known as sebum. Sebum is primarily made of triglycerides and free fatty acids, wax esters, and squalene.

FIGURE 1. Pilosebaceous unit and hyperkeratinization in different types of comedones.

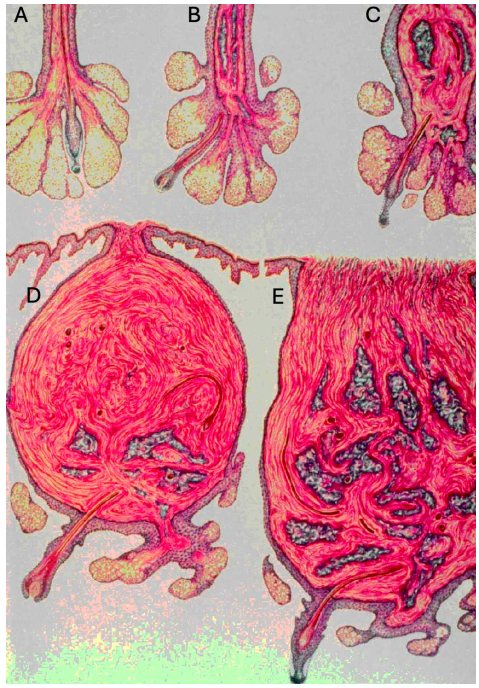


Illustration of hyperkeratinization in different types of comedones. (A) Normal pilosebaceous gland. (B) Micro-comedo in which hyperkeratinization has just begun and corneocytes fill the pilosebaceous canal. (C) Later stage microcomedo, still invisible to the naked eye. Impaction of corneocytes leads to dilation of the pilosebaceous canal. (D) Closed comedo, depicting a relatively narrow follicular ostium compared to the much dilated inferior portion of the pilosebaceous unit. (E) Open comedo, dilation of the pilosebaceous unit involves the follicular ostium at the most superior portion of the pilosebaceous unit. Illustration adapted from: Kligman AM, Acne. In: Plewig G, Kligman AM (eds) Acne and Rosacea, 2nd edn. Springer-Verlag: Berlin, 1993.)

It has been repeatedly demonstrated that those with acne have higher sebum production than those without acne.[6] Sebum output (ie, lipogenesis) from the sebaceous gland is influenced by hormonal influences. At the level of the sebaceous gland, testosterone is converted to 5-dihydrotestosterone (DHT) via the enzyme type 1 5α-reductase. Either testosterone or DHT can bind to the androgen receptor (AR) in the cytoplasm of the sebocyte. The AR is then transported to the nucleus and can bind to response elements located in the promoter regions of androgen-related genes causing signaling cascades that elicit sebum production.[7] Interestingly, the conversion of testosterone to DHT is 30-fold higher in acne-afflicted skin than in normal skin.[8] As we think about the interplay between the four pathogenic factors of acne, it is important

to note that sebum has pro-inflammatory mechanisms and also is a food source for *C. acnes*, allowing it to thrive.[9]

The Presence of *C. Acnes*

C. acnes (formerly known as *Propionibacterium acnes*) is a gram-positive anaerobic bacteria ubiquitous on human skin but can also play a role as a pathogen in acne formation. As a lipophilic bacterium, *C. acnes* resides within the pilosebaceous unit as it feeds on the triglycerides in sebum and then proliferates. This bacterium breaks down the sebum triglycerides into free fatty acids, which are highly inflammatory. The inflammatory response includes the recruitment of immune cells to the site, leading to redness, swelling, and the formation of inflammatory lesions such as papules, pustules, nodules, and cysts.

However, those with acne do not necessarily have more *C. acnes* than those without acne. Instead, it is likely a loss of the typical microbial diversity and ratio of microbes on the skin along with activation of the innate immune system that may relate to the role *C. acnes* plays. The many variants of *C. acnes* have been categorized into phylotypes (ie, acne strains), and in recent years, many studies have sought to understand the role of these different phylotypes in the pathogenesis of acne. While there is some evidence to suggest that certain phylotypes are more pronounced than others in acne, it may not be the phylotype that matters as much as the loss of diversity of phylotypes in healthy skin which may trigger acne. Loss of different *C. acnes* phylotypes plays a role in the development of acne via activating the innate immune system causing cutaneous inflammation. Some evidence suggests that loss of diversity and predominance of IA-1 and IA-2 are most found in severe acne[10] and with phylotypes IB, II, and III associated with healthy skin and deep tissue infections.[11] Some of the *C. acnes* phylotypes, such as IA and II, are more likely to produce biofilms, a type of barrier consisting of extracellular polymeric substances which makes them more likely to adhere to surfaces. Biofilms serve as a protective mechanism for the bacteria, making them less susceptible to immune surveillance and less sensitive to antibiotics[11] as biofilms reduce the penetration of drugs.[10] In addition to protecting the bacteria, biofilms also can stimulate the innate immune system. Acne-associated strains also have a greater propensity to stimulate TH17 cells to secrete interferon (IFN)-gamma and proinflammatory interleukin (IL) 17, whereas healthy skin-associated strains stimulate TH17 cells to produce anti-inflammatory IL-10.[12]

Inflammation

Although hyperkeratinization and sebum production may also lead to inflammation, research in recent years highlights the many proinflammatory effects of *C. acnes*. *C. acnes* can secrete several virulence factors such as CAMP hemolysis, lipase, and RoxP enzyme which lead to the production of interleukin-17 by Th17 lymphocytes. *C. acnes* can also interact with toll-like receptor 2, triggering the release of proinflammatory cytokines (such as IL-8 and IL-12) these cytokines attract neutrophils and the release of neutrophil lysosomal enzymes that promote follicular rupture of the pilosebaceous unit.[13]

Porphyrins produced by *C. acnes* also are thought to contribute to inflammatory and immune responses during acne development. It is theorized that porphyrins can increase the production of cytotoxic substances via oxidation processes and also stimulate mediators of inflammatory and immune responses.[11] *C. acnes* also secrete extracellular vesicles that cause abnormal regulation of antigen Ki67, keratin 10, filaggrin, and desmocollin 1, and upregulate the production of inflammatory cytokines.[14]

Inflammation may be stimulated by other key acne pathogenic factors such as sebum production and hyperkeratinization. While inflammation was previously thought only to play a role in papules, pustules and nodular acne lesions, evidence suggests that inflammation may abound in all acne lesions, even in comedones previously mislabeled as "non-inflammatory". One study found macrophages, CD3+ and CD4+ cells present even within early microcomedone lesions, suggestions that inflammation may be a precursor event to acne rather than a later stage event.[15] Vascular adhesion molecules, E-selectin and integrin were also found activated in such early lesions.[16] This evidence lends us to believe that perhaps inflammation is a trigger of hyperkeratinization rather than the previously thought model that hyperkeratinization preceeds inflammation.

The sebaceous gland also has multiple ways in which it too can contribute to the inflammation in acne. As a producer of interleukin-1 (IL-1), the sebaceous gland is capable of driving an inflammatory cascade in acne and there is evidence that IL-1 expression and secretion is upregulated in the sebaceous gland even during early stages of acne development.[17] The sebaceous gland may also upregulate defensin production during acne lesion development, promoting inflammation. Changes in sebum composition, such as the accumulation of lipid peroxidases also lead to inflammation. Pro-inflammatory peptidases and neuropeptides produced by the sebaceous gland give further weight to the role of the sebaceous gland in inflammation development.[18]

TOPICAL TREATMENTS

Retinoids

Retinoids are a mainstay in acne treatment as they are both comedolytic and anti-inflammatory. Retinoids perform through retinoic acid receptors (RARs) and retinoid X receptors (RXRs). Retinoids lessen keratinocyte accumulation and adhesion in the pilosebaceous unit resulting in comedolytic effects.[19] There are 3 subtypes of RARs, but RAR-gamma is the most predominant type in human skin. Various retinoids may be more specific in binding to one subtype versus another. Yet, there is no evidence demonstrating that retinoid receptor subtypes effect efficacy or tolerability. Tretinoin binds equally to all 3 subtypes but exerts its affect by binding" instead of "is due to RAR-gamma. When tretinoin binds RAR-gamma, the RAR-gamma complex is activated along with the retinoid X receptor (RXR)-alpha. Subsequently, this complex then binds to retinoic acid response elements (RAREs), ultimately activating 300 genes that affect hundreds of proteins expression levels. Tretinoin also downregulates pro-inflammatory nuclear transcription factors which typically upregulate matrix metalloproteases causing acne scars. Retinoids inhibit leukocyte migration, cytokine production, arachidonic metabolism and toll-like receptor activation and therefore reduce inflammation.[20] Some studies have demonstrated that retinoids may improve acne scars via formation of procollagen and types I and III collagen.[19]

Four topical retinoids are approved for treating acne: tretinoin, adapalene, tazarotene, and trifarotene. These can be found in varying formulations and concentrations. Many studies have validated their use in treating acne yet for some patients they can be hindered by the potential of topical retinoids to cause skin dryness and irritation. Although patients may equate this drying of the skin with a reduction of oil, retinoids are not sebosuppressive agents.[21]

Clindamycin

Clindamycin is an antibiotic that eradicates bacteria by disrupting protein synthesis through inhibition of the 50S ribosomal subunit. It is effective against gram-positive cocci and anaerobes (eg, Clostridium perfringens). Clindamycin may be bacteriostatic or bactericidal depending on its concentration.[22] In large, clindamycin aids in reducing acneiform lesions through its action against *C. acnes*, which is a gram-positive anaerobic bacterium.[23]

While clindamycin primarily treats acne through its antibacterial effect, it also appears to have anti-inflammatory properties. *C. acnes* is a pathogen capable of eliciting an immunogenic response, therefore clindamycin indirectly reduces local inflammation by decreasing bacterial load. As bacterial colonization decreases, there are less proinflammatory and chemotactic factors being released to mobilize leukocytes. More interestingly, however, is that clindamycin also has a direct inhibition of leukocyte mobility. In vitro studies have demonstrated that clindamycin inhibits leukocyte chemotaxis even when used at concentrations lower than the therapeutic dose required for antibacterial activity.[24]

IL-1, a proinflammatory cytokine of the innate immune system, has also been evaluated with regards to clindamycin. While in vitro studies show that clindamycin inhibits IL-1β production by peripheral blood monocytes in the setting of *C. acnes*, there seems to be no impact on IL-1α release by keratinocytes.[25] Furthermore, these studies also determined that clindamycin may have an inhibitory effect on IFN-γ and IL-6, but not IL-8 or IL-12.[25] Mouse models infected with pathogens other than *C. acnes* have demonstrated an inhibition of TNF-α production when exposed to clindamycin,[26,27] however studies using human monocytes stimulated by *C. acnes* did not find this inhibitory effect.[25]

Benzoyl Peroxide

Benzoyl peroxide (BPO) is a broad-spectrum antibacterial agent that releases free oxygen radicals to oxidize bacterial proteins. BPO lowers the bacterial population of both aerobes and anaerobes, including *C. acnes*.[28] Its nonspecific peroxidation allows for bactericidal action and a greater degree of suppression of *C. acnes* than topical antibiotics like clindamycin.[29] BPO also decreases colonization rapidly, with an estimated reduction of *C. acnes* by 97% after one week.[30] Consistent with this fast reduction in *C. acnes*, clinical improvement in acne is evident within 3 weeks with maximum improvement seen after 8 to 12 weeks of use.[31] Additionally, no bacterial resistance has been reported to date. In fact, BPO has been shown to reduce the prevalence of resistant strains of *C. acnes*.[32] For this reason, it is recommended that all topical antibiotics be used in combination with BPO.

As the oxidative stress generated by BPO is rather non-selective, treatment can lead to alterations in the skin microbiome. Skin swab studies have revealed reductions in bacterial diversity by one month, with a decrease not only in *C. acnes* but also in coagulase-negative *Staphylococcus* and *Micrococcaceae*.[33,34] Furthermore, BPO causes relative increases in the proportion of *Staphylococcus* in relation to *C. acnes*.[35,36] When control-matched, the post-BPO microbial diversity of acne patients was found to be similar to the skin of individuals without acne.[37] These changes in the microbiome appear to be transient with diversity returning to pre-treatment levels within 3 months.

Azelaic Acid

Azelaic acid is a dicarboxylic acid found in wheat, rye, and barley. It can also be formed endogenously or by yeast living on the skin (eg, *Malassezia furfur*). While the mechanism of action of azelaic is not completely understood, its primary value in treating acne is through its antimicrobial effect. Azelaic acid largely exerts a bacteriostatic effect against *C. acnes*.[38] Trials have found significant reductions in the density of *C. acnes* (by about 30- to 44-fold) after topical application of 20% azelaic acid, in addition to other microorganisms including *Micrococcaceae* and *Staphylococcus*.[39,40]

While azelaic is a much weaker antibacterial agent when compared to true antibiotics, it can remain effective against resistant bacteria in cases where traditional antibiotics (eg, erythromycin, clindamycin) fail.[41] Therefore, azelaic acid may have a role in decreasing bacterial resistance like benzoyl peroxide. Possible antimicrobial mechanisms of azelaic acid include disruptions in mitochondrial respiration and changes in the intracellular pH of *C. acnes*.[42] In vitro analyses have also shown that protein synthesis is impacted more so than RNA and DNA synthesis.[43]

Azelaic acid may also serve as an exfoliant to promote cell turnover, thereby targeting the pathogenic factor of hyperkeratinization. It has been shown to modify epidermal differentiation by normalizing filaggrin distribution with a resultant decrease in the thickness of the stratum corneum.[44] This may be related to changes in kallikrein-5 (KLK5) and cathelicidin, both of which are involved in epidermal proliferation.[45]

Azelaic acid is available both over the counter and as a prescription in different forms. Azelaic acid 20% cream is indicated for the treatment of mild-to-moderate acne vulgaris for use twice daily. In a study of 12 weeks of twice daily use of azelaic acid 20% cream, a significantly higher proportion of patients with papulopustular acne had achieved a "good-to-excellent clinical response" with azelaic acid (64%) compared with vehicle (36%).[46] Prescription gel and foam versions are also available but are only indicated for use in rosacea.

Dapsone

While dapsone was initially developed as an antibiotic, it is primarily used in dermatology for its anti-inflammatory effects. Its antibacterial mechanism is through the inhibition of bacterial folic acid synthesis. The anti-inflammatory mechanism, however, is more nuanced and is likely related to on overall decrease in oxidative damage. Dapsone suppresses neutrophilic chemotaxis and production of free radicals.[47,48] It may also inhibit the release of inflammatory factors such as prostaglandins and leukotrienes from macrophages.[49]

While dapsone is significantly inferior to other antibiotics (clindamycin, tetracycline, and erythromycin) at eradicating *C. acnes* when cultured,[41] it may reduce *C. acnes*-mediated inflammation. For example, human keratinocytes cultured with *C. acnes* release significantly less IL-1α and IL-8 when treated with dapsone. Similarly, dapsone inhibits IL-1β, IL-6, IL-8, and TNF-α in human mononuclear cells affected by *C. acnes*.[50]

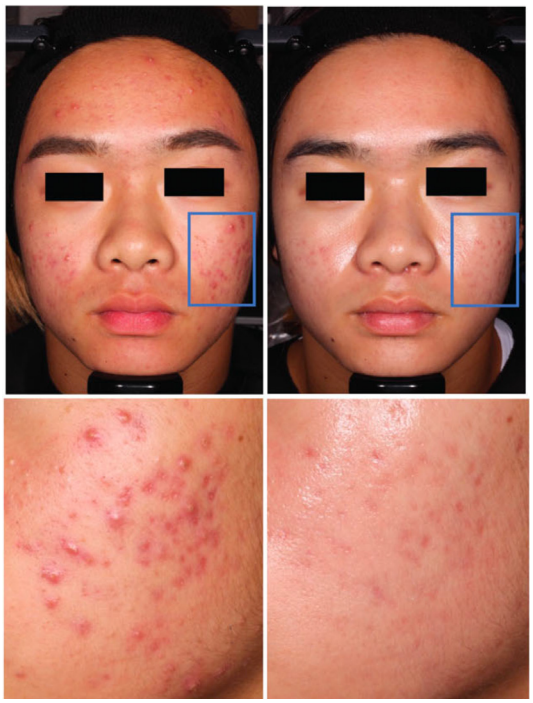
Topical dapsone gel is available as a 5% gel and a 7.5% gel. The dapsone 5% gel is approved for twice daily use in acne patients aged 12 and older. The dapsone 7.5% gel is approved for once daily use in patients with acne aged 9 and older. In phase 3 studies, patients with moderate acne (Global Acne Assessment Score, GAAS, of 3) with treated once daily with dapsone 7.5% gel or vehicle gel for 12 weeks. Although 29.8% of patients using the dapsone 7.5% gel had none or minimal acne (GAAS of 0 or 1) at 12 weeks, 21.1% of patients using the vehicle gel alone had none or minimal acne (GAAS of 0 or 1) at 12 weeks.[51]

Clascoterone

Clascoterone, or cortexolone-17α propionate, is topical antiandrogen that was approved in recent years for the treatment of moderate to severe acne for patients aged 12 and older for twice daily use. It is the only topical treatment that targets the pathophysiologic factor of sebum production. While androgen modulation is commonly addressed with systemic options such as combined oral contraceptive pills and spironolactone, no topical treatment blocking androgen-induced sebum production existed until clascoterone. Furthermore, these oral options are not suitable for treating male patients due to the potential side effects they may cause in this group. However, topical clascoterone can be safety used in both male and female patients. Two, phase III randomized controlled studies evaluated patients with moderate or severe acne (IGA scores of 3 or 4) using topical clascoterone cream bid for 12 weeks. In these two studies, 18.3% and 20.4% of patients using the clascoterone cream achieved clear or almost clear skin (IGA scores of 0 or 1) at week 12.[52]

Clascoterone functions as an antagonist of androgen receptors, which are acted on by testosterone and dihydrotestosterone (DHT). Clascoterone directly binds to these receptors with high affinity and has been found to suppress downstream androgen-regulated transcription in human sebocytes and dermal papilla cells.[53,54] In vitro studies have elucidated that clascoterone suppresses DHT-

FIGURE 2. Before and after 12 weeks of triple combination product clindamycin phosphate 1.2%/benzoyl peroxide 3.1%/adapalene 0.15% gel once daily.



Left: Before, 14 year old. Blue box is magnified in below image. Right: After 12 weeks of once daily use of clindamycin phosphate 1.2%/benzoyl peroxide 3.1%/adapalene 0.15% gel. Image taken from: Eichenfield LF, Stein Gold L, Kircik LH, et al. Triple-combination clindamycin phosphate 1.2%/benzoyl peroxide 3.1%/adapalene 0.15% gel for moderate-to-severe acne in children and adolescents: randomized phase 2 study. *Pediatr Dermatol.* 2023;40(3):452-459. doi: 10.1111/pde.15283. PMID: 36949579.

induced lipid production by sebocytes to the same degree as spironolactone. While antiandrogens are typically not viewed as anti-inflammatory with regards to acne treatment, these studies have also suggested that clascoterone may indirectly modulate inflammatory pathways. For example, clascoterone was found to be superior to spironolactone at limiting the production of inflammatory cytokines such as IL-6, IL-8, and IL-1β.[53]

Clindamycin Phosphate 1.2%/Benzoyl Peroxide 3.1%/Adapalene 0.15% Gel

The novel combination of clindamycin, BPO, and adapalene as a single gel was recently approved to treat acne in patients over the age of 12 years. It is the first FDA-approved triple-combination topical acne product. It combines the well-established topical acne medications discussed above but has the added benefit of being a single formulation and application. This is important because combination products have been found to improve patient adherence to acne regimens.[55] Furthermore, this 3-in-1 gel targets most of the pathophysiologic components of acne including hyperkeratinization (adapalene), *C. acnes* colonization (clindamycin, BPO), and inflammation (adapalene, clindamycin). Therefore, it is not surprising that this triple combination gel has been found to be significantly more effective than 2-in-1 dyad treatments (BPO/adapalene, clindamycin phosphate/BPO, and clindamycin phosphate/adapalene). In a phase II randomized, double-blinded study, participants were assigned to use either the tiple combination gel, one of the three dyads or a vehicle product once a day for 12 weeks. All participants in the study began with moderate or severe acne (IGA scores of 3 or 4). At the end of the study, 52.5% of the patients using the triple combination gel had clear or almost clear skin (IGA scores of 0 or 1), a far better outcome than those using the any of the dyad products or vehicle. The next best group were those using the clindamycin phosphate/BPO gel, of which 30.5% achieved IGA scores of 0 or 1 (Figure 2).[56] It may also be a more tolerable choice for patients, as studies have established a slightly greater safety profile compared to the adapalene/BPO dyad.

SUMMARY

While there is no single factor in the pathogenesis of acne, we as clinicians serve our patients best by understanding the four steps in the pathogenesis and how our therapeutic options target each of these steps. In a network meta-analysis of over 200 acne randomized controlled trials, oral isotretinoin was found to be the most effective agent in

TABLE 1.

Topical Anti-Acne Agents and the Four Steps in Acne Pathogenesis

	C. acnes	Hyperkeratinization	Inflammation	Sebum Production
Retinoids		X	X	
Clindamycin	X		X	
Benzoyl Peroxide	X			
Dapsone			X	
Clascoterone				X
Azelaic Acid	X	X		
Clindamycin/adapalene/benzoyl peroxide	X	X	X	

The primary pathogenic factors in acne that are targeted by each therapeutic is indicated by an "X" in each row of different anti-acne agents.

treating acne. Second to oral isotretinoin in acne efficacy was a combination regimen containing topical benzoyl peroxide, a topical retinoid and a topical antibiotic.[57] Oral isotretinoin is the only single medication that affects all four steps in acne pathogenesis. Despite its efficacy, isotretinoin is plagued by: regulatory inefficiencies that hinder its use, teratogenicity, potential side effects, and patient hesitancies. Topical medications may be favored by patients due to their low potential to cause systemic side effects. Although many topical agents exist for treating acne, all but one of these agents target only one or two steps in acne pathogenesis. Within the last year, the availability of the triple combination topical product has allowed us to target three steps in acne pathogenesis with a single product (Table 1). Despite the newness of this three-in-one product, its triple ingredients have proven efficacy, second only to isotretinoin in treating acne.

DISCLOSURES

Dr Graber has received honorarium and served as a consultant, speaker and researcher for several companies that make acne related products including: Almirall, Cutera, Galderma, La Roche Posay, L'Oreal, Ortho Dermatologics and WoltersKluwer Health; also a Cutera shareholder.

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